

# 6<sup>th</sup> PAN ARAB Human Genetics Conference

January 21-23, 2016 | Al Bustan Rotana, Dubai, UAE

Genetics of Multifactorial Disorders

## PROGRAM BOOK

[www.pahgc.org](http://www.pahgc.org)

Organized By



المركز العربي للدراسات الجينية  
CENTRE FOR ARAB GENOMIC STUDIES

# 6th PAN ARAB Human Genetics Conference

## Genetics of Multifactorial Disorders

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Address: P.O. Box 22252 Dubai, United Arab Emirates

Tel: +971-4-398 6777

Fax: +971-4-398 0999

E-mail: [cags@emirates.net.ae](mailto:cags@emirates.net.ae)

Website: [www.cags.org.ae](http://www.cags.org.ae)

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# 6th PAN ARAB Human Genetics Conference

Genetics of Multifactorial Disorders



## **H.H. SHEIKH HAMDAN BIN RASHID AL MAKTOUM**

Deputy Ruler of Dubai  
UAE Minister of Finance

Patron of the Sheikh Hamdan Award for Medical Sciences

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# 6th PAN ARAB Human Genetics Conference

## Genetics of Multifactorial Disorders

Under the patronage of HH Sheikh Hamdan bin Rashid Al Maktoum, Deputy Ruler of Dubai, the Sheikh Hamdan Award for Medical Sciences has worked tirelessly towards supporting and encouraging medical research around the world. The Centre for Arab Genomic Studies (CAGS) is the direct fruition of one such endeavor. In the last decade of its existence, CAGS has grown from being a local centre dedicated to understanding genetic diseases in the region, to being the hub for information on genetic resources in the entire Arab World.

One of the most important services offered by CAGS has been the Catalogue for Transmission Genetics in Arabs, an online free to access database on genetic disorders in the Arab World. I am extremely proud to say that this compendium is now the largest ethnic database on genetic disorders in the World. Alongside this extremely important and ongoing project, CAGS has also in the past couple of years paid greater emphasis on understanding specific simple and complex genetic disorders within the Arab population, resulting in a series of publications in reputed journals. All this is in addition to organizing the biggest conference on genetics in the region, the Pan Arab Human Genetics Conference, which you are here to attend.

Going by the previous editions of the conference, I hope to see a very productive meeting yet again. I welcome all the participants to this conference and hope you have a satisfying and successful meeting.

### **HE Abdul Rahman Mohammed Al Owais**

UAE Minister of Health

Chairman, Board of Trustees, Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences

# 6th PAN ARAB Human Genetics Conference

## Genetics of Multifactorial Diseases

On behalf of the Centre for Arab Genomic Studies (CAGS), it is our pleasure to welcome you to the 6th Pan Arab Human Genetics Conference (PAHGC). Over the past 12 years, the PAHGC has grown to be one of the most important international conferences in human genetics in the Arab World. Through the organization of the PAHGCs, the Centre has successfully brought together diverse regional and international expertise on human medical genetics, and created a platform for discussion and mutual collaboration on issues relevant to researchers, medical professionals, and patients in this region.

The theme for the conference this year is 'Genetics of Multifactorial Disorders'. Multifactorial disorders are the leading cause of morbidity and mortality in the developed world, and the complex genetics associated with these disorders make studying them very difficult. This year, the conference will feature independent modules, each developed by a team of experts. Each module consists of keynote speeches and oral presentations on the module topic. There will also be opportunities for other researchers to present their work in the form of posters during the entire length of the conference.

The program this year also features an entire day dedicated to a special workshop on Genetic Counselling, organized in collaboration with Wellcome Trust Sanger Institute. We are facing an acute shortage of qualified genetic counselors in the region, and we hope that programmes like these will help in alleviating some of the lacuna.

The successful organization of this conference has required the talents, dedication and time of many volunteers and strong support from sponsors. Special gratitude and appreciation is due to the various module developers as they are primarily responsible for the content of the technical program. Special thanks are also due to the Organizing and Scientific Committees of the conference, who have worked hard to bring this conference to fruition. We would also like to thank the members of the Arab Council and Executive Board of CAGS, who have guided and helped us over the years.

We hope that you will find the conference both enjoyable and valuable, and also take some time to enjoy Dubai.



**Prof. Najib Al-Khaja**

President of the Conference



**Dr. Mahmoud Taleb Al Ali**

Chairperson, Scientific Committee

## Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences

On the 10th of April 1999, the late Sheikh Maktoum Bin Rashid Al Maktoum, UAE Vice President, and Prime Minister and Ruler of Dubai, issued the Supreme Decree No. (5) to establish the Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences, with the objective of honouring scientists from every part of the world who tirelessly pursue distinctive medical research that serves the larger interests of humanity. The Board of Trustees and the General Secretariat of Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences was formed on the 1st of May 1999, under the directives of H.H. Sheikh Hamdan Bin Rashid Al Maktoum, Deputy Ruler of Dubai and Minister of Finance.

Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences is one of the most outstanding awards from the GCC countries, and has consistently acted as a motivating force towards promoting the medical services by honouring the scientists and the distinct working parties in academic and therapeutic scopes alongside with medical and humanitarian services all over the world.

The Award clearly recognizes the importance of scientific research in boosting the progress of UAE, and plays a proactive role in funding domestic health researches through a pioneering program. The Award has proved to be widely successful, as it has been recognized by international observers and was testified by leading researchers vying for the award. This success reflects on the foundation's international reputation and its high scientific credibility and level of performance.

[www.hmaward.org.ae](http://www.hmaward.org.ae)

### Centre for Arab Genomic Studies

In the Arab World, genetic diseases represent a major public health problem. The vision of H.H. Sheikh Hamdan Bin Rashid Al Maktoum to alleviate human suffering from genetic diseases in the Arab World crystallized in the establishment of the Centre for Arab Genomic Studies (CAGS) to characterize and prevent genetic disorders and transfigure the future practice of health care in the region.

Some of the priority objectives of the Centre for Arab Genomic Studies are to educate the public and professionals alike on the important impact of genetic diseases in the Arab World and the methods and benefits of early genetic diagnosis. The Centre for Arab Genomic Studies also plans to provide comprehensive genetic services by translating research achievements into well-integrated patient treatment programs. Concurrently, it will also address the ethical, legal, and social issues that may arise with the implementation of such programs.

CAGS includes two scientific committees: The Executive Board of CAGS is composed of a number of local scientists and it represents the governing body and the legal trustee of all activities of the centre. The Council of CAGS includes a number of regional scientists and it facilitates the exchange of information on genetic disorders occurring in Arab countries. Countries represented in the Council of CAGS currently include: Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Tunisia, and the United Arab Emirates. In the future, CAGS aims to extend memberships to a larger group of scientists and include other Arab countries.

One of the major projects of CAGS is the Catalogue for Transmission Genetics in Arabs (CTGA), an online, freely accessible database of genetic disorders reported from the Arab World. CAGS has been involved in the Human Variome Project as a representative of the Arab region, and has been one of the first organizations to take an active lead in working on the project. CAGS organizes the Pan Arab Human Genetics Conference every alternate year, to provide a platform for discussion and education on genetic issues in the region. The Centre also publishes various books and booklets on genetics aimed at the scientific community and the general public.

[www.cags.org.ae](http://www.cags.org.ae)



## Conference Committees

### President of the Conference

Prof. Najib Al Khaja

### Scientific Committee

Dr. Mahmoud Taleb Al Ali (Chairperson)

Dr. Abdul Rezzak Hamzeh (Vice-Chairperson)

Prof. Andre Megarbane (Lebanon)

Prof. Bassam Ali (UAE)

Dr. Fatma Bastaki (UAE)

Dr. Fatima Al Jasmi (UAE)

Prof. Habiba Chaabouni (Tunisia)

Prof. Hanan Hamamy (Switzerland)

Prof. Lihadh Al Gazali (UAE)

Prof. Lotfi Chouchanne (Qatar)

Prof. Moein Kanaan (Palestine)

Prof. Moiz Bakhiet (Bahrain)

Prof. Riad Bayoumi (UAE)

### Organizing Committee

Mr. Abdulla Bin Souqat (Chairperson)

Dr. Abdul Rezzak Hamzeh

Nirmal Rajah

Pratibha Nair

### Event Organizer

Meeting Minds Experts

### Scientific Program

#### Day One – 21st January 2016

TIME	PROGRAM
08:00 – 09:30	Registration
09:30 – 10:30	Opening Ceremony, Exhibition Inauguration and Coffee Break
10:30 – 13:00	<b>Module 1: Diabetes &amp; Metabolic Disorders</b> <b>Moderators: Bassam Ali &amp; Riad Bayoumi</b>
10:30 – 11:10	Keynote Lecture I: Diamonds in the Dirt: Using Genetics and Genomics to Inform Biology and Treatment of Type 2 Diabetes <b>Mark McCarthy</b>
11:10 – 11:30	Keynote Lecture II: Meta Analyses Conducted by CAGS: HLA Class II and Type 1 Diabetes in Arabs <b>Abdul Rezzak Hamzeh</b>
11:30 – 11:50	High Prevalence of MODY Variants in Patients Previously Diagnosed with Gestational Diabetes <b>Anette Gjesing</b>
11:50 – 12:10	Analysis of Genetic Variation in Obesity Genes in Worldwide Populations and Evolutionary Origin of Obesity <b>Vadim Stepanov</b>
12:10 -12:30	Application of Urinary C-peptide to Creatinine Ratio (UCPCR) for Discrimination of Maturity Onset Diabetes of the Young (MODY) in the Emirati Population <b>Hinda Daggag</b>
12:30 – 13:00	Panel Discussion
13:00 – 14:00	Lunch
14:00 – 17:30	<b>Module 2: Genetics of Neurodevelopmental Disorders</b> <b>Moderators: Habiba Chaabouni &amp; Andre Megarbane</b>
14:00 – 14:45	Keynote Lecture III: Primary Microcephalies and Primordial Microcephalic Dwarfisms <b>Alain Verloes</b>
14:45 – 15:05	CRISPR-Cas9 Genome Editing for Cellular Modeling of Microcephaly <b>Ganeshwaran Mochida</b>
15:05 – 15:30	Whole Exome Sequencing In Genetic Isolates - A Founder Mutation of the C12orf4 Gene Underlies Autosomal Recessive Non-Syndromic Intellectual Disability (NSID) <b>Irma Jarvela</b>
15:30 – 16:00	Coffee Break
16:00 – 16:45	Keynote Lecture IV: Neuromuscular Disorders and Rehabilitation <b>Andre Megarbane</b>
16:45 – 17:05	Computational Approach towards Targeting Aggregate Formation in Synucleinopathies, <b>Mohammad Ansari</b>
17:05 – 17:30	Panel Discussion

### Scientific Program

#### Day Two – 22nd January 2016

TIME	PROGRAM
09:00 – 12:00	<b>Module 3: Role of Sequencing in Diagnosis of Congenital Disorders</b> <b>Moderators: Hanan Hamamy, Moein Kanaan &amp; Lihadh Al Gazali</b>
09:00 – 09:45	Keynote Lecture V: From Genome Exploration to the Genome Clinic <b>Stylios Antonarakis</b>
09:45 – 10:05	KCNA4 Deficiency Leads To A Syndrome Of Abnormal Striatum, Congenital Cataract, And Intellectual Disability <b>Mohammed Al-Owain</b>
10:05 – 10:25	Exome Sequencing Reveals a Novel Gene Associated with Monogenic Form of Systemic Juvenile Idiopathic Arthritis <b>Salma Majid</b>
10:25 – 11:00	Coffee Break
11:00 – 11:20	Consanguinity and Genetic Disorders in Qatar <b>Tawfeg Ben-Omran</b>
11:20 – 11:50	Panel Discussion
12:00 – 14:00	Friday Prayers and Lunch
14:00 – 17:30	<b>Module 4: Cancer Genomics</b> <b>Moderators: Moiz Bakheet &amp; Lofti Chouhane</b>
14:00 – 14:45	Keynote Lecture VI: The Rise and Fall of Genomics <b>John Burn</b>
14:45 – 15:05	Genetics of Breast and Colon Cancer in a Highly Consanguineous Population Challenges and Lessons Learned So Far <b>Abeer Alsaegh</b>
15:05 – 15:25	DNA Methylation Regulated Genes as Diagnostic Markers in Cervical Cancer <b>Shama Prasada Kabekkodu</b>
15:25 – 16:00	Coffee Break
16:00 – 16:20	Machine Learning to Fully Exploit Integrated Genomics and Clinical Data for Cancer Prognostic Systems <b>Emad Elsebakhi</b>
16:20 – 16:30	Panel Discussion
16:30 – 17:40	<b>Closing Session</b>

### Genetic Counselling Workshop Program Day Three – 23rd January 2016

**Tutors:**

Dr Christine Patch, *Consultant Genetic Counsellor, Guy's Hospital, London*

Dr Anna Middleton, *Principal Staff Scientist and Genetic Counsellor, Wellcome Trust Sanger Institute, Cambridge*

TIME	PROGRAM
09:00 – 09:05	Introduction
09:05 – 10:00	What is Genetic Counselling? <ul style="list-style-type: none"><li>- Qualifications And Training Needed to Work as a Genetic Counsellor in the UK and Reciprocity of Registration within the Genetic Counselling Profession</li><li>- Core Theoretical Frameworks that Guide Practice</li><li>- Ethical Principles that Guide Practice</li><li>- Counselling Supervision</li></ul>
10:00 – 10:45	The Work of a Genetic Counsellor <ul style="list-style-type: none"><li>- The Multidisciplinary Approach to Care</li><li>- The Types of Patients Genetic Counselors See on their Own</li><li>- The Specialist Clinics that Genetic Counsellors Run</li></ul>
10:45 – 11:15	Coffee Break
11:15 – 12:00	How Can Genomics be Used in the Clinic? <ul style="list-style-type: none"><li>- Who Can Receive Sequencing in a Clinical Setting</li><li>- The Impact of Genomics on Counselling Practice</li></ul>
12:00 – 12:45	Genomics and Ethics <ul style="list-style-type: none"><li>- What to Do with Incidental Findings from Sequencing Studies</li><li>- What Information Do People Want to Know?</li></ul>
12:45 – 13:00	Lunch
13:00 – 14:00	Case Study 1: Exploring a Diagnosis for Developmental Disorders and the Counselling Issues
14:00 – 14:30	Case Study 2: Pre Symptomatic Testing in Huntington's Disease and Counselling Issues
14:30 – 15:00	Case Study 3: Pre-Natal Testing and PGD and Counselling Issues
15:00 – 15:30	Case Study 4: Genetic Counselling and Disability (Using Deafness as an Example)

# 6th PAN ARAB Human Genetics Conference

## Genetics of Multifactorial Disorders

### Venue

Address: Al Bustan Rotana  
Casablanca Road, Al Garhoud  
P.O. Box 30880, Dubai, U.A.E.  
Tel: +971 (0)4 282 0000



[Click here to View Location Map](#)



### Registration Desks

Registration desks will be located at the foyer of the Rashidiya Ballroom. The registration desks will be open on the following dates and time:

21st January, Thursday	08:30 – 17:30 hrs.
22nd January, Friday	08:30 – 17:30 hrs.
23rd January, Saturday	08:30 – 15:30 hrs.

### Registration Badges

Participants are kindly requested to wear their name badge at all times while attending PAHGC 2016. We regret that participants not wearing their badges will not be allowed access to the sessions and exhibition. Lost or Forgotten badges can be re-issued at a USD 50 Fee at the registration desks onsite.

### Poster Sessions

All printed posters must be affixed on the poster boards with double-sided tape provided by the organisers no later than 9am on 21st January 2016.

Please take out your posters from 5:00 to 6:00 pm on 22nd January 2016. Posters not taken out will be disposed of.

### CME Accreditation

PAHGC 2016 has been accredited with 18 CME Credit Hours by the UAE Ministry of Health.

All badges will be scanned each day and CME hours will be awarded according to the number of sessions attended. All CME Certificates will be sent via email after the conference to the email address provided at time of registration. After the conference, delegates will receive a post-show survey in the form of an online questionnaire which must be filled out. Once the form has been completed, the CME Certificate will be sent immediately. Please ensure that the email provided at the time of registration is accurate.

### Food and Beverages

Complimentary tea, coffee, light refreshments will be provided during the breaks at the Exhibition Area. A working lunch will be provided for delegates during the designated lunch period at:

21st & 22nd January (Thursday & Friday)	Rashidiya Ballroom C
23rd January (Saturday)	Rashidiya Ballroom

### Friday Prayer

Delegates are requested to congregate at the registration area for shuttle service for Friday Prayers. Staff will be at hand to escort the group to the nearest mosque, located approximately 10 minutes from the venue.

### Parking

Free parking is available at the hotel.

### Non Smoking Policy

As per Dubai Municipality Law, smoking is prohibited throughout the entire venue. Corresponding fine will be charged to all violators. Smoking is allowed in designated outdoor areas.

### Silver Sponsor

Molecular Biology & Genetics Laboratory (MBG)



Molecular Biology & Genetics Laboratory (MBG) as a double accredited laboratory (ISO15189 & ISO17025) is a unique facility catering the needs of Healthcare providers and animal clinics. Techniques such as Real Time PCR, Sanger Sequencing, FISH, CGH and SNP arrays are routinely employed for diagnostics while evolving research projects aim at exploiting novel technologies like stem cell therapy and next generation sequencing. The MBG remains one of the most advanced genomic centres in the Middle East.

# 6th PAN ARAB Human Genetics Conference

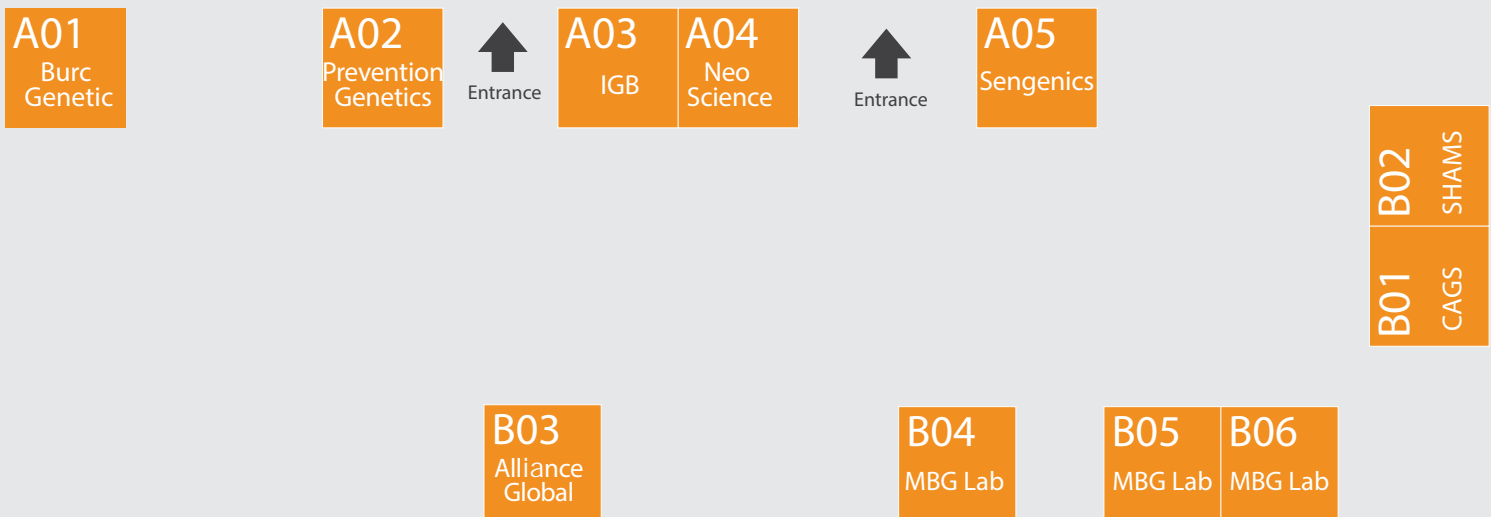
Genetics of Multifactorial Disorders

exhibition

## List of Exhibitors

Company Name	Booth Number
AGBL Group of Companies	B03
Burc Genetic	A01
Integrated Gulf Bio System	A03
Molecular Biology and Genetics Laboratory	B04/B05/B06
Neo-Science & Group	A04
Prevention Genetics	A02
Sengenics	A05

## Exhibition Floorplan





## Company Profiles

### **AGBL Group of Companies**

The AGBL Group of companies is the largest biomedical gateway to the emerging markets of the Middle East, Africa and Asia. The group is dedicated to bringing innovative technologies and products to researchers, clinicians, and diagnostic users in the emerging healthcare markets within the MEAA region.

### **Burc Genetic Diagnostic Center**

Burc Genetic Diagnostic Center has been dedicated to providing high quality comprehensive diagnostic services for over 16 years. Both national and international requests related with routine to rare genetic diseases have been accepted and studied according to best practice guidelines in genetics.

### **Integrated Gulf Biosystems**

The perfect integration of Biology, the centerpiece of Life Sciences, with the latest Technological Advances is what INTEGRATED GULF BIOSYSTEMS (IGB) is all about. It is a complete solution provider to scientists in the fields of life and analytical sciences. No sooner than it was founded in 1999 in UAE, the experience, expertise and commitment demonstrated by the company laid a strong foundation of growth and performance that have helped it expand its footprint significantly across the globe with presence in UAE, Saudi Arabia, Qatar, Bahrain, Egypt, Yemen, Libya and North African region.

We are representing the best product manufacturers of the world such as Thermo Scientific, Applied Biosystems, Invitrogen, Hamilton Robotics, Molecular Devices, ACEA Biosciences, Fast – track Diagnostics, Omni International, DNA Genotek etc., to offer quality products and equipment's.

In Short IGB stands to secure the required quality up-gradation of the world around.

### **Molecular Biology and Genetics Laboratory**

Molecular Biology & Genetics Laboratory (MBG) as a double accredited laboratory (ISO15189 & ISO17025) is a unique facility catering the needs of Healthcare providers and animal clinics. Techniques such as Real Time PCR, Sanger Sequencing, FISH, CGH and SNP arrays are routinely employed for diagnostics while evolving research projects aim at exploiting novel technologies like stem cell therapy and next generation sequencing. The MBG remains one of the most advanced genomic centres in the Middle East.

## Company Profiles

### **Neo-Science & Group**

Neo-Science & Group (NSG) is a trusted provider of high quality tools and services to the Life Science Research and Diagnostics and Analytical, Proteomics, Metabolomics and Bioinformatics industry. We offer one stop solutions to meet the changing needs of the clinical, scientific community. We are associated with renowned manufacturers globally recognized as market leaders in the industry.

### **Prevention Genetics**

PreventionGenetics is a leader in providing comprehensive clinical DNA testing offering NextGen Sequencing, Sanger sequencing and deletion/duplication testing via array CGH for over 1500 genes. PreventionGenetics is CAP/CLIA accredited.

### **Sengenics**

Sengenics is a genomics and proteomics-based research and diagnostics company. To date, Sengenics has carried out the highest number of clinical genomics tests on children with developmental delay in Asia which has been commercialised into GalaxC™, the largest commercial database of human disease mutations in Asia.

### Keynote Lectures

#### K1 Mark McCarthy

Wellcome Trust Centre for Human Genetics, UK

Mark McCarthy is the Robert Turner Professor of Diabetes Medicine at the University of Oxford, based at the Oxford Centre for Diabetes, Endocrinology and Metabolism and the Wellcome Trust Centre for Human Genetics. He is also a Consultant Physician at the Oxford University Hospitals Trust and is currently Visiting Professor at the University of Geneva. Following medical training in Cambridge and London, a spell as an MRC Travelling Fellow at the Whitehead Institute in Massachusetts, and 8 years at Imperial College, he moved to Oxford in 2002. He is a physician-scientist, and human geneticist, interested in the biological basis of complex disease. His research group is focused on the identification and characterisation of genetic variants influencing risk of type 2 diabetes and related traits, and on using those discoveries to drive biological inference and translational opportunities. He works closely with colleagues in Oxford and beyond to establish the mechanisms whereby T2D-risk variants influence islet function, and to explore the value of this information to drive clinical advances. He has played a major role in establishing and leading a number of the global initiatives in this field including the DIAGRAM, MAGIC, GIANT, EGG, GoT2D, ENGAGE and T2D-GENES consortia. He has been a Senior Editor at eLIFE since 2015.

### Diamonds In The Dirt: Using Genetics and Genomics To Inform Biology and Treatment of Type 2 Diabetes

The growing prevalence of type 2 diabetes highlights the limitations of currently available preventative options, and high rates of diabetes complications attest to the inadequacies of current treatment modalities. Novel therapeutic strategies need to be informed by a more complete understanding of the molecular and physiological basis of disease, designed to deliver validated interventional targets, and biomarkers that can be used to define disease risk, progression, and subtype.

My group, in the context of large global consortia, uses human genetics to deliver this understanding. The growing availability of exome sequence data (current n for T2D case-control ~40,000) and exome array data (n~420,000) is beginning to deliver coding variant associations that can plug directly into functional studies and drug development programs. However, the main repository of variant association for T2D remains the ~100 common variant signals so far uncovered by genome wide association studies, most of which map outside coding sequence. We are implementing a multifaceted approach that combines genome-scale and focused functional studies to unlock the biology within these loci.

We use fine-mapping to improve the localisation of causal variants, and map these onto regulatory annotations from key tissues, most notably the human islet. These analyses provide a platform for identifying downstream transcripts through tissue-specific cis-eQTL analyses and conformational capture. We combine these "regulatory variant" data with transcript level information (from human and mouse databases, coding variant associations, high throughput screens) to define the best-supported transcripts in each GWAS region. Finally, we seek evidence of functional enrichment across loci through analyses of protein-protein interaction, co-expression and pathway data. These efforts are starting to bear fruit, with around one-third of GWAS signals now featuring a well-supported priority transcript. We are following up these priority candidates through detailed cellular, molecular, rodent and human studies to consolidate the evidence for a mechanistic role. To build engagement, we are co-developing, via the Accelerating Medicines Partnership, a dedicated T2D knowledge portal that facilitates access to these and other genetic and genomic data for the wider constituency of academic and pharmaceutical researchers.

Keywords: Diabetes, GWAS

## Keynote Lectures

### K2 Abdul Rezzak Hamzeh

Senior Scientific Coordinator, Centre For Arab Genomic Studies, Dubai, UAE

Dr. Abdul Rezzak Hamzeh is the Senior Scientific Coordinator at the Centre for Arab Genomic Studies. Dr. Hamzeh received his PhD in Molecular Biology and Genetics from the University of Manchester (UK) in 2007, and then he moved to Syria to assume a tenure track position at the University of Aleppo. There, he was part of a small academic team who established the University's Cancer Research Laboratory to support academic research and healthcare provision in northern Syria. This facility was the first of its kind there and it provided the opportunity for a good number of projects to be pursued, many of which found their way to internationally peer-reviewed journals. In mid 2012, Dr Abdul left Syria and headed to Dubai to work at the Centre for Arab Genomic Studies (CAGS), mainly to manage existing research activities and help expand them further.

### Meta Analyses Conducted by CAGS: HLA Class II And Type 1 Diabetes in Arabs

Genes from the HLA complex have a major contribution in type 1 diabetes (T1D), which results from an interplay between environmental and genetic factors. The latter can explain some of the geographic variability in T1D occurrence around the world. Of a particular importance in this regard are the HLA-DR, -DP and -DQ loci. Unfortunately, a relatively small number of studies on HLA alleles and their associations with T1D have emerged from Arab countries, mostly with inadequate power on an individual basis. Consequently, we aimed at elucidating the collective genetic profiles of various alleles relating to HLA-DRB1, -DQA1, -DQB1 and -DP in T1D patients throughout the Arab World using the tools of meta-analysis.

Our study showed that significant increases in T1D risk resulted from harboring the alleles DQA1\*03:01, DRB1\*03:01 and DRB1\*04:05. Harboring the haplotypes DR3 and DR4 were also significant risk factors, albeit with high publication heterogeneity. On the other hand, the haplotypes DR7 and DR11 were strongly suggested to be protective in Arabs. Similarly, the protective effects of DQA1\*01:01, DQB1\*05:03, \*06:02, \*06:03, and \*06:04, as well as DRB1\*10:01, \*13:01, \*15:02 and \*16:01 were robustly suggested by all indicators of meta-analyses.

This study fills the above-mentioned information gap by providing significant size effect of human leukocyte antigen (HLA) alleles and completes the continuum of global ethnic differences in this context.

Keywords: Diabetes, Meta-analysis, HLA

### Keynote Lectures

#### K3 Alain Verloes

Université Paris VII-Denis Diderot, France

Alain Verloes is Professor of Medical Genetics at Paris VII-Denis Diderot University, and Head of the Clinical Genetics Unit and Department of Genetics at Robert DEBRE University Hospital in Paris, France. He is also the Head of the Reference Center for Rare Disorders- Ile-de-France. Prof. Verloes obtained his MD from Brussels Free University, and Specialty Training in Pediatrics and Genetics and his Ph.D. from Liege University. He is the co-organizer of the annual European Dysmorphology Meeting, and his research interests focus on RASopathies, primary microcephalies, and the genetic causes of intellectual disabilities. He has been on the editorial board of several prominent journals, including American Journal of Medical Genetics, Clinical Dysmorphology, Orphanet Journal of Rare Diseases, and is the Editor in Chief of the European Journal of Medical Genetics.

### Primary Microcephalies and Primordial Microcephalic Dwarfisms

Alain Verloes, Séverine Drunat, Sandrine Passemard

Primary genetic microcephalies (PM) are a model disease for studying brain growth and organization. PM are rare autosomal recessive disorders with a cumulate incidence from 1/10.000 to 1/100.000 births, depending on geographic origin. Five groups of PM are usually distinguished: MicroCephal, Primitive Hereditary (MCPH), primary microcephaly with chorioretinopathy(MCCRP), and 3 primary microcephalic dwarfisms (PMDW): Seckel syndrome (SCKS), microcephalic osteodysplastic dwarfism type 2 (MOPD2), and Meier-Gorlin syndrome (MGS). PM are characterized by an occipito-frontal head circumference (OFC) more than 2 SD below the mean for sex, age, and ethnicity at birth, and at least below - 3 SD after age six months. Patients exhibit usually no neurologic anomalies except seizures, mild pyramidal syndrome and behavioral disturbances. Ophthalmological anomalies are associated with some of genetic forms, but are inconstant. Cognitive impairment is described as borderline to severe. No systematic neuropsychological study has been conducted on PM patients. Reduced brain volume of these patients is usually associated with a simplified gyral pattern, but not with cortical dysgenesis or infratentorial abnormalities. However, for some genes, patients may exhibit migration or cortical organization defects, albeit without clear genotype/phenotype correlation. The recent discovery of several new genes with mutations causing PM has changed the diagnostic approach and highlighted new ways towards our understanding of the mechanisms involved in brain growth. Currently MCPH phenotype is observed with MCPH1 (MCPH1), WDR62 (MCPH2), CDK5RAP2 (MCPH3), CASC5 (MCPH4), ASPM (MCPH5), STIL (MCPH7), CEP135 (MCPH8), CDK6 (MCPH12)CENPE (MCPH13), SASS6 (MCPH14) and MFSD2A (MCPH15). MCCRP is observed with TUBGPC6 (MCCRP1) TUBGPC4 (MCCRP2) PLK4 (MCCRP3), and KIF11(MCLMR).Only SCKS phenotype was seen with mutations in ATR (SCKL1), NIN (SCKL7), and ATRIP (SCKL8). MCPH, SCKS, and/or intermediate phenotypes are reported with RBBP8(SCKL2), CEP152 (MCPH9/SCKL5), CENPJ (MCPH6/SCKL4), CEP63 (SCKL6) andPHC1 (MCPH11). Two third to one half of MCPH patients have no identified gene mutation. The proportion of SCKL cases not assigned to a known gene is not established. PCNT is the only known MOPD2 gene. MGS is caused by ORC1 (MGS1), ORC4 (MGS2), ORC6 (MGS3), CDT1 (MGS4), and CDC6 (MGS5) mutations. Digenic inheritance has not been reported. The cellular defect of most PM alter fundamental cellular processes linked tothe mitotic cell cycle, such as general control of licensing of DNA replication (in MGS), control of the G1/S and S/M checkpoints, centrosome biogenesis, kinetics of spindle pole during mitosis, and kinetochore function at anaphasis. The common physiopathologic endpoint of these processes is an alteration in cell cycle timing and fate determination of neuronal progenitors. This may result in a premature neuronal differentiation and a reduced number of neurons, although the exact mechanisms remain unclear for most MP genes so far, whereas more severe mitotic dysfunction may explain reduced cell number and short stature. Besides their canonic role in cell cycle, some genes further have alternative roles explaining more complex brain malformations (such as holoprosencephaly or schizencephaly), involvement of retina, brain vessels, bone or skeletal development that characterize the phenotype of some of these them.

Keywords: Microcephaly, Primordial dwarfism

### Keynote Lectures

#### K4 Andre Megarbane

University St. Joseph, Lebanon; Centre Médical et Psychopédagogique, Lebanon

Dr. Andre Megarbane is a professor of medical genetics and head of the Medical Genetic Unit, St Joseph University, Lebanon. Dr. Megarbane is an author and co-author of more than 150 publications. He is a member of the Lebanese National Bioethics Committee, French Society of Genetics and Genetic Counseling, the American Society of Human Genetics, and the European Society of Human Genetics. Dr. Megarbane is also a member of the editorial board of the European Journal of Medical Genetics and the Rammal Rammal Prize Committee. He is a recipient of four scientific awards, namely: Abdel Hamid Shuman Award; Rammal Rammal Medal, Mohammad El-Fasi Young Researcher, and Makhzoumi Association Award. Dr. Megarbane has an active research with interest in the domains of mental retardations, dysmorphology, osseous malformations, and others.

### Neuromuscular Disorders and Rehabilitation

Andoni Urtizberea, Andre Megarbane

For years and years, neuromuscular disorders (NMD), basically defined as an impairment of one component of the motor unit, have been neglected due to their complexity, the lack of accurate biomarkers and their generally poor prognosis. Among the commonest of these conditions are Duchenne muscular dystrophy and Spinal Muscular Atrophies. Although a great deal of PMR specialists see such patients, they have been facing difficulties to follow them up routinely and to apply to them the standards of care usually recommended worldwide. Times are hopefully changing: the many advances achieved in molecular biology (including the next generation sequencing programs) enable us to label precisely which of the 200 or so NMD genes is the causative defect. More importantly, such labelling is the first step towards curative therapies such as exon-skipping, read-through techniques, gene therapy and more to come.

It is now essential that the neuromuscular patient remains in good shape in order to benefit from these innovative therapies. Each neuromuscular patient requires a specific, tailored, medical and, if necessary, surgical approach. Based on the most accurate diagnosis possible (hence the importance of closely collaborating with medical geneticists), the management is meant to prolong life as much as possible while maintaining a good quality of life. Standards of care are now available mainly in the commonest diseases such as Duchenne Muscular Dystrophy and Spinal Muscular Atrophies (SMA). The PMR specialist could/should play an important role by leading the multidisciplinary team surrounding the patient. Physiotherapy, technical advices, non-invasive ventilation, tendon and/spine surgery, heart protection, prevention of all sorts of hazards (denutrition, immunizations, others) are clearly within its scope of expertise. Social support is also important to consider as such disorders are a real burden for most families, especially in the Middle-East.

Keywords: Neuromuscular disorders, Rehabilitation

### Keynote Lectures

#### **K5 Stylianos E. Antonarakis**

University of Geneva, President, Human Genome Organization

Stylianos E. Antonarakis is currently Professor and Chairman of Genetic Medicine at the University of Geneva Medical School, and the founding director of iGE3 (institute of Genetics and Genomics of Geneva). He is a medical, molecular, human geneticist, physician-scientist, who studied extensively the relationship between genomic and phenotypic variation. He received his MD (1975) and DSc (1982) from the University of Athens Medical School, and after a specialization in Pediatrics in the University Hospital, Athens Greece, he moved to Baltimore, Maryland to the program of Medical Genetics at the Johns Hopkins University School of Medicine with Haig H. Kazazian and Victor McKusick (1980-1983). He joined the faculty of the Johns Hopkins University in 1983 and rose to full professor of Pediatric Genetics, Biology and Medicine in 1990. In 1992 he moved to Geneva, Switzerland to chair Genetic Medicine in the University of Geneva.

His research work includes the molecular bases of monogenic disorders and complex genetic disorders including the beta-thalassemias, hemophilias, and trisomy 21. His laboratory participated in the human genome sequence and functional analysis, particularly on chromosome 21. He is an international expert on disorders of chromosome 21, cloning of genes for genetic disorders, development of diagnostic tests, genome structure and function, studies of the genome variability, and conserved non-coding sequences in human DNA. He has published extensively (more than 660 well-cited papers) in the scientific literature, and is co-editor of the current edition of the classic textbook "Genetics in Medicine"; he is listed as one of the highly cited scientists by the ISI institute (more than 51,000 citations; h-index 107). He was the President of the European Society of Human Genetics (2001-2002), and currently the President of HUGO for 2013-2017, foreign member of the Academy of Athens (2003), member of EMBO (2006). He was the co-organizer of the European School of Genetic Medicine, and in the last 32 years taught in the Bar Harbor Genetics Course, Maine.

He was awarded the Society of Pediatric Research Young Investigator Award (1984), International Jerome Lejeune Prize (2004), the European Society of Human Genetics Award (2005), and was elected to the Society of Scholars of the Johns Hopkins University (2006), and the American Academy of Physicians (2010). He was awarded the Commander of the Order of Phoenix medal from the Hellenic Democracy (2007). More than 70 talented young scientists were trained in his laboratory (graduate students and postdoctoral fellows); in addition more than 25 young physicians were trained in the Medical Genetics Clinic of his department. With Haig Kazazian he has established one of the first molecular diagnostic laboratories in USA as early as 1982. He is a member of the Swiss National Science Foundation Research Council, and the Chair of the Genetics Review Panel of the EU ERC. His research laboratory was/is supported by grants from the National Institutes of Health, the European Union (including the European Research Council), and the Swiss National Science Foundation and numerous other Foundations including the Gebert and Lejeune Foundations. He is the originator of the World Down Syndrome Day ([http://en.wikipedia.org/wiki/World\\_Down\\_Syndrome\\_Day](http://en.wikipedia.org/wiki/World_Down_Syndrome_Day)). His current interests and research projects are the functional analysis of the genome, effect of human genetic variation to phenotypic variation, the molecular pathogenesis of trisomy 21 and polygenic phenotypes, the functional characterization of the conserved fraction of the genome, diagnostics and prevention of genetic disorders, and the societal implications of genetics and genome research

### Keynote Lectures

#### K5 From Genome Exploration to The Genome Clinic

A large number of human disorders (including cancer) and other phenotypic traits are caused by or are associated with germline or somatic genomic alterations. The current goal of genetic medicine is to perform the matchmaking between the genomic variability and the phenotypic variability. The completion of the sequence of the human genome, and that of the genomes of other species provided unprecedented opportunities to determine the functional elements and the functional variability of these genomes. The elucidation of the cause of monogenic disorders, was a great success of the past decade, and will certainly continue in the next several years not only to provide precise diagnostic tools, but also to understand the molecular pathophysiology. The completion of recent genomewide association studies for numerous phenotypes, made it clear that common variation in the genome only accounts for a small fraction of the genetic etiology of complex, multifactorial diseases. The rapid, accurate, and relatively inexpensive sequence of individual genomes now provides an enormous challenge in the discovery of causative or predisposing genomic variants that could be used for diagnosis, prevention, or treatment. In addition the majority of the monogenic phenotypes will soon be determined by focusing on denovo variants (for dominant phenotypes), consanguineous marriages (for recessive phenotypes), and all other Mendelian disorders by using international collaborative projects. Furthermore, most of the genes/mutations driving cancer or metastases will also be identified from the large international projects. Comparative genomic analysis between species and between individuals, knowledge of the polymorphic structure of the genomes of different human populations, introduction of new tools to assess gene function, transcriptome analysis, exchange of DNA sequence variants, and assessment of the quantitative variability of gene expression, are all necessary requirements to meet this enormous challenge of genomic and epigenetic pathology. In addition, the remarkable similarity of functional genomic elements in mammalian and other species, provides further opportunities of animal experimentation for disease allele identification. In turn, functional analysis of the genome, and characterization of the functional variability are likely to provide new therapeutic opportunities. The mission of HUGO is to promote the provision of genetic services to all human populations worldwide, to ensure that the relevant data are available to the health professionals, and to provide leadership in the ethical, legal, social and financial issues associated with the medical genome and its associated phenotypes. The integration of the genomic information in the Genome Clinics is gradually changing the medical practice. The Geneva experience of the Genome Clinic will be presented and discussed.

Keywords: Genome clinic



### Keynote Lectures

#### K6 Yves-Jean Bignon

Centre Jean Perrin, France

Yves-Jean Bignon is the Director of the Oncogenetics Department at the Centre Jean Perrin. He pioneered oncogenetics in France, by founding both clinic facility and a molecular biology laboratory devoted to the hereditary predisposition to cancers in 1988. His scientific activities are based on research combining genomics and basic cancer research with translational research applied to clinics for families with different hereditary risks of cancers, in the field of predictive medicine. He founded the French cooperative network in oncogenetics in 1991, and wrote the first French scientific book in oncogenetics. Through international networks, he contributed to determine the role of BRCA1 and BRCA2 germ-line mutations in cancer risk and the role of other genes in breast cancer and colon cancer hereditary predisposition. He was also the first to demonstrate at the molecular level, links between nutrients and their potential protective effects on breast cancer through BRCA1 expression regulation. He created the International School of Franco-Romanian oncogenetics in 2012. Prof. Bignon is an elected Vice-president of the excellence cluster Innovatherm, Deputy Mayor of Vichy since 2014, the former scientific director of the Centre Jean Perrin 2004-2011 and elected member of the board of the Medical school at Auvergne University.

### New Medical Challenges in The Four Milestones of Oncogenetics

Oncogenetics is defined as the diagnosis and the medical management of families with a suspicion of hereditary predisposition to cancers (HPC). Amongst multiple risk factors, HPC has the far highest positive/negative predictive values allowing personalized predictive and preventive medicine for patients and their relatives ("precision medicine").

The four milestones of oncogenetics comprise successively:

- 1- Medical genetic consultation which aims to suspect or not an inherited predisposition to cancers according to the family history and the structure of family tree.
- 2- Gene tests in accredited laboratories according to the familial phenotype of cancer aggregation, after the signature of an informed consent sheet.
- 3- Personalized Programme of Oncogenetics Follow-up (POF-up) is proposed to high-risk patients and organized with their usual physicians, including early diagnosis of all cancers at risk, prevention whenever possible (usually surgery). POF-up has been demonstrated efficient since 2004 and save lives!
- 4- Targeted therapy of cancer: paradigm is PARP-inhibitors treatment in BRCA-mutated tumours. Oncogenetics has still to face many challenges.
  - 1- If medical oncogenetics consultations developed in the late 80's and mainly in the 90's in developed countries, regrettably they are still missing in too many countries world-wide in 2016. Nevertheless, highly-educated people of those countries are aware of oncogenetics benefits and claimant for medical support.
  - 2- NGS (next generation sequencing) machines now allow gene profiling instead of gene-by-gene tests. This permits to test all known genes for a given familial syndrome (21 genes for breast cancer familial syndrome instead of BRCA1/BRCA2 genes only). On the other hand incidental germ-line mutations can be found, for instance inherited predisposition to endometrial and colon cancers in a breast-ovarian cancer family in which no colon cancer is known. Initial informed consent of tested patients is questionable as well the medical speech and medical knowledge of all cancer inherited predisposition genes.
  - 3- POF-up is what families are waiting for, when a germ-line mutation is found. This needs well coordinated multidisciplinary medical supports, usually more difficult to practice than to say. Ideally it supposes a central shared data base to be sure high-risk people have the right exam at the right moment with the right physicians. Which medical support, oncogeneticists have to propose to cancer high-risk families without germ-line mutation? There is still no consensus but specific evaluations have to be conducted considering the waits of so many families (more than 60% of tested families).
  - 4- PARP-inhibitors treatment supposes to perform BRCA test to any patient with ovarian cancer whatever their familial background. In the next future it might be possible to extent PARP-inhibitors treatments to breast cancers, increasing 100-fold the needs for BRCA tests and the cost of the tests. Moreover, BRCA tests should be performed at both somatic & germ-line levels, imposing oncogenetics consultation (often in emergency) to explain the personal and familial consequences of the test, whose benefits may be sometimes considered contradictory. In conclusion, nobody should anymore ignore oncogenetics in its current medical practice. Henceforth, good medical practices must address patients and their families to highly specialized multidisciplinary oncogenetics clinics when a hereditary predisposition to cancer is suspected. Oncogenetics is a paradigm for personalized predictive medicine through identification of the genetic « soil » of cancer in healthy people. But many people still ignore medical oncogenetics in 2016 in too many countries: there are urgent needs for international network & oncogenetics school collaborations widely opened.

Keywords: Oncogenetics, Hereditary predisposition to cancer

## Keynote Lectures

### K7 Sir John Burn

Professor of Clinical Genetics, Newcastle University, UK

John Burn became captivated by genetics as a teenager after hearing the genetic code explained and has been sharing that enthusiasm for more than four decades since. After more than 30 years as a consultant his enthusiasm remains undimmed as he leads an international cancer prevention trial, CaPP3, helps lead the NHS in England and chairs a company, QuantuMDx Ltd, developing an exciting DNA point of care testing device. He conceived and help bring to fruition the Millennium landmark Centre for Life which attracts a quarter million visitors per annum and teaches practical science to 40,000 school children. He was knighted for services to Medicine and Healthcare in 2010.

### The Rise and Fall of Genomics

In under 50 years the term genomics has moved centre stage but is likely to lose identity as it becomes a routine part of care in drug prescribing, cancer management and across a range of diagnostic settings. Variant interpretation is the next traffic jam in need of a global response.

In a global setting the rapid improvement in low cost sequencing offers the prospect of front line whole genome sequencing, possibly with selective reporting of genes considered relevant to the disease state. Point of care testing for specific genotypes is now feasible which will impact on the pressing need for Pharmacogenetic testing to avoid iatrogenic illness, tumour marker testing and urgent pathogen identification.

Keywords: Genomics

## Oral Presentations

### 01 High Prevalence of MODY Variants in Patients Previously Diagnosed with Gestational Diabetes

Peter Damm<sup>1</sup>, Gao Rui<sup>2</sup>, Anette Gjesing<sup>3</sup>, Mette Hollensted<sup>3</sup>, Jihua Sun<sup>2</sup>, Oluf Pedersen<sup>3</sup>, Christian Theil Have<sup>3</sup>, Torben Hansen<sup>3</sup>, Jeannet Lauenborg<sup>1</sup>, Ivan Brandslund<sup>4</sup>, <sup>1</sup>Department of Gynecology and Obstetrics, Hvidovre Hospital, Hvidovre, Denmark; <sup>2</sup>BGI-Shenzhen, Shenzhen, China; <sup>3</sup>The Novo Nordisk Foundation Center for Basic Metabolic Research, Denmark; <sup>4</sup>Department of Clinical Biochemistry, Vejle Hospital, Denmark

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Previous studies evaluating the prevalence of the monogenic form of diabetes called maturity onset diabetes of the young (MODY) among women with GDM reports variable results. Therefore, the aim was to screen for MODY-mutations among women with GDM to estimate the prevalence and impact on future diabetes.

The cohort includes 380 women with diet-treated GDM re-examined on average 9.8 years after the index pregnancy. Targeted resequencing was performed in the coding regions of GCK, HNF1A, HNF4A, HNF1B and INS and variants are characterised as potentially MODY-causing if they are both 1) located in coding or splice-site regions, 2) have a minor allele frequency <0.01% in public databases, and 3) not present among 1000 glucose tolerant Danes. Among such variants, variants were characterised as deleterious if they were 1) previously reported in MODY-families or 2) have an in vitro or in silico damaging function and 3) there is concordance with the phenotypic presentation and family history of GDM and the MODY subtype.

Fifty variants were identified of which 18 fulfilled the criteria for being deleterious. These 18 variants were found in 22 patients. Thus, in total we classify 22 out of the 380 women as MODY-patients, revealing a MODY prevalence of 5.7%. At follow up, identified MODY mutations explained 11% of the GADA-negative diabetes in this cohort.

Among these women previously diagnosed with diet-treated GDM, 5.7% had a monogenic form of diabetes. As early detection of MODY can improve diabetes detection, clinical follow-up of patients and ensure optimal treatment, it should be considered to offer genetic diagnostics of the most common forms of MODY to women with GDM.

Keywords: MODY, Gestational diabetes, variant

## Oral Presentations

### 02 Analysis of Genetic Variation in Obesity Genes in Worldwide Populations and Evolutionary Origin of Obesity

Vladimir Kharkov<sup>1</sup>, Vadim Stepanov<sup>1</sup>, Irina Khitrinskaya<sup>2</sup>

<sup>1</sup>Tomsk State University, Tomsk, Russia; <sup>2</sup>Institute for Medical Genetics, Tomsk, Russia

Since the thrifty genes hypothesis, obesity-related phenotypes have been considered as traits dependent on gene-environment interaction. Recent hypotheses of ancestral susceptibility and decanalization may provide further conceptual bases on the evolutionary origin and population prevalence of obesity and related traits. In order to estimate the evolutionary pattern of genetic diversity in obesity genes we have investigated the distribution of SNPs associated with obesity according to recent genome-wide association studies (GWAS) in worldwide populations. Twenty GWAS SNPs were genotyped in 11 North Eurasian populations and data were pooled with data on HapMap populations from Africa and South Asia. Analysis of genetic diversity, correlation of allele frequency with climatic parameters, natural selection and principal component analysis were performed.

Obesity-associated genetic markers are divided into two equal groups characterized by principally different patterns of genetic diversity. First group demonstrate significant correlations of allele frequencies with key climatic parameters; accumulation of positive signals of natural selection; and systematic decrease of ancestral allele frequency from Africa to Eurasia. This part of genetic component of obesity may be considered as non-neutral and decanalized by natural selection during human dispersal out of Africa. Second part of obesity genetic markers follows the features of neutral genetic variability, i.e., is not correlated with climate, does not demonstrate signals of natural selection. 'Decanalized' and 'neutral' sets of SNPs are also different in their total genetic diversity patterns: 'decanalized' SNPs as opposed to 'neutral' ones have significantly higher average  $F_{st}$  levels and show the decrease of genetic diversity from Africa to Eurasia, unlike 'neutral' SNPs and opposite to trend for genome-wide genetic variation.

Observed pattern of worldwide frequency spectrum in obesity-associated genes may be, at least partially, explained by the hypothesis of canalization/decanalization of genotype-environment relationships under the pressure of natural selection.

Keywords: Obesity, Decanalized, neutral SNPs, GWAS

### Oral Presentations

#### 03 Application of Urinary C-peptide to Creatinine Ratio (UCPCR) for Discrimination of Maturity Onset Diabetes of the Young (MODY) in the Emirati Population

Alia Al-Tikriti<sup>1</sup>, Maha T Barakat<sup>1</sup>, Adam Buckley<sup>1</sup>, Kevin Colclough<sup>2</sup>, Hinda Daggag<sup>1</sup>, Sian Ellard<sup>2</sup>, Nader Lessan<sup>1</sup>  
<sup>1</sup>Imperial College London Diabetes Centre, Abu Dhabi, UAE; <sup>2</sup>Royal Devon and Exeter NHS foundation Trust, UK

Obesity and type 2 diabetes have reached epidemic proportions in the UAE and other Gulf States, and are increasingly diagnosed in young adults. As a consequence, it may become more challenging to distinguish between type 1, type 2 and monogenic diabetes using the standard parameters such as age, BMI and absence of islet cell or GAD antibodies. Besser et al. (2011) and Besser et al. (2013) have shown distinction is possible by utilising UCPCR. We examined the clinical utility of current screening criteria and UCPCR testing in the Emirati Arabic population. Paediatric and adult cases were recruited and 2 hour post-prandial UCPCR was determined. Subsequently, next generation sequencing of known monogenic diabetes genes will confirm a diagnosis of MODY and identify patients for the investigation of novel genetic aetiologies in the Emirati population.

Recruited patients were 126 type 1 diabetes and 16 type 2 diabetes paediatric patients and 67 type 1 diabetes and 64 type 2 diabetes adult patients. 2 Tailed Spearman correlation test showed that in type 1 diabetes patients, UCPCR was negatively correlated with duration of diabetes ( $r=-.6$ ,  $p< 0.001$ ); there was a weak correlation between UCPCR and duration of diabetes in patients with type 2 diabetes ( $r=-.23$ ,  $p= 0.044$ ). UCPCR was significantly lower in paediatric patients with type 1 diabetes with duration of less than 1 year (median 0.583) compared to more than 1 year (median 0.015) ( $p< 0.001$ ).

We suggest that UCPCR test could be valuable for discrimination between type 1 diabetes and type 2 diabetes and/or MODY in both paediatric and adult Emirati patients. Furthermore, if clinically implemented, UCPCR test can potentially be applied on paediatric and adult patients with diabetes duration less than 2 and 5 years, respectively, and as such lead to an earlier clinical diagnosis and adequate management.

Keywords: MODY, UCPCR test

### Oral Presentations

#### O4 CRISPR-CAS9 Genome Editing for Cellular Modeling of Microcephaly

Mert Mestanoglu<sup>1</sup>, Jennifer Partlow<sup>2</sup>, Tojo Nakayama<sup>3</sup>, Muna Al-Saffar<sup>4</sup>, Ganeshwaran Mochida<sup>1</sup>, Elizabeth Ross<sup>2</sup>, Anna Rajab<sup>3</sup>, Atyah Al Zahrani<sup>4</sup>, Dylan Vaughan<sup>1</sup>, Chiara Manzini<sup>5</sup>, <sup>1</sup>*Division of Genetics and Genomics, Boston Children's Hospital, USA;* <sup>2</sup>*Department of Neurology and Neuroscience, Weill Cornell Medical College, USA;* <sup>3</sup>*National Genetics Center, Ministry of Health, Sultanate of Oman;* <sup>4</sup>*Neonatal Intensive Care Unit, King Fahad Medical City, Kingdom of Saudi Arabia;* <sup>5</sup>*Dept. of Pharmacology and Physiology, The George Washington University, USA*

With the widespread availability of whole-exome sequencing, many mutations associated with neurodevelopmental disorders have recently been identified. However, patient-derived tissue is often not available for functional studies, and modeling these disorders remains a labor-intensive and time-consuming process. In this study, we aimed to apply a newly developed technique, clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 genome editing, to create a cellular model for a microcephaly syndrome, asparagine synthetase (ASNS) deficiency.

We ascertained two families (Omani and Saudi) with a total of 6 children presenting with congenital microcephaly, seizures and death during infancy. We performed genomic analysis using whole-exome and Sanger sequencing. ASNS cDNA with mutations were created by standard methods. ASNS-deficient HEK293FT cell lines were generated by CRISPR-Cas9 genome editing. Cell proliferation and apoptosis were analyzed using PrestoBlue and Apo-ONE assays, respectively, and compared between the wild-type and mutant cells.

We identified homozygous mutations in ASNS in both families: p.Leu190\* (Omani) and p.Arg404His (Saudi). Mutant cDNAs showed significantly reduced protein abundance compared to the wild-type when transfected to HEK293FT cells, suggesting that these mutants represent a loss of function. Analysis of ASNS-deficient HEK293FT cell lines revealed an almost complete lack of cell proliferation as well as increased apoptosis. However, when the culture medium was supplemented with asparagine, cell proliferation and apoptosis rate returned close to that of the wild-type cells.

Our results show that CRISPR-Cas9 genome editing can be an effective method for creating cellular models of neurodevelopmental disorders. We show that ASNS deficiency leads to reduced proliferation and increased apoptosis, and suggest that these are likely pathogenetic mechanisms of microcephaly in this condition. We also show that asparagine supplementation alleviates the cellular phenotype, implicating a path toward potential treatment of this devastating condition.

Keywords: CRISPR,-Cas9, microcephaly, cellular model

### Oral Presentations

#### 05 Whole Exome Sequencing in Genetic Isolates - A Founder Mutation of The C12ORF4 Gene Underlies Autosomal Recessive Non-syndromic Intellectual Disability (NSID)

Sergio Coccozza<sup>1</sup>, Tuomo Maatta<sup>2</sup>, Giovanni Scala<sup>1</sup>, Christian Gilissen<sup>3</sup>, Heleen H Aarts<sup>3</sup>, Aki Mustonen<sup>4</sup>, Michele Pinelli<sup>1</sup>, Anju Phi<sup>5</sup>, Teppo Varilo<sup>5</sup>, Irma Jarvela<sup>5</sup>, <sup>1</sup>Department of Human Genetics, Donders Centre for Neuroscience, Radboud University, Nijmegen, Netherlands; <sup>2</sup>Joint Authority for Kainuu, Disability Services, Kainuu, Finland; <sup>3</sup>Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Universita Degli; <sup>4</sup>Department of Clinical Genetics, PEDEGO Research Unit and Medical Research Centre, University of Oulo, Finland; <sup>5</sup>Department of Medical Genetics, Haartmaninkatu 8, University of Helsinki, Finland

Intellectual disability is a major health problem in our society. Non-syndromic intellectual disability (NSID) represents a heterogeneous group of diseases that is often a diagnostic challenge in clinical medicine. The purpose of this study was to identify novel genes underlying intellectual disability in the Finnish families.

To facilitate gene identification, we applied whole-exome sequencing (WES) in a consanguineous family with four affected males who had moderate to severe non-syndromic ID (NSID) of unknown cause. The family originates from an isolated population in North-Eastern Finland. Libraries were prepared using the Illumina TruSeq Kit, multiplexed and captured using Roche's SeqCap EZ Human Exome Library v2.0, as per manufacturer's instructions. The Ethical Committee of the Helsinki University Central Hospital approved this study.

We found a novel missense variant L328P in the C12orf4 gene on chromosome 12 that is inherited as an autosomal recessive trait in the extended pedigree and enriched in the North Eastern sub-isolate of Finland with a carrier frequency of 1:53 among the local blood donors, characteristic to a founder effect. Seven individuals characterized by non-syndromic intellectual disability and delayed speech development were homozygous for the L328P mutation. Screening of our cohort of 200 NSID patients resulted in the identification of two additional carriers of the C12orf4 mutation. In one of them, a previously known de novo mutation in SMAD4, causing Myhre syndrome, was identified. Clinical phenotype of the homozygous individuals for C12orf4 mutation ranged from mild to severe NSID and delayed speech development. A frameshift mutation in exon 6 of the C12orf4 gene has been previously reported in a Saudi family with global developmental delay (Alazami et al. 2015).

Our findings suggest that C12orf4 is a novel gene enriched in the Finnish population that underlies autosomal recessive NSID.

Keywords: Intellectual disability, Founder effect, Whole exome sequencing

### Oral Presentations

#### 06 Computational Approach Towards Targeting Aggregate Formation in Synucleinopathies

Zarfishan Shabbir, Sheela Thogaru, Mohammad Ansari, Hafiz Muhammad  
<sup>1</sup>*School of Life Sciences, Manipal University Dubai, United Arab Emirates*

Synucleinopathies is a diverse group of neurodegenerative diseases including Parkinson's disease (PD), dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). A common characteristic of these synucleinopathies is presence of intracellular pathologic inclusions in certain brain cells that are primarily composed of  $\alpha$ -synuclein (SNCA). Targeting the initial oligomerization steps remains one of the primary focus areas for therapeutic strategies towards synucleinopathies. We have used computational tools to understand the role of a significant 11-mer region of SNCA, its involvement in the polymerization, and discuss ways to use this insight towards synucleinopathies therapeutics. Dimerization of SNCA was studied using protein-docking experiments using GRAMM-X and interface interactions that stabilize the assembly were analysed using Protein Interactions Calculator (PIC) server. SCWRL was used to generate a peptide library differing at those positions of 11-mer which were involved in the stabilization of SNCA dimer. Docking of the peptide from the combinatorial library was performed on this 11-mer region of SNCA and best binders were analysed.

Sequence and structural analysis of predicted dockings models of SNCA-SNCA and SNCA-11-mer region showed that the 2nd Val, 6th Ala and 10th Val of the 11-mer are primarily involved in the hydrophobic interactions. By comparing binding energies of various peptides differing at these positions we found that the central Ala at 6th position in the 11-mer is most critical in dimerization.

Using predicted docked models of SNCA dimers, we identified key residues involved in the interaction of the assembly. Using combinatorial approaches to mutate these key residues, we found several peptides that have better binding energies. The central hydrophobic residue is found to be most critical and potential target for inhibitory molecules. These findings may guide therapeutic strategies towards major neurodegenerative disorders involving synucleinopathies.

Keywords: Synucleinopathies, synuclein, computational analysis, Protein docking



### Oral Presentations

#### 07 Consanguinity and Genetic Disorders in Qatar

Tawfeg Ben-Omran

*Department of Pediatrics, Hamad Medical Corporation, Qatar*

Consanguineous marriages are common in the Middle East including Gulf countries, and in Qatar is approximately 54%. This cross-sectional study was conducted at two centres in Qatar: Hamad Medical Corporation (HMC) and Shafallah Centre (SC).

Consanguineous marriages were in 397 (67.7%) of 599 Qatari families seen during the period of August 2012 to August 2013. The participants ages ranged between 1 year to 58 years (with a mean of  $13.2 \pm 7.4$  years) with male to female ratio 1.4:1. Fathers and mothers education beyond secondary school was found to be 28.1% and 28.5% and approximately 80% of them were employed.

At HMC, all consanguineous marriages had a significantly higher risk of autosomal recessive [45.5% vs 22.4%; (Odds ratio=2.89; 95% CI: 1.37, 6.09;  $p=0.005$ )] and in the total cohort, all consanguineous marriages had a significantly higher risk of autosomal recessive [27.7% vs 16.4%; (Odds ratio=1.95; 95% CI: 1.25, 3.04;  $p=0.003$ )]. Non-consanguineous couples had a slightly higher risk of autosomal dominant in both HMC (8.2% vs 3.4%;  $p=0.188$ ) and total cohort (2.1% vs 1.3%;  $p=0.43$ ), however this difference did not reach to statistical significance. At HMC, undiagnosed genetic disorders were observed to be higher among non-consanguineous marriages and in contrast it was higher among consanguineous marriages in the total cohort.

Our data suggests a significant role of parental consanguinity in increase prevalence of genetic disorders, as expected; mainly autosomal recessive disorders. Undiagnosed genetic disorders were significantly higher among non-consanguineous marriages. Presented research highlights the importance of increasing public awareness and family education on consanguinity and its effect in genetic disorders, and can be enriched and integrated into the national health management and patient care systems to prevent genetic disorders in the Qatari population.

Keywords: Consanguinity, Genetic risk

### Oral Presentations

#### 08 **KCNA4 Deficiency Leads to a Syndrome of Abnormal Striatum Congenital Cataract, and Intellectual Disability**

Banan Alyounes<sup>1</sup>, Faten Almutairi<sup>1</sup>, Mazhor Aldosary<sup>1</sup>, Rosan Kenana<sup>1</sup>, Maysoon Alsagob<sup>1</sup>, Mohammed Al-Owain<sup>1</sup>, Albandary AlBakheet<sup>1</sup>, Dilek Colak<sup>1</sup>, Jawaher Al-Zahrani<sup>1</sup>, Namik Kaya<sup>2</sup>, <sup>1</sup>*Department of Genetics, KSFHRC, Riyadh, Saudi Arabia;* <sup>2</sup>*Alfaisal University, Riyadh, Saudi Arabia*

Voltage-gated potassium channels are highly diverse proteins representing the most complex class of voltage-gated ion channels from structural and functional perspectives. Deficiency of these channels usually results in various human disorders. We recently described a novel syndrome linked to chromosome 11 that involving the lens and the basal ganglia. It is characterized by cognitive impairment, microcephaly, growth retardation, congenital cataract, dystonia, and unusual pattern of swelling of the caudate heads and thinning of the putamina.

We utilized SNP arrays, autozygome and linkage analyses coupled with exome sequencing and gene filtering in addition to transcriptional profiling of lymphocytes.

We identified a missense mutation in KCNA4 in four patients from a consanguineous family characterized by the novel syndrome of congenital cataract and abnormal striatum. The mutation (p.Arg89Gln) segregated in the family and was absent in ethnically matching cohort (n=428) and exome sets (n=747). Gene expression profiling identified perturbed gene networks and disease related pathways. KCNA4 interacts with several molecules including quinidine, dipeptidyl peptidase-related ancillary subunit, synaptotagmin I, DLG1, and DLG2. The channel colocalizes with cholinergic amacrine and rod bipolar cells in rats and widely distributed in the central nervous system. It is highly expressed in outer retina, rod inner segments, hippocampus and concentrated in axonal membranes.

Our study highlights a novel role for Kv1.4 in cataract and ocular genetics in addition to basal ganglia involvement, and illuminates potassium channels' role in human disease pathogenesis that etiologically leads to this novel syndrome. It is hoped that our study findings will accelerate further research in the diagnostic and therapeutic approaches to the potassium voltage-gated ion channels-related disorders.

Keywords: Potassium channel, Novel syndrome, cataract, autozygome analysis

### Oral Presentations

#### 09 **IRF6 Mutations in Van Der Woude Syndrome Families from Sub-saharan African Populations and Phenotypes in Zebrafish**

Pius Agbenorku<sup>1</sup>, Tamara Busch<sup>2</sup>, Peter Donkor<sup>3</sup>, Mekonen Eshete<sup>4</sup>, Azeez Butali<sup>3</sup>, Lord Gowans<sup>2</sup>, Wasiu Adeyemo<sup>4</sup>  
<sup>1</sup>University of Lagos, Nigeria; <sup>2</sup>Department of Orthodontics, Dundee Dental School; <sup>3</sup>Department of Oral Pathology, Radiology and Medicine, University of Iowa, USA; <sup>4</sup>Addis Ababa University, Ethiopia

Orofacial clefts (OFCs) are the most common craniofacial disorders in Humans with a global prevalence of 1 in 700 live births. OFCs may be syndromic or nonsyndromic, with the syndromic forms characterized by other congenital malformations in addition to the facial clefts. Mutations in IRF6 has been implicated in Van der Woude Syndrome (VWS, OMIM:119300) and Popliteal Pterygium Syndrome (PPS, OMIM:119500). In this study, we showed molecular and functional evidence of potentially pathogenic variants in VWS cohorts from Africa.

We carried out Sanger Sequencing on DNA from 184 individuals with NSCL/P and 82 individuals with multiple congenital anomalies (MCAs) which include VWS that present with OFCs.

Novel variants were observed in VWS cases (p.Glu69Lys, p.Asn185Thr, c.175-2A>C, p.Gly65Val, p.Lys320Asn and c.379+1 G>T). Previously reported etiologic variants were also observed. Functional validation of p.Glu69Lys and p.Gly65Val by injecting mRNAs containing these variants into zebra fish showed abnormal development of the craniofacial region. The craniofacial abnormality was more prominent in embryos injected with the p.Glu69Lys variant. This study demonstrates the phenotypic impact of IRF6 mutations and confirms a role for these mutations in VWS from Africa.

Our study has shown the need for molecular evidence in addition to clinical examination before an OFC can be classified as syndromic or non-syndromic. This is particularly important for genetic counselling in families with VWS where the recurrence rate increases from 5% to 12%.

Keywords: Orofacial cleft, Van der Woude Syndrome, Novel variants, Zebrafish

### Oral Presentations

#### **O10** **Genetics of Breast and Colon Cancer in a Highly Consanguineous Population, Challenges and Lessons Learned so far**

Abeer Alsaegh  
*Sultan Qaboos University, Oman*

Cancer genetics service was officially established in Sultanate of Oman in August 2012 at Sultan Qaboos University Hospital. Oman is situated in the southeast part of the Arabian Peninsula and it's characterized by high rate of consanguinity. A database was formulated to capture all patients referred to the cancer genetics service from August 2012. It included details about the personal medical history, family history and pathological data of those referred patients. From August 2012 to current, a total of 80 patients were referred for personal and/or family history of breast cancer, of which 63 individuals underwent molecular testing. 25% were found to have BRCA mutations, 5.6% had PTEN mutations, 5.6% had PMS2 mutations and 2.8% had BRIP1 mutation. 50 patients were referred for personal and/or family of colon cancer, 38% were found to have genetic mutations associated with Lynch Syndrome, 20% with APC mutations and 42% with no mutations.

There were a number of challenges that were identified: lack of confirmatory data on other affected individuals of the family, concealing family history due to cultural beliefs, fear of stigma and some patients were treated outside the country. In addition, one major difficulty was selecting the right test when medical and pathological data was missing on other affected members of the family.

BRCA genes are to be considered in the Omani population. In some families, the predisposition to cancer was illustrating an autosomal recessive mode of inheritance. These families are to be approached differently to reveal their molecular aetiology. The study highlights the importance of increasing awareness and education among doctors and the general public for early referrals and recommending screening for high risk families.

Keywords: Breast cancer, BRCA, Familial cancer, Screening

### Oral Presentations

#### 011 DNA Methylation Regulated Genes as Diagnostic Markers in Cervical Cancer

Vinay Koshy Varghese<sup>1</sup>, Shama Prasada Kabekkodu<sup>1</sup>, Deeksha Pandey<sup>2</sup>, Kapaettu Satyamoorthy<sup>1</sup>, Vaibhav Shukla<sup>1</sup>, Samatha Bhat<sup>1</sup>, Sanjiban Chakrabarty<sup>1</sup>, <sup>1</sup>Department of Biotechnology, School of Life Sciences, Manipal University, India; <sup>2</sup>Department of OBG, Kasturba Medical College, Manipal University, India

The sensitivity and specificity of cervical cancer screening can be improved by the introduction of appropriate molecular markers. Although several DNA methylated genes have been proposed for cervical cancer screening, many more remain to be evaluated as sensitive, specific and globally acceptable markers. The aim of our study was to identify novel hypermethylated regions of diagnostic potential in cervical cancer.

Genome wide methylation profiling was performed in normal, premalignant (LSIL and HSIL) and malignant cervical samples by differential methylation hybridization microarray experiment followed by their validate using bisulfite based next generation sequencing technology to identify the diagnostic potential of differentially methylated regions for early screening of cervical cancer.

We identified distinct methylation patterns of PROX1, PCDH10, HAND2, NKX2-2, PITX2, DOC2B, DAPK1, NNAT and RAB6C that could discriminate effectively among the various groups analyzed with sensitivity and specificity of 80-100% respectively ( $P < 0.05$ ). The robustness of these gene promoters as markers were further confirmed in an independent biological cohort consisting of 191 normal, 10 LSIL, 21 HSIL and 335 malignant samples. ARHGAP6, HAND2, LHX9, HEY2, NKX2-2, PCDH10, PITX2, PROX1, TBX3, DOC2B, IKBKG, RAB6C and DAPK1 were found to be methylated in one or more cervical cancer cell lines tested. The comparison of DNA methylation data with gene expression data in normal and tumor samples identified ARHGAP6, HAND2, PCDH10, PITX2, PROX1, TBX3, IREB2, DAPK1, NNAT and RAB6C with significantly reduced expression while ATM, IKBKG, SLC5A6 and LRPPRC showed significantly higher expression in tumor samples ( $P < 0.05$ ). The in silico analysis identified functional and biological relevant pathways in cancer regulated by common transcription factors.

The methylation profiles of the genes identified in our study can be used to distinguish various stages of cervical cancer progression and could serve as promising biomarkers for early detection of cervical cancer.

Keywords: Cervical cancer, Methylation, Early detection

### Oral Presentations

#### 012 Machine Learning to Fully Exploit Integrated Genomics and Clinical Data for Cancer Prognostic Systems

Anwar Haque, [Emad Elsebakh](#)i, Tanwir Habib, Najeeb Syed, Rashid AlAli, Mahmud Barmada, Puthen Jithesh, Eric Schendel

*Sidra Medical and Research Center, Doha, Qatar*

The promise of genomic medicine research is to have earlier prognosis system that identifies human chronic diseases and avoids drug side effects of each individual using their molecular profiling and available phenotypic data. Although there are essential needs of adopting emerging genomic applications in cancer prevention and treatment, we still facing limitations in having efficient-reliable prognosis system for future clinical practice. Yet, identifying the causes of complex diseases is still based on the single nucleotide polymorphisms (SNPs), clinical data, and environmental factors, which have significant impact on the future personalized medicine. The generated large-scale molecular profiling (genomic, transcriptomic, and proteomic) data may be informative for multiple aspects of oncology practice; it promises to advance the clinical management of cancer, but the benefits of integrating molecular profiling with traditional phenotypic data and are still challenging and it has to be addressed.

The recent advances in The Cancer Genome Atlas (TCGA) project assessed us in developing innovative discoveries in numerous aspects of oncology as a complex disease and many biological insights through the generated NGS samples of genomic data from individual. The motivation of this research is to develop dynamical translational medicine platform that integrates diverse biomedical data with a reliable novel machine learning framework within Sidra biomedical informatics service hub to be used as a platform study is considered as an initial starting architecture for Qatar Genome Project (QGP) pilot phase.

The obtained results will show that the integration of molecular data with clinical variables will have high significant impact and improved predictions for different types of cancers. Comparative studies and advanced analyses across tumor will be carried-out to determine the identified relevant genes across twelve cancer types.

The future outlooks and expansions is drawn towards personalized medicine.

Keywords: Personalized medicine, Cancer prognosis, Machine learning



Molecular Biology and Genetics (MBG) is a unique accredited (ISO15189 & ISO17025) genomics laboratory providing both diagnostic and research services.

The MBG Laboratory is one of the most advanced genomic centres in the Middle East. MGB boasts an expert team of scientists, who have the skills and expertise to routinely utilise techniques such as Real Time PCR, Sanger Sequencing, FISH, CGH and SNP arrays. MBG provides a diagnostic service of the highest quality within its uniquely designed laboratory further enabling it to support a diverse range of scientific research to the highest quality.

MBG is at the forefront of safeguarding our community from outbreaks. MBG prides itself on always being the first to provide its services which have been instrumental in safeguarding our community during the recent outbreaks of Swine Flu (H1N1), MERS-CoV, Bird Flu (H5N1) and Ebola haemorrhagic fever.

Through national and international collaborations MBG has contributed to numerous scientific breakthroughs; from fertility studies investigating mitochondrial function and acrosomal integrity to being involved in the first Emirati GWAS study into Type 2 Diabetes.

The recent exciting introduction of Next Generation Sequencing (NGS) technology into the laboratory has placed MBG in the enviable position to expand its repertoire of tests into areas such as meta-genomics, whole genome & exome sequencing along with high throughput targeted panel sequencing in the near future.

MBG is committed to providing novel scientific research and diagnostic services of the highest quality.

### Posters

#### **P1** Can Epigenetic Modifiers Help in Designing a Human-based Adipogenic Model For Anti-obesity Drug Testing?

*Ahmed El-Serafi<sup>1</sup>, Divyasree Sandeep<sup>2</sup>, Yassmin Lozansson<sup>3</sup>,<sup>1</sup>University of Sharjah, UAE; <sup>2</sup>Sharjah Institute for Medical Research, UAE; <sup>3</sup>College of Pharmacy, Uppsala University, Sweden*

Obesity is a global epidemic, particularly common in our community. There is a growing list of drugs and/or remedies which claim to affect the fat content in the cells. To evaluate the action and safety of these agents, we need a model that can correlate the genetic changes to the fat content and show the effect on developing versus developed fat cells. Mesenchymal stem cells have been studied for their ability to differentiate into adipocytes. The latter is required for reconstructive surgery after mastectomy or severe burns. Unfortunately, the differentiation of these cells is not very efficient. In this study we investigated the effect of the DNA methylation inhibitor 5-Aza-dC and the histone deacetylation inhibitor Suberoylanilide hydroxamic acid (SAHA) as an additive to the classical adipogenic differentiation media. We followed our protocol for enhancing osteogenesis and chondrogenesis. Briefly, when MG63 cells reached 50% confluency, they were serum-starved for 24 hours followed by a daily application of one or both modifiers for three days. The adipogenesis protocol consisted of two types of media; the complete media that contained high glucose, insulin, isobutyl methylxanthine, dexamethasone and Indomethacin for three days followed by 24 hours in high glucose media with only insulin. This protocol was repeated for three cycles.

Oil red staining showed that 5-Aza-dC pretreatment increased the cell number with fat droplets within their cytoplasm as well as the intensity of the stain in comparison to control and SAHA, which indicated better adipogenic differentiation. Treatment with both agents seems to be toxic to cells. Gene expression studies by real time PCR confirmed these results.

Pretreatment of stem cells with 5-Aza-dC can enhance their adipogenic differentiation. We recommend this protocol for studying the molecular effect of anti-obesity drug on different stages of fat cell maturation.

Keywords: Obesity, Anti-obesity drug, drug testing,



### Posters

#### **P2 Associations of Genetic Variants In/near Body Mass Index-associated Genes with Type 2 Diabetes: Observations from A Meta-analysis**

Nadia Hussain

*Al Ain University of Science and Technology, UAE*

Genome-wide association studies have been able to pinpoint several obesity/body mass index (BMI) loci in East Asians and Europeans. There have been many studies that have investigated the role of these loci in the development of type 2 diabetes (T2D). The results have been subject to inconsistency. The object of this study was to investigate the associations of eleven of these loci with the risk of developing T2D.

Databases such as PubMed and Embase were used till the point of January 2015. The pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using fixed- or random-effect models.

Using the selection criteria, 45 studies that looked at 11 obesity/BMI-associated loci were included. A statistically significant association of the FTO rs9939609 polymorphism (67 455 T2D cases/293 649 normoglycaemic subjects;  $P = 1.00 \times 10^{-41}$ ) and six other variants with T2D risk (18 900 T2D cases/25 511 normoglycaemic individuals:  $n = 40\,629$ ;  $P = 1.30 \times 10^{-130}$ ; all  $P < .001$  for SH2B1 rs7498665, FAIM2 rs7138803, TMEM18 rs7561317, GNPDA2 rs10938397, BDNF rs925946 and NEGR1 rs2568958) were observed. After adjustment for BMI, the association still remained statistically significant for four of the seven variants (all  $P < 0.05$  for FTO rs9939609, SH2B1 rs7498665, FAIM2 rs7138803, GNPDA2 rs10938397). The results of this meta-analysis indicates that there are several BMI-associated variants that significantly increase the risk of T2D. Some variants increase the T2D risk independent of obesity, while others mediate this risk through obesity.

Keywords: BMI, variants, meta-analysis, Diabetes

### Posters

#### **P3 Relationship between Vitamin D Receptor Gene Polymorphisms, Circulating Vitamin D and Type 2 Diabetes Mellitus among Emirati Population**

*Sarah El Hajj Chehadeh<sup>1</sup>, Fatme Al Anouti<sup>2</sup>, Gehad El Ghazali<sup>3</sup>, Habiba Al Safar<sup>4</sup>; <sup>1</sup>Center of Biotechnology, Khalifa University, UAE; <sup>2</sup>Zayed University, Abu Dhabi, UAE; <sup>3</sup>Institute of Laboratory Medicine, Sheikh Khalifa Medical City, Abu Dhabi, UAE; <sup>4</sup>Biomedical Department, Khalifa University of Science, Technology & Research, UAE*

At a prevalence rate close to 19.5%, the UAE has one of the highest rates of Type 2 Diabetes (T2DM) in the world. Genome wide association studies have led to the identification of several genetic variants that are associated with T2DM. Recently, genes involved in vitamin D metabolism have gained a lot of interest because of the association between vitamin D deficiency (VDD) and increased risk for T2DM. Some of the genetic determinants for Vitamin D status such as vitamin D receptor (VDR) is a good candidate for T2DM susceptibility. The aim of this study was to investigate the association between VDR polymorphisms in the context of VDD and T2DM among Emirati population.

Two hundred and sixty four patients with T2DM and ninety-one healthy controls were enrolled in this cross-sectional study. DNA was extracted from participant's saliva samples and genotyped for three VDR single nucleotide polymorphisms SNPs (rs731236, rs2228570, and rs1544410) using TaqMan real-Time PCR assays.

The mutant alleles G of rs2228570 and T of rs1544410 were associated with increased risk of T2DM. All genotypes of rs2228570 show a strong association with increased risk of T2DM. Also, the TT genotype and CT+TT of rs1544410 were associated with increased risk of T2DM. In regards to T2DM-related complications, the AG and GG genotypes of rs731236 were associated with higher total cholesterol and LDL-cholesterol levels in the patients with T2DM. On the contrary, the CT and TT genotypes of rs1544410 were associated with lower BMI and LDL-cholesterol level respectively, in T2DM patients.

In this study we found high association between SNPs of VDR gene studied and T2DM per se, except rs731236 in the Emirati population. Rs731236 can be used as markers for high cholesterol and LDL-cholesterol levels in T2DM patients, while rs1544410 have protective effects on the risk of T2DM.

Keywords: Diabetes, Vitamin D Deficiency, Vitamin D Receptor, Variant

### Posters

#### **P4 Analysis of Mendelian Randomization Studies of Biomarkers and Type 2 Diabetes: Observations From Analysis**

Nadia Hussain

*Al Ain University of Science and Technology, UAE*

In epidemiology, many biomarkers are noted to be associated with type 2 diabetes (T2D) risk. The aim of this study was to identify and summarize current evidence for causal effects of biomarkers on T2D.

A systematic literature search in PubMed and EMBASE (until October 2015) was done to identify Mendelian randomization studies that examined potential causal effects of biomarkers on T2D. Data from two large-scale genome-wide association studies (GWAS) were used: the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) for glycaemic traits and DIAbetes Genetics Replication And Meta-analysis (DIAGRAMv3) for T2D. GWAS summary statistics were extracted for the same genetic variants which were used in the original Mendelian randomization studies.

Twelve out of 21 biomarkers (from 32 studies) have been reported to be causally associated with T2D in Mendelian randomization. Most biomarkers that were investigated were from a single cohort study or population. Of the 12 identified biomarkers, nominally significant associations with T2D or glycaemic traits were achieved for those genetic variants related to bilirubin, pro-B-type natriuretic peptide, Delta-6 desaturase and dimethylglycine.

Several Mendelian randomization studies have investigated the nature of associations of biomarkers with T2D. However, there were only few biomarkers that may have causal effects on T2D. Further research is required to evaluate the causal effects of multiple biomarkers on T2D and glycaemic traits using data from large-scale cohorts.

Keywords: Diabetes, biomarker, Meta-analysis, Mendelian Randomization Studies

### Posters

#### **P5** Assessment of Autosomal Genetic Polymorphism in United Arab Emirates Population

Habiba Al Safar<sup>1</sup>, Wafa Al Tayyare<sup>2</sup>, K Guan Tay<sup>3</sup>, Osamah Alhmoudi<sup>4</sup>, [Rebecca Jones](#)<sup>3</sup>, <sup>1</sup>Khalifa University Science, Technology and Research, Abu Dhabi, UAE; <sup>2</sup>University of Central Lancashire, Preston, United Kingdom; <sup>3</sup>The University of Western Australia, Crawley, Western Australia; <sup>4</sup>Abu Dhabi Police General Head Quarters, Abu Dhabi, UAE

The study of human migration enhances our understanding of the distribution of genetic variations and associations with disease. This study examined relationships between genetic polymorphisms and migration patterns of different Middle Eastern ethnic populations. This region is significantly located at the crossroads of bidirectional migration. However, population genetic studies in the region have not been extensively researched.

STUDY 1: Oragene-DNA kit (Genotek, Ottawa, Canada) collected samples from 519 Emirati individuals. GlobalFiler®P-CR amplification kit (Life Technologies, Foster City, USA) amplified 21 autosomal Short Tandem Repeats (STRs) with profiles generated on a DNA sequencer. PowerStats v1.2 (Promega, Madison, USA) and Arlequin v3.11 (Excoffier and Schneider, 2005) calculated allele frequencies and forensic parameters (discrimination power, match probability, exclusion power). P-values calculated by exact test between UAE nationals and published data from Iran, Kuwait, Saudi Arabia, Egypt and Indian populations; considered significantly different when less than 0.05.

STUDY 2: Samples from 477 Emirati individuals; using the same DNA kits and statistical programs as Study 1. Additionally, PowerPlex®21 System (Promega) and PowerPlex®CS7 System amplified 3 and 5 STR markers respectively. Forensic parameters were compared to Study 1, investigating the effects of increasing amplification to 29 STR markers.

Study 1 showed greater genetic relationships (p-values > 0.05) between UAE and Iran, Kuwait and Saudi Arabia in contrast to UAE and India (p-values < 0.05). Study 2 showed high discrimination power in both studies; with an increase in exclusion power and decrease in random match probability with the additional STR markers.

Both studies show parameters with a degree of genetic variation within Emirati individuals. Greater genetic relationships between geographically close populations to UAE were observed. A future meta-analysis of allele frequencies from Middle East, North Africa and South Asia will extensively analyse human migration effects and the impact on genetic variations.

Keywords: Human migration, Genetic variation, STR marker

### Posters

#### **P6** The G20210A Transition in the Prothrombin Gene and Peripheral Artery Disease in East Algerian Population

Cherifa Benlatreche<sup>1</sup>, Karima Sifi<sup>1</sup>, Nacera Kerouaz<sup>2</sup>, Salima Zekri<sup>1</sup>, Nouredine Abadi<sup>3</sup>, Khalida Boudaoud<sup>4</sup>, Daoud Roula<sup>2</sup>, Sabah Hanachi<sup>1</sup>, <sup>1</sup>Laboratory of Biology and Molecular Genetics, Faculty of Medicine, Ibn Badis Hospital, Algeria; <sup>2</sup>Department of Internal Medicine, Ibn Badis hospital, Algeria; <sup>3</sup>Biochemistry Service, Faculty of Medicine, IbnBadis Hospital, Algeria; <sup>4</sup>Department of Endocrinology, Ibn Badis hospital, Constantine, Algeria

Poort and others (1996) have identified a new abnormality of clotting associated with a thrombotic tendency: G20210A transition in the 3'untranslated region of the prothrombin gene. The role of this mutation in arterial disease is controversial with conflicting results from different studies. Available evidence suggests that the G20210A mutation is not a major risk factor for arterial thrombosis. However, it may interact with other environmental and genetic risk factors in promoting arterial thrombosis. The aim of our study was to estimate the prevalence of this mutation in peripheral artery disease patients and to establish a possible association between peripheral artery disease (PAD) and G 20210A prothrombin gene mutation.

Genomic DNA from 83 cases and 73 healthy controls was isolated from EDTA blood samples using standard salting out procedure. Presence of prothrombin G20210A mutation was checked by real-time PCR (RT-PCR) using the Light-Cycler system. All patients and controls gave informed consent to participate.

The frequency of prothrombin G20210A mutation showed 2.4% in PAD subject, 97.6% were carriers of the GG wild genotype. In the control group, the frequency of the mutation was found in 1.4% of cases. The other 72 control subjects were carriers of GG genotype with a prevalence of 98.6%. No homozygous mutated genotype AA was found both in the patient than in the control group. The G allele is predominant in both groups (98.8% in patients vs 99.32% in controls). The frequency of the mutated allele A is only about 1.20% in cases and 0.68% in controls.

In our study, no association between PAD and prothrombin G20210A mutation was detected. Our results agree with some studies but not with others. These results may be due to the small sample size, another study on a larger sample would be desirable.

Keywords: Peripheral Artery Disease, Prothrombin

### Posters

#### **P7** Frequency of Factor V Leiden Mutation in Patients With Peripheral Artery Disease: A Study In East Algerian Population

Sabah Hanachi<sup>1</sup>, Cherifa Benlatreche<sup>2</sup>, Daoud Roula<sup>3</sup>, Nouredine Abadi<sup>1</sup>, Karima Sifi<sup>1</sup>, Nacera Kerouaz<sup>1</sup>, Khalida Boudaoud<sup>4</sup>, Salima Zekri<sup>2</sup>, <sup>1</sup>Laboratory of Biology and Molecular Genetics, Faculty of Medicine, Constantine, Algeria; <sup>2</sup>Biochemistry Service, Ibn Badis Hospital, Faculty of Medicine, Algeria; <sup>3</sup>Department of Internal Medicine, Ibn Badis Hospital, Algeria; <sup>4</sup>Department of Endocrinology, Ibn Badis Hospital, Algeria

Factor V Leiden is a point mutation in the factor V gene resulting in a substitution of arginine for glutamine at position 506. This abolishes a cleavage site in factor V for activated protein C, causing a functional activated protein C resistance. This mutation in arterial disease has been subject of numerous reports. Many of them have had negative results. In contrast, some studies report positive associations, particularly when the interaction of this polymorphism with environmental factors has been formally evaluated. We analyzed the frequency of Factor V Leiden in patients with peripheral artery disease and compared it to healthy controls

The study consisted of 41 patients with PAD and 37 healthy controls. Blood samples were collected into tubes with EDTA. Extraction of genomic DNA from peripheral leukocytes was performed using standard salting out method. Real-time PCR (RT-PCR) method using the Light-Cycler system was used to identify the variant allele at position 1691 of the factor V gene. Informed consent was obtained from all participants. Factor V Leiden mutation had been detected in 2.6% of healthy controls, while patients with PAD had exclusively wild genotype GG with genotypic frequency of 100%. No homozygous mutated genotype AA was found in our study population. The G allele (wild) is predominant in control group with a frequency of 98.68%; allele A represents only 1.32% in this group. In our patients group, only the wild allele was present with a frequency of 100%.

No association between Factor V Leiden mutation and PAD was found in our study. Our results confirm those of most studies. However, the weak effective of all published series makes definitive conclusions difficult.

Keywords: Peripheral Artery Disease, Factor V Leiden

### Posters

#### **P8 Association of Vitamin-D receptor Genetic Polymorphisms with Type 2 Diabetes Mellitus: A Meta-analysis**

Naushad Rais

*Manipal University, UAE*

The genetic polymorphism of Vitamin-D receptor (VDR) gene has been studied in various ethnic groups in association with Type 2 diabetes mellitus (T2DM) risk and related complications. However, contradictory results were reported for most of studies. Hence, we performed a large meta-analysis examining association of T2DM with polymorphisms in the VDR gene in various ethnicities, containing FokI (rs10735810), BsmI (rs1544410), TaqI (rs731236) and Apal (rs7975232) polymorphisms.

A literature-based searching to collect data and two methods, that is, fixed-effects and random-effects meta-analysis, were performed for each variant in both dominant and recessive model to pool the odds ratio (OR). Publication bias and study-between heterogeneity were also examined.

For T2DM and BsmI polymorphism, 21 studies comprising of 3313 cases and 3913 controls had pooled OR 1.27 for random effects and 0.86 for fixed effects. Fourteen studies on the Taq-1 allele T2DM association included 2234 cases and 3098 controls. Also TaqI Recessive model (GG vs. AG + AA) showed increasing statistical significance for association. Ten studies on the Fok-1 allele with T2D association recruited 2073 cases and 1673 controls. The analysis of the alleles did not suggest any strong genetic effect. The summary OR was 0.81 for fixed and 0.74 for random effects. FokI showed significant associations in both fixed and random effect of dominant model (AA vs. AG + GG) and also significant results were seen also in recessive model (GG vs. AG + AA). Thirteen studies on the Apal allele with T2D association recruited 2314 cases and 3062 controls. The analysis of the alleles did not suggest any strong genetic effect. The summary OR was 1.02 for fixed and 0.98 for random effects.

This meta-analysis demonstrates that out of four most common variants of VDR gene only two BsmI and FokI are associated with T2DM.

Keywords: Diabetes, Vitamin D Receptor, Meta-analysis

### Posters

#### P9 **Complicated Diabetes Mellitus Type2 and MTHFR C677T Polymorphism: Case-control Study**

Sabah Hanachi<sup>1</sup>, Nouredine Abadi<sup>2</sup>, Salima Zekri<sup>2</sup>, Khalida Boudaoud<sup>3</sup>, Karima Sifi<sup>2</sup>, Cherifa Benlatreche<sup>4</sup>, Daoud Roula<sup>2</sup>, Nacera Kerouaz<sup>4</sup>, <sup>1</sup>Laboratory of Biology and Molecular Genetics, Faculty of Medicine, Constantine, Algeria; <sup>2</sup>Biochemistry Service, Ibn Badis Hospital, Faculty of Medicine, Algeria; <sup>3</sup>Department of Endocrinology, Ibn Badis Hospital, Algeria; <sup>4</sup>Department of Internal Medicine, Ibn Badis Hospital, Algeria

Diabetes mellitus is a complex, multifactorial and polygenic disease. Patients with diabetes mellitus have 2-6 fold increase in the prevalence of cardiovascular disease. There has been a worldwide effort in the identification of susceptibility genes for type 2 diabetes mellitus (T2DM). The C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene has been reported to be associated with type 2 diabetes mellitus and its complications. The aim of the present study was to investigate the possible association between MTHFR gene C677T mutation and Diabetes mellitus among East Algeria population.

The study included 97 patients affected by Diabetes mellitus (mean age  $\hat{\pm}$  SD 46.53  $\hat{\pm}$  6.53 years) and 190 healthy controls (mean age  $\hat{\pm}$  SD 46.53  $\hat{\pm}$  6.53 years). Genomic DNA was extracted from whole venous blood samples using salting out method and genotyped using the polymerase chain reaction-based restriction fragment length polymorphism assay for the MTHFR gene C677T mutation. Statistical analysis was performed using the Epi Info software package version 7. All participants gave written informed consent before enrolling in the study.

The frequency of the CC, CT, and TT genotypes of the C677T mutation in the patients was 44.33%, 35.05 %, and 20.62%, respectively, and in the controls, the frequency was 54.6%, 31.7%, and 13.7 %, respectively. The C and T allele frequencies were 61.86 % and 38.14%, respectively, in the patient group and 70.49 % and 29.51 %, respectively, in the control group. CT+TT VS CC odds ratio (OR)=1.52 IC (0.90-2.56) P=0.095 and TT VS CT+CC OR=1.64 IC (0.82-3.26) P=0.13.

No significance in the distribution of MTHFR genotypes between healthy and T2DM subjects is found, the size of the studied population was relatively small and therefore, large-scale prospective studies are needed to confirm these findings.

Keywords: Diabetes, MTHFR



### Posters

#### **P10 Association of the Insertion Allele of the Common ACE Gene Polymorphism with Type 2 Diabetes Mellitus Among Kuwaiti Cardiovascular Disease Patients**

Ibrahim Al-Rashdan<sup>1</sup>, Suzanne Al-Boustan<sup>2</sup>, Fatma Ismael<sup>2</sup>, Ahmad Al-Serri<sup>2</sup>

<sup>1</sup>Department of Medicine, Faculty of Medicine, Kuwait University; <sup>2</sup>Department of Biological Sciences, Faculty of Science, Kuwait University

The D allele of the common angiotensin-converting enzyme (ACE) I/D gene polymorphism (rs4646994) predisposes to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). However, results on which allele predisposes to disease susceptibility remain controversial in Asian populations. This study was performed to evaluate the association of the common ACE I/D gene polymorphism with both T2DM and CVD susceptibility in the Kuwaiti population.

We genotyped the ACE I/D polymorphisms by direct allele-specific PCR in 183 healthy controls and 400 CVD patients with diabetes (n=204) and without (n=196). Statistical analysis comparing between the different groups were conducted using R statistic package 'SNPassoc' .

Two genetic models were used: the additive and co-dominant models. The I allele was found to be associated with T2DM (OR=1.84, p=0.00009) after adjusting for age, sex and body mass index. However, there was no association with CVD susceptibility (p>0.05).

The ACE I allele is found to be associated with T2DM; however, no association was observed with CVD. The inconsistency between studies is suggested to be attributed to the existence of sub-populations within Asian/Arab populations.

Keywords: Diabetes, Cardiovascular disease, ACE

### Posters

#### **P11 Relationship Between MTHFR C677T and A1298C Gene Polymorphisms and Complications of Type 2 Diabetes Mellitus In An Emirati Population**

Guan Tay<sup>1</sup>, Unini Odama<sup>2</sup>, Sarah El Hajj Chehadeh<sup>3</sup>, Wael Al Mahmeed<sup>4</sup>, Zain Al Yafei<sup>5</sup>, Gehad Elghazali<sup>5</sup>, Habiba Al Safar<sup>3</sup>

<sup>1</sup>Centre for Forensic Science, University of Western Australia, Perth, Australia; <sup>2</sup>Landmark Nephrology and Hypertension Clinic, Talladega, Alabama, USA; <sup>3</sup>Center for Biotechnology, Khalifa University, UAE; <sup>4</sup>Institute of Cardiac Science, Sheikh Khalifa Medical City, Abu Dhabi, UAE; <sup>5</sup>Institute of Laboratory Medicine, Sheikh Khalifa Medical City, Abu Dhabi, UAE

Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes with clinical consequences giving rise to various chronic complications. Methylenetetrahydrofolate reductase (MTHFR) polymorphisms are genetic variations that have been linked to T2DM and some of these complications. The objective of this study was to investigate the possible association between two MTHFR polymorphisms (C677T and A1298C) and T2DM and specifically examine if there are any association with clinical and demographic characteristics among patients in the United Arab Emirates (UAE).

The study included 169 T2DM patients and 209 healthy controls. Genomic DNA was isolated and genotyped using TaqMan real-Time PCR assays for the MTHFR C677T and A1298C polymorphisms.

There were no significant differences in genotype and haplotype distribution observed between the patients with T2DM and the healthy controls. A significant association was observed between the C677T polymorphism and history of Cerebrovascular accident (CVA) ( $p=0.0330$ ), history of nephropathy ( $p=0.0280$ ) and levels of LDL cholesterol ( $p=0.0409$ ). Also, the A1298C polymorphism was associated with hypertriglyceridemia ( $p=0.0305$ ) in T2DM patients. These findings demonstrate that the MTHFR gene polymorphisms are not related to T2DM among Emirati population. However, these polymorphisms can be used as markers for assessment of CVA, nephropathy, high LDL cholesterol and triglycerides in T2D patients.

Keywords: Diabetes, MTHFR

### Posters

#### **P12** Differential Gene Expression in Bahraini Patients with Multiple Sclerosis

Safa Taha, Moudi Al-Nashm, Moiz Bakhiet  
*Arabian Gulf University, Bahrain*

Multiple sclerosis (MS) disease is an autoimmune disease of the CNS, affects young adults that leads to a physical and cognitive behavioral disabilities over time. The main etiology of MS remains unknown, but both genetic and environmental factors have been implicated. MS is now believed to be much more common in Gulf area. Literature reviews showed that genetic variation is an important determinant of susceptibility to MS. Such genetic variations are not known in Bahrain where MS has notably increased. Accordingly, this project is designed to identify such target genes in Bahraini multiple sclerosis patients for future immunotherapy. The objectives of this study was to measure changes in the expression of potential genes in the Bahraini MS patients and to characterized the effectors molecules of the expressed upregulated genes.

We used microarray technique to measure mRNA expression from 12 MS Bahraini patients and 12 Bahraini control subjects, the data analysis was performed by Partek Genomics Suite software. Also, 80 MS patients and 80 control subjects were analyzed to measure the effectors molecules by ELISA technique and statistical analysis was also performed ADAP software 2008.

The study showed considerable four expressed significant genes with one gene IL-1RA being significant and associated with MS patients. Five genes were expressed significantly, including: IL-1RA, OASL, CLC, and DOCK4. Further analysis by ELISA for the selected 4 genes expressed compared to control subjects. Eighty three MS patients had positive serum level of OASL, 87 MS patients had positive serum levels of IL-1RA, and none of the 88 MS patients showed detectable serum levels of CLC and DOCK4.

The study showed considerable four expressed significant genes with one gene IL-1RA being significant and associated with MS. Two novel genes CLC and DOCK4 were expressed.

Keywords: Multiple Sclerosis, Microarray, IL-1RA

### Posters

#### **P13** Recessive Pathogenic Variants In The MICU1 Gene: Expanding the Phenotypic and Genotypic Spectrum

Jane Juusola<sup>1</sup>, Samantha Schrier Vergano<sup>2</sup>, Qais Abu Ali<sup>1</sup>, Patricia Wheeler<sup>3</sup>, Tawfeg Ben-Omran<sup>4</sup>, Richard Finkel<sup>3</sup>, Matthew Deardorff<sup>5</sup>, Rehab Ali<sup>4</sup>, Mariam Al-Mureikhi<sup>4</sup>, Francisca Millan<sup>1</sup>

<sup>1</sup>GeneDx, Gaithersburg, MD, USA; <sup>2</sup>Children's Hospital of The King's Daughters, Norfolk, VA, USA; <sup>3</sup>Nemours Children's Hospital, Orlando, FL, USA; <sup>4</sup>Hamad Medical Corporation, Doha, Qatar; <sup>5</sup>The Children's Hospital of Philadelphia, Philadelphia, PA, USA

The expanding genetic heterogeneity and clinical variability make diagnosing mitochondrial disorders challenging. The MICU1 gene, which encodes mitochondrial uniporter subunit and regulates opening of dimeric calcium channel, MCU, is identified as the cause of a novel mitochondrial disorder. Two homozygous canonical splice site variants in MICU1 have been reported. Phenotypic features include myopathy, learning difficulties and extrapyramidal movement disorder. However, hepatic involvement has not been previously reported.

Using whole exome sequencing (WES) we identified 9 affected individuals from 9 unrelated families, harboring either homozygous or compound heterozygous novel pathogenic variants in MICU1. Targeted testing identified two affected siblings with the MICU1 pathogenic variant originally identified by WES in their affected sibling.

Patients from six Middle Eastern families were homozygous for a novel nonsense variant, p.Q185\*. Another Middle Eastern patient was compound heterozygous for p.Q185\* and intragenic duplication of exons 9 and 10. One European patient was homozygous for intragenic deletion encompassing exons 2 through 9. Another European patient was compound heterozygous for a novel nonsense variant, p.R119\*, and a rare missense variant, p.R129P. Six patients had developmental delay and hypotonia during infancy, three had developmental regression between 2 to 6 years. Most patients developed weakness, ataxia, chorea or other stereotypic movements. All patients had elevated serum creatine phosphokinase. Muscle biopsy showed non-specific myopathic changes in two patients and features of storage disorders in two others. All patients had mildly elevated liver transaminases, three had hepatomegaly, both features previously unreported in MICU1-related disorder.

Our detailed phenotypic and genotypic characterization of 9 additional individuals expands the MICU1-related mitochondrial disorder spectrum and highlights myopathy, hypotonia with development motor delay and/or childhood regression, movement disorders and newly described liver involvement as major clinical features. Furthermore, targeted analysis of MICU1 pathogenic variants in Middle Eastern patients is warranted.

Keywords: Mitochondrial disorder, MICU1, Variants

### Posters

#### **P14** A Recurrent Homozygous Mutation in the KCTD7 Gene as a Cause of Progressive Myoclonic Epilepsy

Zandre Bruwer<sup>1</sup>, Patrick Scott<sup>1</sup>, Fathiya Al-Murshedi<sup>1</sup>, Roshan Koul<sup>2</sup>, Sami Al-Kalbani<sup>1</sup>, Almaha Al-Maqbali<sup>1</sup>, Lina Al-Mashhadani<sup>1</sup>, Douja Meftah<sup>1</sup>, Amna Al-Futaisi<sup>2</sup>, Khalid Al-Thihli<sup>1</sup>

<sup>1</sup>Genetics Department, Sultan Qaboos University Hospital, Muscat, Oman; <sup>2</sup>Child Health Department, Sultan Qaboos University Hospital, Muscat, Oman

Progressive myoclonic epilepsy refers to a heterogeneous group of epilepsies characterized by myoclonus, seizures and progressive neuroregression. Molecular studies were performed on a consanguineous family marked by the presence of two affected individuals related as first cousins. Both patients showed early-onset epilepsy followed by neuroregression. Autozygosity mapping using genome-wide SNP array analysis identified three epilepsy-associated genes. The available evidence strongly suggested that the potassium channel tetramerization domain containing 7 gene (KCTD7) was the most probable gene linked to the disorder segregating in this family. Sanger sequencing analysis revealed a homozygous pathogenic missense mutation affecting a conserved amino acid (p.Arg112His) within exon 3. The same mutation was independently observed in an apparently unrelated family via exome sequencing. This is the first report of KCTD7 mutations as a cause of progressive myoclonic epilepsy in Omani families. These results further expand the genetic heterogeneity of epilepsy in Oman.

Keywords: Progressive myoclonic epilepsy, KCTD7, Autozygosity mapping

### Posters

#### **P15 Identification of Nuclear Gene Defects In Mitochondrial Encephalopathy, Lactic Acidosis and Stroke like Episode Patients by Exome Sequencing**

Sanjiban Chakrabarty<sup>1</sup>, Vinay Koshi Varghese<sup>1</sup>, Kurupath Radhakrishnan<sup>2</sup>, Puthiya M Gopinath<sup>1</sup>, Kumarasamy Thangaraj<sup>3</sup>, Kapaettu Satyamoorthy<sup>1</sup>, Sandeep Mallya<sup>1</sup>

<sup>1</sup>Department of Biotechnology, School of Life Sciences, Manipal University India; <sup>2</sup>Department of Neurology, Kasturba Medical College, Manipal University India; <sup>3</sup>CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a multisystem disorder affecting the brain, nervous system (encephalopathy) and muscles (myopathy). Clinical presentation of MELAS includes muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures. Presently, most of the diagnosis of MELAS mainly relies upon biochemical analysis of mitochondrial respiratory chain complex (RCC) enzymes in muscle biopsy tissues or by radiological diagnosis. Till date, at least 17 different mitochondrial DNA mutations have been identified with most prevalent A3243G tRNA<sup>Leu</sup> (UUR) gene mutation, responsible for about 80% of the cases. However, no single study has highlighted the role of nuclear DNA mutation which may play a significant role in the pathogenicity of the MELAS phenotype. The altered expression of mutant nuclear genes could play a significant role in the aetiology of the disease in association with known and novel mtDNA variation and their interaction might play a critical role in the pathogenesis of MELAS leading to its clinical presentation.

Whole exome sequencing of patients with clinically confirmed MELAS phenotype was performed using Ion Proton NGS platform. Mitochondrial DNA variations identified and annotated from whole exome data using MitoSeek and Mitomap.org. Potential causal mutations were analyzed by PolyPhen and SIFT analysis and overlap analysis with other public databases. Pathogenic mutations identified in MELAS patients were mapped to ontological processes and metabolic pathways. Selected pathogenic mutations were validated using Sanger sequencing in a panel of MELAS patients DNA samples.

Significant enrichment in possible causal variants identified in gene involved in neuromuscular disorders (RYR1, TMEM216). Additionally, we found mutation in nuclear genes involved in mitochondrial function (MTFMT, SDHFA1) with known clinical phenotype.

Identification of causal nuclear gene mutation associated with MELAS will facilitate early screening and diagnosis of MELAS phenotype for better clinical management.

Keywords: MELAS, Mitochondrial disorder, Variants

### Posters

#### **P16** Whole Exome Sequencing in Rare and Complex Disorders

Douja Meftah, Zandre Bruwer, Adila Al-Kindy, Fathiya Al-Murshedi, Patrick Scott, Khalsa Kharusi, Amel Alfoori, Abeer Alsayegh, Almundher Al-Maawali, Khalid Al-Thihli

*Department of Genetics, Sultan Qaboos University Hospital, Muscat, Oman*

Whole exome sequencing (WES) is increasingly used in establishing an accurate diagnosis for patients with suspicion of an inherited Mendelian disease.

In this study, the results of 105 consecutive patients with undiagnosed complex disorders at the Genetics and Developmental Clinic of Sultan Qaboos University Hospital from September 2013 to September 2015 are presented. Whole exome sequencing was performed on all patients. The most common referral indication was intellectual disability (47%). Analysis of the WES generated data was first limited to a predetermined disease gene panel whose selection was based on the patient's clinical presentation. In the absence of a pathogenic or likely pathogenic mutation, sequence data analysis was then extended to the entire exome.

A pathogenic or likely pathogenic mutation was identified in 33 patients. Consistent with the relatively high rate of consanguinity in our population, the mutations observed were inherited in autosomal recessive manner (28/33). A total of 6 patients had a combination of 2 single gene disorders. Variants of unknown significance (VUS) were frequently observed, in about 23% of our cases.

The overall detection rate of pathogenic / likely pathogenic mutations achieved in this cohort is consistent with the expected yield in the context of proband-only WES analysis. Challenges remain with the identification of VUS and highlights the importance of further studies, segregation and/or functional.

Keywords: Whole Exome Sequencing, Variants of unknown significance, Intellectual disability

### Posters

#### **P18** Identification of a Novel CNTNAP1 Mutation Causing Arthrogryposis Multiplex Congenita with Cerebral and Cerebellar Atrophy

Mariam Almureikhi<sup>1</sup>, Christopher A Walsh<sup>2</sup>, Ryan Doan<sup>3</sup>, A. James Barkovich<sup>4</sup>, Tawfeg Ben-Omran<sup>1</sup>, Muna Al Saffar<sup>5</sup>, Nada Alaaraj<sup>1</sup>, Jennifer Partlow<sup>3</sup>, Jennifer Lakhani<sup>1</sup>, Mahmoud F. Elsaid<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Hamad Medical Corporation, Qatar; <sup>2</sup>Howard Hughes Medical Institute, Boston Children's Hospital, Boston, USA; <sup>3</sup>Division of Genetics and Genomics, Boston Children's Hospital, Boston, USA; <sup>4</sup>Pediatric Neuroradiology, University of California San Francisco, USA; <sup>5</sup>Faculty of Medicine and Health Sciences, United Arab Emirates University, UAE

Arthrogryposis multiplex congenita (AMC) is a rare disorder characterized by insufficient peripheral nerve myelination, muscular hypotonia, reduced tendon reflexes, limited joint mobility and respiratory insufficiency. Mutations in CASPR/CNTN1 complex genes were recently implicated in similar severe phenotypes and contactin associated protein 1 (CNTNAP1) gene mutations, leading to loss of the CASPR protein, were attributed to severe, prenatal onset AMC in four families. We sought to identify the genetic cause of unexplained AMC in three children of a consanguineous Arab family from Qatar.

The family enrolled in a collaborative research project, supported by the Qatar National Research Fund, investigating the genetic causes of undiagnosed neurodevelopmental conditions in Qatar. Clinical investigations, including whole exome sequencing (WES) data, were collected and analyzed. Genomic DNA was obtained for standard PCR of candidate variants.

We report three children with an early lethal form of AMC with polyhydramnios, distal joint contractures, severe hypotonia, myopathic facies, and a lack of swallowing and autonomous respiration. Clinical investigations suggested neurogenic muscular atrophy; MRI revealed profound cerebral and cerebellar atrophy. Clinical WES identified a non-contributory inherited heterozygous COL6A2 variant. Our subsequent analysis of WES data in the research setting uncovered a CNTNAP1 frameshift insertion (Exon 10: c.1561dup p.Leu521Profs\*12) that segregated with disease in the family. The resulting predicted loss of the CASPR protein is expected to prevent formation of the CASPR/CNTN1 complex, cause improper axo-glia junction organization and lead to the observed severe neurological disorder.

We present a novel CNTNAP1 mutation causing AMC, expand known manifestations to include profound cerebral and cerebellar atrophy, and support the role of CASPR/CNTN1 complex genes in rare recessive AMC syndromes. This study emphasizes the importance of reanalyzing WES data from which mutations were not previously identified using updated annotation and reference information.

Keywords: Arthrogryposis multiplex congenita, CNTNAP1, Whole Exome Sequencing



### Posters

#### **P20** Application of Array-based Comparative Genomic Hybridization to Pediatric

Brahim Tabarki, Amal Alhashem, Bashaier Albulushi  
*Prince Sultan Military Medical City*

We included 700 patients from the pediatric neurology clinic with at least one of the following features: developmental delay/intellectual disability, dysmorphic features, microcephaly, multiple congenital anomalies or refractory epilepsy. Results are compared with G-band karyotyping. The results were analyzed with findings reported in recent publications and internet databases.

Array CGH yielded abnormal (pathogenic) results in 189 of 700 patients (27%), and normal in 511 patients (73%). Although there were relatively small number of tests in patients with pediatric neurologic disease, this study demonstrated that array-CGH is a very useful tool for clinical diagnosis of unknown genome abnormalities performed in pediatric neurology clinics.

Keywords: Array-CGH, Pediatric neurological disease

### Posters

#### **P21 The Common 5-HTTLPR Gene Variant of the Serotonin Transporter Gene is not Associated with Migraine in Sudanese Families**

Muntaser E.Ibrahim<sup>1</sup>, Salah Magzoub<sup>2</sup>, Hiba Salah<sup>3</sup>, Sara Ibrahim<sup>3</sup>

<sup>1</sup>Institute of Endemic diseases, Faculty of Medicine, University of Khartoum, Sudan; <sup>2</sup>Faculty of Medicine, Ribat University, Sudan; <sup>3</sup>Medical College, Taibah University, Saudi Arabia

The role of serotonin in pain modulation, neural and vascular involvement in migraine has long been recognized. Many studies linked serotonin transporter polymorphisms 5-HTTLPR allele to migraine. The less active short (S) allele was reported to increase in migraineurs with aura but not in migraineurs without aura in comparison with the control population. The aim of this study is therefore, to investigate the association between the common 5-HTTLPR polymorphism and migraine in Sudan.

A cross sectional study that involved 175 subjects from 12 large Sudanese families. DNA was extracted from 165 subjects who agreed to participate. Individual DNA samples were genotyped using polymorphism in the promoter region of the serotonin transporter gene. Data analysis performed using family based association test (FBAT) was used, including the Haplotype Based Association Test (HBAT) to determine if any HTTLPR alleles are associated with migraine in study group. Vassarstat online software package was also used.

The 5-HTTLPR genotypes in migraine subjects against controls were distributed as follows: L/L 49% versus 20%, L/S 14.2% versus 9.7%, and S/S 5.8% versus 1.25%. The L allele and S allele frequency did not deviate from Hardy-Weinberg expectations ( $P > 0.4$ ). The homozygous mutant SS genotype showed very low frequency in the study group.

In the present study, no association between the 5-HTTLPR polymorphism gene variant and migraine was observed in Sudanese families. In our study group the frequency of LL is greater than LS allele, while the SS is apparently discrete. The lack of association could be due to the ethnic variation of the Sudanese population.

Keywords: Array-CGH, Migraine, 5-HTTLPR

### Posters

#### **P22 The Dopamine Receptor D2(Rs1076560) and M-Opioid Receptor (Rs1799971) Polymorphisms are Not Associated with Substance use Disorder in UAE Population**

Ahmed El Kashef<sup>1</sup>, Habiba Al Safar<sup>2</sup>, Hiba Alblooshi<sup>3</sup>, Guan Tay<sup>4</sup>, Hamad Al Ghaferi<sup>1</sup>, Gary Hulse<sup>3</sup>  
<sup>1</sup>United Arab Emirates National Rehabilitation Centre, Abu Dhabi, UAE; <sup>2</sup>Centre for Biotechnology, Khalifa University Science, Technology and Research, A; <sup>3</sup>School of Psychiatry and Clinical Neurosciences, University of Western Australia, Australia; <sup>4</sup>Centre for Forensic Science, The University of Western Australia, Crawley, Australia

The Dopamine receptor D2 (rs1076560) and  $\mu$ -opioid receptor (rs1799971) are two common single nucleotide polymorphisms (SNPs) that have been shown to be associated with different substances of misuse in some, but not every, ethnic groups studied. This study investigates the association of these SNPs with substance use disorder from the first-ever cohort of patients that were recruited from United Arab Emirates National Rehabilitation Centre (NRC). One hundred and ten male patients that were clinically diagnosed with substance use disorder were recruited from the NRC in Abu Dhabi, UAE. All participants were diagnosed with substance use disorder based on the DSM-IV criteria. Saliva samples were collected using DNA Oragene saliva kit (DNA Genotek, Canada). SNP genotypings for rs1076560 and rs1799971 were performed using TaqMan SNP genotyping assay on a 7500 platform (Applied Biosystems Inc., USA). Allele and genotype frequencies in the cohort were calculated using GenAlex (Peakall and Smouse 2006, 2012) and association was determined using STATA statistical software (College Station, USA). P-values, calculated by the chi squared test; that were less than 0.05; were considered to be significant.

There were no significant associations between rs1076560 (p-value=0.265) and rs1799971 (p-value=0.71) and substance use disorder. Further studies are required to identify the role of the genetic variation in members of Dopamine and Opioid receptor gene families.

In this specific study, the two SNPs: rs1076560 and rs1799971; were not associated with substance use disorder in the UAE population. However, this does not exclude these genes in pathways that are relevant to substance use disorder. A larger sample size may be required to obtain sufficient statistical power to interrogate the involvement of these genes in substance use disorder. Further studies are also required to investigate the involvement of these SNPs in the reward pathway and other associated indicators.

Keywords: Substance abuse, Dopamine receptor D2, Opioid receptor

### Posters

#### **P23 Association of Apolipoprotein E, Methylenetetrahydrofolate Genotypes, Lipid Levels and Alzheimer Disease in an Algerian Population**

Karima Sifi<sup>1</sup>, Yamina Sifi<sup>2</sup>, Ahmed Ouldjaoui<sup>1</sup>, Noureddine Abadi<sup>1</sup>, Abdelmadjid Hamri<sup>2</sup>, Cherifa Benlatreche<sup>2</sup>  
<sup>1</sup>Biochemistry Service, Medicine Faculty, Ibn Badis Hospital, Algeria; <sup>2</sup>Neurology Service, Ibn Badis Hospital, Medicine Faculty, Algeria

Alzheimer's disease is the most common form of neurodegenerative dementia. Recent research suggested that several pathogenetic factors influence risk and expression. The aim of the study was to investigate the association of Apo E, MTHFR genotypes and lipids as risk factors for AD.

A cross-sectional study on original sample of 195 referrals to a neurology clinic, 65 were given a diagnosis of AD (mean age  $73.47 \pm 7.61$  years, mean MMSE  $20.0 \pm 5.7$ ) according to (DSM IV – NINCDS - ADRDA) criteria; and 130 cognitively normal subjects (mean age  $67.17 \pm 10.84$  years).

ApoE allele frequencies of AD and controls were 5.5% vs. 7.2% for  $\epsilon 2$ , 63.5% vs. 83.9% for  $\epsilon 3$  and 31% vs. 8.9% for  $\epsilon 4$ . The AD patients compared with controls had significantly higher mean of total Cholesterol ( $191 \pm 37$ mg/dl vs.  $175 \pm 37$ mg/dl,  $p < 0.05$ ), LDL-C ( $122 \pm 29$  mg/dl vs.  $110 \pm 32$  mg/dl,  $p < 0.05$ ) levels in men and lower HDL cholesterol with mean values of ( $37 \pm 08$  mg/dl vs.  $44 \pm 07$  mg/dl,  $p < 0.05$ ) in men and ( $42 \pm 08$  mg/dl vs.  $47 \pm 08$  mg/dl,  $p < 0.05$ ) in women respectively, the triglycerides mean values were no significant in our study. The carriers of allele  $\epsilon 4$  and  $\epsilon 3/\epsilon 4$  subjects compared with  $\epsilon 3/\epsilon 3$  are associated with an increased incidence of AD with odds ratio of 5.01 [95%CI, 2.36 to 10.71]  $p < 0.001$  and 3.86 [95%CI, 1.72 to 8.72]  $p < 0.001$ , respectively.

These results indicated that AD patients with APOE- $\epsilon 4$  allele have a distinct plasma lipid profile and carrier of this allele with high (TC), LDL-C and low levels of HDL-C may be more susceptible to AD.

No significant association of MTHFR C677T allele and genotype with AD was observed in total samples.

Keywords: Apolipoprotein E, MTHFR, Association study, Alzheimer's disease

### Posters

#### **P25 Phenotypic Analysis of Algerian Patients with LIMB-GIRDLE Muscular Dystrophy Type 2c**

Karima Sifi<sup>1</sup>, Isabelle Richard<sup>2</sup>, Yamina Sifi<sup>3</sup>, Imene Dalichaouche<sup>1</sup>, Nouredine Abadi<sup>1</sup>, Abdelmadjid Hamri<sup>4</sup>  
*<sup>1</sup>Laboratory of Genetics and Molecular Biology, University 3 of Constantine, Algeria; <sup>2</sup>Service of Neurology CHU of Constantine, Algeria; <sup>3</sup>University Constantine, Algeria; <sup>4</sup>INSERM, U951, Evry, F-91002, France*

LGMD 2C is the most common genetic form encountered and the majority of AR-LGMD Algerian patients share the del521T mutation in the SGCG gene. Here, we investigated the clinical and molecular characteristics of 19 patients from 14 Algerian families with LGM2C phenotype

Our patients were selected according to the following criteria: symmetrical muscle weakness of trunk and limbs, prominent proximal muscles weakness compared to distal muscles, myopathic changes in electromyogram and elevated serum creatine kinase level. Family history was supportive of recessive autosomal or X-linked inheritances or de novo mutations, with homozygous del 521-T mutation in the SGCG gene. The complementary investigations comprised: a biological systematic assessment of CK. The electromyogram as well as the cardiac assessment (EMG) was carried out on all the index cases. The diagnosis of LGMD2C was made on the basis of molecular genetic analysis as described by Sanger et al.

Nineteen LGMD2C patients from 14 unrelated Algerian families, the mean age at assessment was 11, 3 years (ranging from 8-21 years), with 10 males and 9 females. The average age of onset was 6 years (4-7 years). Family history revealed a similar affected member in 9 families. All the patients presented a symmetrical muscle weakness of trunk and limbs, prominent proximal muscles weakness compared to distal muscles. Twelve patients had lost the walking ability at the average age of 13, 5 years (12-15 years). Calf hypertrophy was observed in 16 patients. Ten patients had macroglossia, three patients had developed respiratory complications. No cardiac involvement has been observed in any of the patients. The genetic study confirmed the diagnosis of LGMD2C in all the cases.

Phenotypic and genotypic analysis of Algerian patients with LGM2C approaches those observed in the other countries.

Keywords: Limb-Girdle Muscular Dystrophy Type 2C, SGCG gene

### Posters

#### P26 Clinical and Genetic Features in Patients with Werdnig Hoffman Disease

Sabah Hanachi, Karima Sifi, Abdelmadjid Hamri, Noredine Abadi, Yamina Sifi, Cherifa Benlatreche  
*Laboratory of Biology and Molecular Genetics, University 3 of Constantine, Algeria*

Homozygous deletion of the telomeric copy, survival motor neuron gene SMN1, is correlated with the development of spinal muscular atrophy SMA. Many molecular studies have shown that approximately 95% SMA patients have homozygous deletions of exons 7 and /or 8 of telomeric SMN1 copies independently of the severity of the phenotype and the NAIP gene located next to the SMN gene appears to contribute to the severity of the phenotype. The aim of our study was to report the clinical and molecular aspects of 19 Werdnig Hoffmann patients observed during 2001-2015.

All our 19 patients fulfilled the diagnostic criteria of proximal SMA as defined by the International SMA Consortium and underwent a genetic study exploring the exons 7 and 8 of the SMN gene and exon 4 and 5 of the NAIP gene respectively and assay the copies number of SMN2 gene by Multiplex ligation dependent probe amplification analysis. The PCR products of exons 7 and 8 of the SMN gene, were digested with restriction enzyme Dra I and Ddel respectively.

Our patients were divided into 12 boys and 07 girls aged on average of 15 months with an early mean age of 06.6 months. All patients had a deficit engines of both lower limbs associated with hypotonia in 73 % of cases, for swallowing disorders in 55% of cases, breathing disorders in 61.8 % of cases and precipitated the death in 52.6 % of patients. The genetic study realized showed homozygous deletion of exons 7 and 8 of SMN gene in 64% of patients and exon 4 and 5 of the NAIP gene in 42 % of patients. The majority of patients carry 2 copies of SMN2 gene. The results of our study are similar to the literature data.

Keywords: Spinal muscular atrophy, SMN2, NAIP

### Posters

#### **P27** **Molecular Diagnosis of Mental Retardation in Children: Our Experience in Algeria**

Chami Zahra, Kemmache Amine, Berhoune Arezki, Hallal Siham, Sadi Mahammed Zahra, Azouaoui Dassine, Djennane Asma, Yargui Lyes

*Laboratory of Biochemistry at the Hospital University of Mustapha-Algiers-ALGERI, Algeria*

Mental retardation (MR) is a major handicap, it may be syndromic involving neurological abnormalities, morphological, biochemical or visceral. Or more frequently non syndromic, defined by a single RM, without other clinical abnormalities. The number of genes responsible for RM is estimated at about 1000, only 90 of them have been identified.

Our laboratory performed in the last few years the molecular diagnosis of some syndromes such as Fragile X syndrome (FMR1 gene), the Prader Willi syndrome (SNRPN), Angelman syndrome (UBE3A) and Rett syndrome (MECP2). Although the evocation of these syndromes is clinical, the identification of the molecular defect responsible for the RM is required to confirm the diagnosis.

Our study was conducted on 857 childrens from the different departments of pediatrics and neurology of the country, over a period that spans six years (2009-2015).

The analysis of our activity report shows that these affections are not rare in our population. A reliable etiologic diagnosis of RM is essential, ensuring better care for patients, and so is a suitable genetic counseling to affected families.

Keywords: Mental retardation

### Posters

#### **P28** Test-negative Angelman Syndrome's with Thyroid Dysfunction: A Rarity but a Reality; First Ever Case Report From Pakistan on Clinically Diagnosed Angelman Syndrome in the Absence of Abnormal Molecular Genetic Testing

Muhammad Usman Ali  
*University of Sussex, UK*

Angelman Syndrome (AS) is believed to be a complex neuro-developmental genetic disorder that is mainly linked to the presence of chromosomal mutations involving deletions in maternal chromosome 15q11-q13, accounting for 70-80% cases of AS. In 10% cases, classic phenotypic features of AS are reported in presence of normal genetic analysis. AS or Angelman-like syndromes, in general or with associated thyroid dysfunction, have never been reported from Pakistan. This is the first ever case report from Pakistan reporting a rare case of clinically diagnosed AS with associated thyroid dysfunction in the presence of normal molecular genetic analysis.

An 18 year old female patient resident of District Peshawar presented to our department for evaluation for her thyroid status. Being a known case of hypothyroidism, she was taking oral Thyroxine Sodium at dose of 5mcg/kg/day and her recent investigations showed evidence of subclinical hyperthyroidism. Interestingly she also reported characteristic consistent features of AS. Most noteworthy examination finding included; behavioral uniqueness with frequent and inappropriate episodes of laughter while answering questions about her illness, speech impairment including minimal use of words and use of non-verbal communication skills like head nodding during conversation, tremulous movements of hands more pronounced when attempting to perform a task and mild ataxia of gait. She was tested with DNA methylation test and UBE3A gene sequencing that turned out to be negative in her case.

In light of such findings, presence of characteristic consistent features of AS, significantly increased the probability of having 'test-negative' AS, as the likely diagnosis. It is therefore imperative, that clinicians from our part of the world should increase awareness about Angelman and other related syndromes, and efforts should be made in documenting similar cases with associated clinical profiles; thereby contributing to the local and regional epidemiology of these syndromes.

Keywords: Angelman syndrome, Thyroid dysfunction



### Posters

#### **P29 A High Diagnostic Yield of Whole Exome Sequencing in Middle Eastern Patients with Neurocognitive Phenotypes**

Tawfeg Ben-Omran

*Department of Pediatrics, Hamad Medical Corporation, Qatar*

The clinical and genetic heterogeneity of neurogenetic disorders poses a significant challenge in the diagnostic workup of affected patients. Whole Exome Sequencing (WES) has become an increasingly popular diagnostic tool in patients with heterogeneous genetic disorders, especially in those with neurocognitive phenotypes.

A clinical cohort of 149 probands from Qatar with various neurocognitive phenotypes underwent WES from July 2012 to June 2014. Patients referred to the Medical Genetics Clinic at HMC from July 2012 to June 2014 with neurocognitive conditions were selected for WES, typically after reaching no conclusive diagnostic results from cytogenetic, molecular, and biochemical investigations.

Intellectual disability and global developmental delay were the most common clinical presentations but our cohort displayed other phenotypes such as epilepsy, dysmorphism, microcephaly and other structural brain anomalies and autism. A likely causal mutation, including pathogenic CNVs, was identified in 89 probands for a diagnostic yield of 60%. Consanguinity and positive family history predicted a higher diagnostic yield. In 5% (7/149) of cases, CES implicated novel candidate disease genes (MANF, GJA9, GLG1, COL15A1, SLC35F5, MAGE4, and NEUROG1). CES uncovered two coexisting genetic disorders in 4% (6/149) and actionable incidental findings in 2% (3/149) of cases. Average time to diagnosis was reduced from 27 months to 5 months.

The high yield of WES in our population and its ability to call pathogenic CNVs, shorten the time to reach the diagnosis, and uncover the co-existence of multiple conditions argue for this to be the diagnostic test of choice for neurogenetic disorders and our study suggests that this diagnostic method is particularly suited to populations with high rates of consanguinity.

Keywords: Whole exome sequencing, Intellectual disability, Global developmental delay, Neurogenetic disorders

### Posters

#### **P30 Novel Loss-of-function Variants in DIAPH1 Associated with Syndromic Microcephaly, Blindness and Early Onset Seizures**

A James Barkovich<sup>1</sup>, Ganeshwaran Mochida<sup>2</sup>, Almundher Al-Maawali<sup>2</sup>, Edward Yang<sup>3</sup>, Joan Stoler<sup>2</sup>, Brenda Barry<sup>2</sup>, Malak El-Quessny<sup>2</sup>, Christopher Walsh<sup>2</sup>, Anna Rajab<sup>4</sup>

<sup>1</sup>Dept. of Radiology, University of California, San Francisco, CA, USA; <sup>2</sup>Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA, USA; <sup>3</sup>Dept. of Radiology, Boston Children's Hospital, Boston, MA, USA; <sup>4</sup>National Genetics Center, Ministry of Health, Muscat, Oman

Microcephaly in which head circumference is greater than 3 standard deviations below the mean for given age, sex and gestation, is a heterogeneous condition. Exome sequencing is establishing molecular diagnoses in cases of microcephaly. A homozygous nonsense DIAPH1 mutation was recently reported in 1 Saudi family with autosomal recessive microcephaly, seizures, bronchiectasis and blindness. DIAPH1 is considered important in microtubule stabilization and cell migration. We report two additional consanguineous Middle Eastern families with homozygous biallelic loss-of-function mutations in DIAPH1, confirming and expanding the phenotype.

The first child presented with metopic craniosynostosis, microcephaly, vision impairment, seizures and recurrent respiratory infections. Clinical exome sequencing showed a homozygous mutation in DIAPH1. Subsequent search of our research series of individuals with post-natal microcephaly and seizures showed an additional family with mutations in DIAPH1 determined by exome sequencing. Presumed loss of function homozygous mutations in DIAPH1 (R1049X and F923fs) were identified and Sanger confirmed. The parents were heterozygous for the mutations.

These additional families confirm the features of post-natal microcephaly, short stature, early onset seizures, cortical visual impairment and chronic respiratory issues. DIAPH1 was originally reported as associated with AD nonsyndromic sensorineural progressive low-frequency hearing loss (DFNA1). None of the individuals in these families have any hearing problems.

Keywords: Microcephaly seizures bronchiectasis and blindness, DIAPH1 gene, Whole exome sequencing

### Posters

#### **P31 Exome Sequencing Reveals A Novel Gene Associated with Monogenic Form of Systemic Juvenile Idiopathic Arthritis**

Brian Meyer<sup>1</sup>, Dorota Monies<sup>1</sup>, Sulaiman Al Mayouf<sup>1</sup>, Salma Majid<sup>1</sup>, Haya Al Duseery<sup>2</sup>

<sup>1</sup>Department of Genetics, KFSHRC, Saudi Arabia; <sup>2</sup>Department of Pediatrics, KFSHRC, Saudi Arabia

Genomic technologies have emerged as powerful tools delving and dissecting human genome that allows the rapid evaluation of the underlying genetic causes of diseases in various autoimmune and auto inflammatory etiologies. Juvenile idiopathic arthritis constitutes a heterogeneous group of different forms of childhood chronic arthritis such as systemic juvenile arthritis (sJIA) involving various immunopathogenic, distinct genetic and environmental factors. Several monogenic autoinflammatory disorders have been described but thus far sJIA has only been attributed to mutation of MEFV in rare cases and has been weakly associated with the HLA class II locus.

Using high throughput genomics advances, we explored the familial clustering that helped to dissect the heterogeneity of JIA. We studied 13 unrelated patients from five consanguineous families classified as having systemic JIA according to International League of Associations for Rheumatology criteria for JIA. Using combined homozygosity mapping and whole exome sequencing, we underlined the disease associated gene and mutation.

Linkage analysis revealed sJIA to a region on chromosome 13 with a maximal LOD score of 11.33 representing strongest linkage to date for this disorder. Further the homozygous region narrowed the critical region to 1.02 Mb on chromosome 13q14.11. Refining the region with exome sequencing identified a homoallelic missense mutation in LACC1 encoding the enzyme laccase (multicopper oxidoreductase) domain containing 1. Segregation of this variant with the disease was confirmed by Sanger sequencing in all family members.

Our findings provide strong genetic evidence associating mutation of LACC1 with sJIA in the families studied. Association of LACC1 with Crohn's disease and leprosy has been reported and justifies investigation of its role in autoinflammatory disorders. While such studies combining in-depth genetic studies with epigenetics and immunological studies could not only help to redefine the classification of JIA, but also lead to more specific, individualized treatment.

Keywords: Arthritis, LACC1, Linkage analysis

### Posters

#### P32 PITX2 Regulates Multiple Atrial Fibrillation Associated GWAS Genes

Amel Haj Khelil<sup>1</sup>, Ricardo Caballero<sup>2</sup>, Houria Daimi<sup>1</sup>, Antonio Caruz<sup>3</sup>, Leif Hove-Madsen<sup>4</sup>, Jorge Nicolas J N Dominguez<sup>3</sup>, Jemni Chibani<sup>1</sup>, Diego Franco<sup>3</sup>, Francisco F Hernandez-Torres<sup>3</sup>, Amelia A Aranega<sup>3</sup>

<sup>1</sup>University of Monastir, Tunisia; <sup>2</sup>Complutense University of Madrid, Spain; <sup>3</sup>Department of Experimental Biology, University of Jaen, Spain; <sup>4</sup>Hospital de la Santa Creu i Sant Pau, Department of Pharmacy, Spain

Atrial fibrillation is the most common arrhythmogenic disease in humans, with an estimate prevalence of 0.5-5% in the general population, representing a serious burden in terms of morbidity and mortality. Despite its high prevalence, the genetic causes of atrial fibrillation remained largely unknown. Genome-wide association studies have provided novel insights into the genetic bases of AF. Four distinct loci (PITX2, KCNN3, ZFHX3 and IL6R) have been linked to lone AF, and more recently, a GWAS meta-analysis identified another six new loci. Experimental and functional evidence of the involvement of these genes in AF has only been reported for PITX2 describing that Pitx2 haploinsufficiency in mice had an increased susceptibility to atrial arrhythmias and leads to deregulation of Shox2, Tbx3 and Hcn4, as well as sodium and potassium channels. In addition, decreased expression of PITX2 in both right and left atrial appendages of AF patients undergoing surgery was reported. Based on these data, it seems that PITX2 insufficiency leads to cellular, molecular and electrophysiological changes which promote atrial fibrillation. However, it remains to be determined the causal relationship between risk variants and PITX2 expression as well as if PITX2 exert modulatory roles in other genes linked to atrial fibrillation. In this study we surveyed the genetic relationships between distinct AF GWAS associated SNPs in a Spanish AF patient cohort at the allelic, haplotypic and epistatic level. Secondly, we investigated the effect of 4q25 risk variant carriers in the expression of PITX2 as well as other AF GWAS associated genes and thirdly we search for molecular functional links of Pitx2 and those genes contributing to AF pathophysiology in experimental mouse models of Pitx2 insufficiency.

Genotype analysis of 130 AF patients demonstrate that only risk variants associated to PITX2, KCNN3, ZFHX3 are significantly linked to AF. Haplotype association was only significant for the 4q25 SNPs. Importantly epistatic relationships were observed for 4q25 (PITX2) and the KCNE1 and KCNN3 risk variants, respectively. Moreover, Pitx2 gain- and loss-of-function analyses demonstrate a pivotal role of Pitx2 regulating Zfhx3, Kcnn3, il6r, Pde4d and Wtn8a expression. Overall these data demonstrate that transcriptional regulation of the homeobox transcription factor Pitx2 is hierarchically controlling multiple aspects leading to cellular, molecular and electrophysiological changes linked to atrial fibrillation.

Keywords: Atrial fibrillation, PITX2, Haplotype association

### Posters

#### **P33 Identify Causal Mutations Using Gene Function and Causal Analytics In Conjunction with Patient DNA Sequence and Phenotype Data**

Greg Eley<sup>1</sup>, Joseph Devaney<sup>2</sup>, Andreas Kramer<sup>3</sup>, Sean Hofherr<sup>2</sup>, Ramon Felciano<sup>3</sup>, Rupert Yip<sup>3</sup>, Ben Solomon<sup>1</sup>, Kim Boycott<sup>4</sup>, Sohela Shah<sup>3</sup>, Daniel Richards<sup>3</sup>

<sup>1</sup>Inova Translational Medicine Institute; <sup>2</sup>Children's National Medical Center; <sup>3</sup>QIAGEN Bioinformatics; <sup>4</sup>Children's Hospital of Eastern Ontario (CHEO), Canada

A current challenge for identifying genetic variants underlying rare inherited diseases, from next generation sequencing (NGS) data, lies in picking out the true disease causing mutation from the list of hundreds and sometimes thousands of deleterious variants. Ingenuity Variant Analysis is a cloud-based application that provides a suite of algorithms and tools to extract valuable insights from such large amount of genetic variation data, by leveraging the large-scale causal network derived from the Ingenuity .

The Knowledge Base is a large structured collection of observations in various experimental contexts with over 11 million findings manually curated from the biomedical literature or integrated from third-party databases. Curated findings includes mutations, biological interactions, and functional annotations created from individually modeled relationships between proteins, genes, complexes, drugs, and diseases, along with contextual details such as site and type of mutation, cell and/or tissue specific gene expression, molecular interaction, post-translational modifications, details of the experimental design and methods used, and more.

We analyzed the sequence data from 80 patients, afflicted with severe congenital abnormalities, for which the causal variant was previously known. By providing a biological context, such as disease name, patient phenotypes, or pathways and processes users leverage the causal network analytics to can uncover these mutations. In addition, we have developed a scoring method to rank variants, using syndrome inference from phenotypes listed as the biological context to uncover novel or known variants in disease causing gene(s).

In 86% of cases, the causal variant was identified from among the top 100 variants. Furthermore, the causal variant was among the top 20 and 5 variants, in 65% and 41% of cases, respectively.

Ingenuity Variant Analysis is a state-of-the-art application that leverages biological knowledge to enable fast and accurate discovery of rare disease-causing variants within human genome data.

Keywords: causal variants, Knowledge Base, Ingenuity Variant Analysis

### Posters

#### **P34 Genomic Crowdsourcing: Allele Frequency Community Provides Expansive, Ethnically Diverse, Community Resource for Allele Frequency Annotation**

Frank Schacherer, Laura Furmanski, Rupert Yip, Sohela Shah, Dan Richards  
*QIAGEN Bioinformatics*

A challenge in genome interpretation is the lack of an extensive, high quality, ethnically-diverse collection of human genomes as a reference set. A candidate disease-causing variant that appears to be based on publicly available sequence may in fact be a polymorphism in an ethnic population under-represented in public databases. Resources such as the Exome Variant Server, the 1000 Genomes Project, and ExAC have been valuable to the community, but have not been funded to provide broad and deep ethnic representation. The Allele Frequency Community (AFC) has been formed to address this interpretation need. Community members contribute human exome- and genome-wide variant call datasets in a secure, anonymized, pooled fashion to create the largest, freely-accessible database of allele frequencies ever available.

QIAGEN Ingenuity Variant Analysis (IVA) is already the world's largest collection of interpreted human samples with over 400,000 samples. IVA users have recognized the value of pooling their samples to create the world's largest pool of summarized statistics based on consented, anonymized samples. AFC samples must pass 4 levels of quality before consideration: all duplicate samples must be removed, related family members are removed, samples with known pathogenic variants are removed, and samples that have been used as case samples within analysis are removed. More than 120,000 human exome/genome variant call datasets, including over 13,500 whole genomes, are already included in the AFC. The content is ethnically diverse, representing over 100 countries of origin. We show AFC to be more effective (~20%) at removing genetic 'noise' than ExAC. As well we've identified over 10 distinct ethnic clusters with over 100 samples, some of which are unique to AFC.

Within the past year the AFC has grown to be the world's largest collection of healthy human exome/genomes as well as the most ethnically diverse.

Keywords: Ingenuity Variant Analysis, Ethnic variants

### Posters

#### **P35** Pharmacological Induction of FOXO3 is a Potential Treatment for Sickle Cell Disease

Dipanshu Sur

*ILS Hospital, Kolkata, India*

Although it seems that individuals with sickle cell anemia apparently have a monogenetic disease, they exhibit wide variability in the degree of clinical severity. One of the most powerful and reproducible predictors of disease severity is the level of endogenous fetal hemoglobin (HbF), composed of two  $\alpha$ -globin and two  $\gamma$ -globin chains.

Taking a genomics approach to this question, we are investigating the natural human variation and its correlation with HbF levels to identify novel genes important for  $\alpha$ -globin regulation.

We enrolled a total of 160 pediatric sickle cell anemia patients (HbSS, age 3-18 years). In this study we performed whole exome sequencing (WES) and used gene-based analysis to find correlations between rare variants and endogenous HbF levels. In order to verify the association between FOXO3 and endogenous HbF levels, we performed functional studies in K562 cells, an erythroid leukemia cell line that expresses  $\alpha$ -globin. We knocked down FOXO3 in K562 cells using silencing RNA (siRNA). RT-qPCR and Western blot analysis detected a substantial decrease in  $\alpha$ -globin expression with FOXO3 knockdown.

We found seven unique non-synonymous variations in a Forkhead box O transcription factor, FOXO3, to be significantly associated with lower HbF ( $p=0.00053$ ,  $\hat{r}^2$ -value In HbF -0.56).

These results strongly suggest that FOXO3 is a positive regulator of  $\alpha$ -globin. The  $\alpha$ -globin specific effect of FOXO3 is critical; FOXO3 is an excellent therapeutic target for the treatment of sickle cell disease, as it selectively induces HbF, which does not sickle, without inducing HbS. The results indicate that FOXO3 is a positive regulator of  $\alpha$ -globin expression and an excellent therapeutic target for fetal hemoglobin induction. This finding supports a new mechanism underlying fetal hemoglobin regulation and helps identify potential new HbF inducing agents.

Keywords: FoxO3, Sickle cell disease, Whole exome sequencing

### Posters

#### **P36** Non Invasive Prenatal Testing: An Islamic Perspective

Aida Al-Aqeel

*Prince Sultan Military Medical City, Saudi Arabia*

NIPT that will allow genetic testing of a fetus within the first trimester of pregnancy by isolating cell-free fetal DNA (cffDNA) in the mother's plasma raises a range of ethical and legal issues. The goal of this study is to provide an Islamic ethical framework for health care providers and government agencies providing NIPT.

We refer to our previous experience in medical genetics, screening tests and ethics in combination with the Islamic 'Sharia' (Figh) principles and authoritative 'consensus edicts' 'fatwas' of Islamic scholars, literature review and our publications. We developed a set of best practices for the provision of NIPT within an Islamic framework.

Applying the Islamic 'Sharia' principle 'The basic concept in useful matters is permissiveness' which indicates that everything is lawful, as long as it is useful to people, our principal recommendations include promotion of NIPT to high risk pregnant women for the prevention of fetal aneuploidy and in certain cases at high risk of single gene disorders, with the amendment of current informed consent procedures to include attention to the noninvasive nature of this new testing and the potential for a broader range of results earlier in the pregnancy. However, the need for confirmatory testing by amniocentesis must be discussed carefully with the pregnant woman.

Pregnant women at increased risk of aneuploidy can be offered cffDNA testing. Its performance in low-risk women and women with multiple gestations is unclear. Such test should be regulated by government agencies. Since limited professional guidance is available clinician performing the test should adopt responsible best practices in the provision of the test within an ethical framework that combines appeal to written precedent with sensitivity to the options of individuals and families dealing with choices and necessities within the laws, traditions of their society.

Keywords: Prenatal testing, Sharia, cell-free fetal DNA



### Posters

#### **P38 Combined Pituitary Hormone Deficiency Associated with Cervical Rigidity and Sensorineural Hearing Loss: Report of Two Novel LHX3 Mutations and Differential Diagnosis**

Faiqa Imtiaz<sup>1</sup>, Bassam Bin-Abbas<sup>2</sup>, Mohammed Al-Owain<sup>3</sup>, Rabab Allam<sup>1</sup>, Khushnooda Ramzan<sup>1</sup>

<sup>1</sup>Dept of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; <sup>2</sup>Dept of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; <sup>3</sup>Dept of Medical Genetics, King Faisal Specialist Hospital, Riyadh, Saudi Arabia

Congenital combined pituitary hormone deficiency (CPHD) is a rare condition. CPHD type3 is caused by mutations in LHX3 LIM-homeodomain transcription factor gene, which is critical for pituitary gland formation. Here, we summarize features of three patients from two unrelated families with novel LHX3 mutations.

We ascertained patients with syndromic symptoms associated with CPHD. An informed written consent was used. Laboratory testing, pituitary examination, radiological investigations, MRI, skeletal survey and audiology was performed. DNA extraction was done on blood samples using PUREGENE DNA Extraction Kit (Gentra Systems). All exons and exon-intron boundaries of LHX3 were amplified. PCR products were sequenced using Genetic Analyzer (Applied Biosystems).

Clinical evaluation revealed that all patients had severe CPHD coupled with cervical vertebral malformations (rigid neck, scoliosis), mild developmental delay and moderate hearing loss. A novel missense LHX3 mutation (p.C146F) and a novel nonsense mutation (p.R156\*), both in homozygous form, were found. Accession numbers correspond to NCBI reference sequence accession number NM\_014564.3 for the cDNA. The cysteine at p.146 in LIM2 domain of the encoded protein is a phylogenetically conserved residue. LIM domains, composed of two contiguous zinc fingers, are protein structural domains and mediate protein:protein interactions that are critical to cellular processes. This replacement of p.C146F will disrupt of the bonding of protein with zinc, thus leading to its impaired function. p.R156\* results in a severely truncated protein lacking the entire DNA-binding homeodomain and carboxyl terminus of the normal, functional protein. In addition PolyPhen-2, SIFT, and MutationTaster suggest these variants to be disease causing. This report describes the first LHX3 mutations from Saudi patients. The results of our analysis of these patients expand the knowledge of LHX3-related CPHD3 phenotype and the allelic spectrum for this gene.

Keywords: Combined pituitary hormone deficiency, LHX3

### Posters

#### **P40** **Establishing A Genetic Database for Autosomal Dominant Polycystic Kidney Disease Patients: A Step Towards a Better Diagnosis, Management and Treatment**

Medhat Naim<sup>1</sup>, Naser Hussain<sup>1</sup>, Fahd Al-Mulla<sup>2</sup>, Hamad Ali<sup>3</sup>

<sup>1</sup>Division of Nephrology, Mubarak Al-Kabeer Hospital, Ministry of Health, Kuwait; <sup>2</sup>Molecular Pathology Unit, Department of Pathology, Faculty of Medicine, Kuwait University, Kuwait; <sup>3</sup>Department of Medical Laboratory Sciences (MLS), Health Sciences Center, Kuwait

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common form of Polycystic Kidney Disease (PKD) and occurs at a frequency of 1/800 to 1/1000 affecting all ethnic groups worldwide. ADPKD is characterized by accumulation of renal cysts leading to impairment of kidney functions which makes it one of the leading causes of end stage renal disease (ESRD) with around 4-10% of patients with kidney failure having this disorder. Mutations to the PKD1 or PKD2 genes cause ADPKD, with around 85% of cases having PKD1 mutations. ADPKD shows significant phenotypic variability in the rate of disease progression and extra-renal manifestations. Understanding the molecular basis behind disease phenotypic variability would aid our understanding of disease pathogenesis and improve disease management. It can also provide insights toward the development of potential therapies.

Families showing ADPKD symptoms have been clinically evaluated and a genetic screening for PKD1 and PKD2 were performed using long range PCR technique to identify disease causing mutations. Whole exome sequencing was performed on patients to identify potential genetic modifiers.

We have established a genetic database for ADPKD patients in Kuwait. Novel ADPKD mutations and novel disease modifying genetic variants were identified and listed.

Our genetic database of ADPKD exomes can help in diagnosis and prediction of disease outcomes. It can also be incorporated in existing pre-implantation genetic diagnosis (PGD) programs. Understanding the genetic basis of disease variability can improve disease diagnosis, management and treatment.

Keywords: Autosomal Dominant Polycystic Kidney Disease, PKD1, PKD2, Database, Whole exome sequencing

### Posters

#### **P41 Family Initiative Attitude Towards Prevention of Lamellar Ichthyosis through Premarital Genetic Counseling for A Familial Mutation: A Five Year Experience**

Khalsa Al-Kharusi

*Sultan Qaboos University Hospital, Oman*

Targeted testing for a known familial mutation can be a powerful tool in countries with limited options for recurrence risk reduction or prevention such as termination of affected fetus. Oman is one of the countries that follow regulations against termination of fetus unless for maternal indications. Preimplantation genetic diagnosis is allowed under regulations but not available within the country. Considering the fact that family intermarriage is favored, providing premarital genetic counseling and testing for individuals at risk should aid risk reduction.

This is a case report of a family attitude towards prevention of a familial genetic disorder within a time of five years. A highly inbred family with autosomal recessive Lamellar Ichthyosis has had a known familial mutation in the TGM1 gene since 2008. Despite the availability of the test the number of individuals considering carrier status testing was unremarkable for four years. The main barrier of premarital testing is the geographic distance to the testing center, where the family have to travel thousands of miles for counseling and testing. Avoidance of social and cultural stigma had also discouraged the testing. In the last two years, three new births of affected children from distantly related parents facilitated the family affinity towards testing; hence number of individuals attended the clinic for carrier status counseling and testing has dramatically increased. To date, 48 individuals had attended for genetic counseling and testing in comparison to seven before the new births.

Driver and attitudes of the family towards prevention of the disease have been dramatically changed within five years. There are still barriers to overcome so the family can access the service effectively; like distance travelling and cost. Training a genetic nurse or organizing mobile genetic counseling clinic might facilitate better premarital planning and avoidance of new cases.

Keywords: Familial attitude, Lamellar Ichthyosis, Stigma

## Posters

### **P42 In more than 20% of Children with Chronic Kidney Disease (CKD) a Monogenic Cause of Disease can be Detected**

Friedhelm Hildebrandt<sup>1</sup>, Muna Al Saffar<sup>2</sup>, Weizhen Tan<sup>3</sup>, Svjetlana Lovric<sup>3</sup>

<sup>1</sup>Howard Hughes Medical Institute Chevy Chase, MD, USA; <sup>2</sup>UAE University, UAE; <sup>3</sup>Division of Nephrology, Boston Children's Hospital, Harvard Medical School, USA

Childhood chronic kidney disease (CKD) manifests early in life and often progresses to end-stage renal disease (ESRD), requiring dialysis or renal transplantation for survival. The most frequent causes of CKD in the first 20 years of life are congenital anomalies of the kidneys and urinary tract (CAKUT) (45%), nephrotic syndrome (15%), and renal cystic disease (6%), accounting for two thirds of all children diagnosed with CKD. Approximately 30% of cases with childhood CKD are caused by single gene mutations and increases to ~50%, in consanguineous families. As the underlying genetic causes of CKD are very heterogeneous, there is no general curative or preventative treatment for CKD that is currently available.

We performed homozygosity mapping (HM), whole exome sequencing (WES) and multiplex PCR with next generation sequencing (NGS) in individuals of families with CKD to identify the underlying mutations.

Mutation analysis with NGS techniques of over 5,000 families worldwide with CKD has uncovered that >15-30% of these cases can be explained by a monogenic causative mutation in over 200 single gene causes of CKD. Specifically, we have discovered the causative mutation in the following worldwide cohorts of children with CKD in: i) 70% of 880 families with cystic kidney disease (100 different genes) ii) 30% of 1,783 families with nephrotic syndrome (31 genes) 12% of 900 families with CAKUT (30 genes), and in 30% of children and adults with renal stones (31 genes).

Mutation analysis with NGS techniques in patients with CKD provides a surprisingly high fraction of families with an unequivocal molecular genetic (etiologic) diagnosis. Identification of the underlying cause enables etiology-based 'personalized' clinical management of CKD with implications for prevention, supportive treatment, or management of CKD.

Keywords: Chronic kidney disease, Whole exome sequencing, Homozygosity mapping

### Posters

#### **P43 Predicting of Potential Correlation between Missense Mutations and Inhibitor Formation in Severe Hemophilia A**

Meriem Abdi, Faouzia Zemani, Maissa Nadege Chaalan, Amira Zoubir, Nadira Saadi-Mehtar  
*Laboratoire de Génétique Moléculaire et Cellulaire, Université des Sciences et de la Technologie d'Oran Mohamed Boudiaf, Oran, Algeria*

Deleterious substitutions of F8 gene are responsible for Hemophilia A which is genetic disease of coagulation disorders in blood. The most complication in the treatment is inhibitors development toward therapeutic factor VIII. In this study, the effects of deleterious amino acid substitutions in F8 gene upon protein structure and function were assayed by means of computational methods from the CHAMP database. We performed an in silico analysis of deleterious mutations using five software: Sift, Polyphen-2, Align-GVGD, KD4v and Mutation taster, in order to analyze the correlation between mutation and the disease. Also we studied the correlation between these mutations and inhibitors formation.

Our analysis showed that these tools are coherent and that there are more mutations on the A then on the C domains. Moreover, we noticed that there are more deleterious mutations than neutral mutations on each of the A and C domains.

Moreover, we found that 13.51% of the patients with severe form of Hemophilia A and that carrier missense mutations developed inhibitors. Also, for the first time, we determined that a mutation nature is not associated to inhibitors formation. Furthermore, this analysis showed that the risk of developing inhibitors increase when the mutation cause a change of amino acid class.

This study will help to correctly associate the mutation with inhibitor development and aid early characterization of novel variants.

Keywords: Hemophilia A, F8, in-silico analysis

### Posters

#### **P44 A Review of The Diverse Genetic Disorders in The Lebanese Population: Highlighting The Urgency for Community Genetic Services**

Soha Yazbek<sup>1</sup>, Ghunwa Nakouzi<sup>2</sup>, Khalil Kriedieh<sup>3</sup>

<sup>1</sup>American University of Beirut, Lebanon; <sup>2</sup>Department of Clinical Pathology, Cleveland Clinic Hospital, Cleveland, OH, USA;

<sup>3</sup>Medical Laboratory Sciences, American University of Beirut, Lebanon

The review lists the genetic diseases reported in Lebanese individuals, surveys genetic programs and services, and highlights the absence of basic genetic health services at the individual and community level.

We conducted a comprehensive literature search of CTGA database, Online OMIM database, and PubMed articles, reviews, and book chapters written on genetic diseases in the region. We contacted the Ministry of Public Health, private and public hospitals, and private medical laboratories. We conducted search on governmental websites, contacted 180 private and public hospitals and 50 private labs.

The incidence of individual diseases is not determined, yet the variety of genetic diseases reported is tremendous, most follow autosomal recessive inheritance reflecting the social norms in the population, including high rates of consanguinity. Genetic services including all activities for the diagnosis, care, and prevention of genetic diseases at community level are extremely inadequate. Services are limited to some clinical and laboratory diagnosis with no genetic counseling. These are localized within the capital, preventing their accessibility to high-risk communities. Screening programs, which are at the core of public health prevention services, are minimal and not nationally mandated. The absence of adequate genetic services is attributed to many factors undermining the importance of genetic diseases and their burden on society, the most important of which is genetic illiteracy at all levels of the population, including high-risk families, the general public, and most importantly health care providers and public health officials.

Thus, a country like Lebanon, where genetic diseases are expected to be highly prevalent, is in utmost need for community genetics services. Strategies need to be developed to familiarize public health officials and medical professionals with medical genetics leading to a public health infrastructure that delivers community genetics services for the prevention and care of genetic disorders at community level.

Keywords: Genetic disorders, Community genetics

### Posters

#### **P45 A Novel Missense Mutation In The C2C Domain of Otoferlin causes profound Hearing Impairment in an Omani Family with Auditory Neuropathy**

Fatemeh Al Asti<sup>1</sup>, Mazin Al Khabouri<sup>2</sup>, Yahya Al Tamimi<sup>3</sup>, Guy Van Camp<sup>1</sup>, Nadia Al Wardy<sup>3</sup>, Mohammed Al Kindi<sup>3</sup>  
<sup>1</sup>Centre of Medical Genetics, University of Antwerp, Belgium; <sup>2</sup>Department of ENT, Al Nahda Hospital, Ministry of Health, Oman; <sup>3</sup>Department of Biochemistry, CoM&HS, Sultan Qaboos University, Oman

Nonsyndromic recessive hearing loss can occur as a consequence of defective molecular mechanisms ruling hair cell synaptic neurotransmitters secretion, among many other pathways. In this study, a consanguineous Omani family diagnosed with nonsyndromic recessive hearing disorder neuropathy was investigated to identify the gene associated with the disease. Using microsatellites markers, the disease was linked to D2S2144, D2S2223, D2S174, D2S365, and D2S366 markers located on chromosome-2 and covering the OTOF (DFNB9) gene. The OTOF gene encodes the otoferlin protein reported to have an active role in hair cell vesicle exocytosis and the release of synaptic neurotransmitters through C2 domains. The coding area of the OTOF gene that is composed of 48 exons was screened for mutations. A novel missense mutation that changed nucleotide C to G at position c.1469 and consequently the amino acid Proline to Arginine (P490R) on exon 15 was detected. Protein modeling analysis revealed the impact of the mutation on the protein structure and the relevant C2C domain in particular. The mutation seems to create a new protein isoform homologous to the complement component C1q. These findings suggest that the mutation found in the C2C domain of the OTOF gene is likely to cause deafness in the studied family reflecting the importance of C2 domains of otoferlin in hearing loss.

Keywords: Nonsyndromic hearing loss, OTOF

### Posters

#### **P46 Genetic Polymorphisms in E-NOS, ARG1 and GSNOR Genes in Omani Sickle Cell Disease Patients-Correlation with Acute Chest Syndrome**

Salam Alkindi<sup>1</sup>, Shoaib Al Zadjali<sup>1</sup>, Anil Pathare<sup>1</sup>, Aiman Al Wahaibi<sup>2</sup>, Rajagopal Krishnamoorthy<sup>1</sup>, Naglaa Fawaa<sup>1</sup>, Mohamed Al Rawahi<sup>1</sup>

<sup>1</sup>Department of Haematology, Sultan Qaboos University Hospital, Oman; <sup>2</sup>Department of Medicine, Sultan Qaboos University Hospital, Oman

Acute chest syndrome (ACS) is an important complications of sickle cell disease (SCD) and associated with reduced nitric oxide (NO). NO induces vasodilatation and the helps recruitment of neutrophils. However, the T-786C polymorphism significantly reduces eNOS gene promoter activity, whereas the E298D polymorphism changes an amino acid in the enzyme's oxygenase domain. The normal expression of eNOS related to 27 bp repeat VNTRs in intron 4, but the 4bb genotype is associated with decreased eNOS mRNA expression, whereas, homozygosity for the minor allele of GSNOR SNP rs28730619 is associated with increased risk of asthma. The purpose of this study was to look for endothelial nitric oxide synthase (e-NOS3) gene polymorphisms (T-786C, E298D and Intron 4 VNTR) as well as ARG1 and GSNOR gene polymorphisms in SCD Omani patients and correlate with ACS.

Genomic DNA was isolated using the standard techniques and stored at -20oC pending analysis. DNA sequence polymorphisms for HBB gene( $\beta$ 6Glu>Val), NOS3 gene polymorphisms (T-786C, E298D and Intron 4 VNTR) as well as ARG1 and GSNOR gene polymorphisms were studied by direct sequencing of the relevant genomic segment amplified by polymerase chain reaction on an ABI PRISM 3100 genetic analyzer using appropriate primers described in literature.

Our results showed that only the eNOS promoter C-786 allele showed a statistically significant association ( $P=0.001$ ) in ACS cases, especially so with the female gender ( $p=0.005$ ). There was no correlation observed with eNOS polymorphisms E298D and Intron 4VNTR, ARG1 and GSNOR gene polymorphisms studied in this cohort of SCD patients with ACS.

eNOS promoter C-786 variant which reduces eNOS gene activity was observed as a genetic risk factor for ACS in adult female sickle cell anemia patients, explained by the fact that activity of eNOS gene is known to be influenced/regulated by oestrogens.

Keywords: eNOS, sickle cell disease, Acute chest syndrome



### Posters

#### **P47 Molecular Cytogenetics Characterization of DiGeorge Syndrome in Children with Conotruncal Heart Defects from The Kingdom Of Bahrain**

Neale Kalis<sup>1</sup>, Cristina Skrypnyk<sup>2</sup>, Sara Al-Othman<sup>2</sup>, Mohammed Rahman K<sup>2</sup>

<sup>1</sup>MK Cardiac Center, Bahrain Defense Force Hospital, Kingdom of Bahrain; <sup>2</sup>Arabian Gulf University, College of Medicine and Medical Sciences, Kingdom of Bahrain

DiGeorge Syndrome (DGS) is caused by 22q11.2 microdeletion and is responsible of 30% of conotruncal heart defects (CHDs) cases. Some patients with DGS phenotype, including cardiac defects, were reported to have deletions 10p14 (DiGeorge Syndrome II). The aim of the study was to identify the molecular cytogenetics background of the CHDs patients using fluorescent in situ hybridization (FISH) technique for del22q11.2 and del10p14, and genome wide array analysis.

47 patients with conotruncal heart defects, referred from MK Cardiac Centre, BDF Hospital Bahrain were investigated by FISH analysis, using specific DNA probes that covered DGS Critical Region I on 22q11.2 (TBX1/ SHANK3, TUPLE1, N25 " Cytocell) and DGS Critical Region II on 10 p14 (BRUNOL3- Cytocell). Genome wide array was performed independently using Affymetrix CytoScan HD SNP array platform.

13% (6/47) del22q11.2 patients were detected by FISH. None of the patients had a detectable deletion of chromosomal region 10p14. The genome wide array analysis confirmed the del22q11.2 in 6/47 patients, no atypical nested 22q11.2 deletions or 10p14 deletions were identified. 1/6 of patients had a deletion of 3.15 Mb, 5/6 had a deletion in between 2.5 and 2.8 Mb and 4/6 had the identical proximal breakpoint. All deletions contained the TBX1 gene associated with conotruncal heart defects. Tetralogy of Fallot was the most frequent conotruncal heart defect of the del22q11.2 patients. Genome wide array identified other two different chromosomal deletions (del2q12, del 7q11.21). Our study suggests that screening for 22q11.2 microdeletion should be performed in children with conotruncal heart defects. FISH test for DGS region is reliable but genome wide array analysis is a very useful tool in the genetic investigation of CHDs, allows for accurate genotype-phenotype correlation and can reveal cryptic anomalies that are not possible to be identified by targeted FISH.

Keywords: DiGeorge Syndrome, 22q11.2 microdeletion, FISH

### Posters

#### **P48** **A Novel DGAT1 Mutation Induces Congenital Diarrhea and Protein Losing Enteropathy**

Jay Thiagarajah, Nina Gluchowski, Daniel Kamin  
*Division of Gastroenterology, Boston Children's Hospital, USA*

The diacylglycerol acyltransferase enzymes, DGAT1 and DGAT2, catalyze the final step in triglyceride biosynthesis and are involved in lipid droplet formation. A splice mutation in the DGAT1 gene resulting in complete loss of function has previously been described in the Ashkenazi Jewish population. The initial report included two affected siblings, both with congenital diarrhea and protein losing enteropathy, one of whom died from complications of malnutrition. There are now several children with this mutation and diarrheal disease.

In this report, we describe identical male twins of Southeast Asian descent with a novel mutation in the DGAT1 gene and severe congenital diarrhea and protein losing enteropathy. These patients were born at 36 weeks gestational age and developed watery diarrhea shortly after birth that persisted despite multiple formula changes. They presented with failure to thrive, protein losing enteropathy as evidenced by elevated stool alpha-1 antitrypsin, hypogammaglobulinemia, and vitamin D, and iron deficiencies. Extensive work-up culminated with whole exome sequencing and a point mutation in DGAT1, L105P was identified. At two-years old, one twin required hospitalization with total parenteral nutrition and then was transitioned to a very low fat enteral diet. His twin had improved growth on the same enteral regimen. The diarrhea and protein losing enteropathy appears to be substrate induced and diarrhea and protein loss returns when fat intake exceeds 10% total caloric intake.

In conclusion, we describe a novel mutation in the DGAT1 gene that results in a congenital diarrhea syndrome. Functional studies are currently underway to investigate how this mutation alters DGAT activity. In addition we describe an enteral feeding regimen that results in normal stool output and improved growth and other nutritional parameters.

Keywords: Congenital diarrhea, Protein losing enteropathy, DGAT1

### Posters

#### **P49 Disorders of Sexual Development (DSD): Karyotype Based Etiologic Diagnosis Algorithm**

Khalida Boudaoud, Sabah Hannachi, Noredine Abadi  
*Faculty of Medicine, Biochemistry Laboratory, University Hospital, Algeria*

The aim of the present study is to propose an interpretation of the clinical and paraclinical data according to the karyotype in the DSD.

Thirty-six patients were explored for hypergonadotropic hypogonadism(HH), sexual ambiguity or infertility. The etiologic diagnosis was established on a clinical, hormonal, radiological, cytogenetic and histological bases. The cases are distributed in 3 main groups:Group 1 of 23 female phenotypes [15 Turnerien phenotypes, 2 male pseudohermaphrodisms (MPH), 2 HH with retinitis pigmentosa, 2 amenorrheas by Mullerian aplasia and 2 isolated HH]. The karyotype directed the diagnosis to 13 Turner syndromes, 2 cases 46XX dysgenesis of BBS, 2 cases of Mayer-Rokitansky syndrome, 1 case 46XX pure dysgenesis, 1 case 46XY of Complete Androgen Insensibility Syndrome(CAIS), 1 case 46XY of leydig cells hypoplasia and 1 case 46XY dysgenesis. Group 2 of 7 male phenotypes, [5 anorchia, 1 testicular hypotrophy with azoospermia, 1 HH testicular ectopia associated with gonadoblastoma]. The karyotype confirmed 5 cases 46XY of testicular regression syndromes and 2 cases 47XXY of Klinefelter syndrome.Group 3 of 6 sexual ambiguities [3 MPH, 1 hypospadias associated with cryptorchidism, 2 cases of 21-hydroxylase deficiency]. The karyotype confirmed 2 cases 46XY of partial AIS and 1 case 46XY agenesis.

Based on the karyotype, the causes of the DSD in our patients are divided into 13 cases of sex chromosome abnormalities, 8 cases of 46 XX DSD and 12 cases of 46 XY DSD.

A DSD etiological investigation initially based on the karyotyping allows a better exploration and interpretation of the clinical and paraclinical data for a more precise etiological diagnosis.

A classification of the DSD based on karyotype facilitate therapeutic decision making, especially in the case of gonadal malignancy risk estimation.

Keywords: Disorders of sexual development, karyotype

### Posters

#### **P50 The use of CRISPR/CAS9 Mediated Knock-out Of Sel1l and Proteasomal Inhibition For Dissecting The Endoplasmic Reticulum Quality Control Pathways Involved in The Degradation of Trafficking Defective Proteins**

Lihadh Al-Gazali<sup>1</sup>, Anne John<sup>2</sup>, Bassam Ali<sup>2</sup>, Praseetha Kizhakkedath<sup>2</sup>, Salman Toor<sup>3</sup>

<sup>1</sup>Department of Pediatrics, CMHS, UAEU, UAE; <sup>2</sup>Department of Pathology, College of Medicine and Health Sciences, UAEU, UAE; <sup>3</sup>Department of Medical Microbiology and Immunology, CMHS, UAEU, UAE

ER retention of misfolded Endoglin (ENG) proteins has been implicated in the pathogenicity of the autosomal dominant disorder, Hereditary hemorrhagic telangiectasia (HHT). Terminally misfolded proteins in the early secretory pathway are degraded by a process known as ER-associated degradation (ERAD). The mammalian HRD1-SEL1L complex provides a scaffold for ERAD, thereby connecting luminal substrates for ubiquitination at the cytoplasmic surface after their retrotranslocation through the endoplasmic reticulum membrane. Down-modulation of the ERAD pathway has been shown to prevent the degradation of several mis-folded proteins.

The wild type and mutant ENG proteins were transiently expressed in mammalian cell lines and the effect of the pharmacological proteasomal inhibitors were analyzed. Confocal microscopy and Western blotting was employed to compare the subcellular localization of the wild type and mutant proteins followed by proteasome inhibition. For genetic down-modulation of the ERAD machinery, CRISPR/Cas9 mediated gene editing was employed. For gene editing, guide RNA targeting exon 3 of the SEL1L gene was cloned in the CRISPR OFP Nuclease vector (GeneArt). Transfection and clone enrichment was carried out according to the manufacturer's instructions.

Confocal microscopy images indicated increased co-localization of ENG mutants with plasma membrane markers after proteasomal inhibition. Immunoblot analysis revealed increased expression of the wild type and mutant proteins and accumulation of polyubiquitylated protein forms after MG132 treatment. For characterizing the mutants further, a cell line deficient in the SEL1L gene was generated by CRISPR/Cas9 gene editing. Two bi-allelic clones and several mono-allelic Knockout clones of SEL1L were obtained and the functional knockout of the gene was confirmed by western blotting.

Preliminary results indicate that some of the Endoglin mutants are stabilized after pharmacological inhibition of proteasomal activity by MG132. The folding and subcellular localization of the mutants will be further analyzed in the SEL1L deficient cell line.

Keywords: Hereditary hemorrhagic telangiectasia, CRISPR/Cas9, SEL1L, ER-associated degradation

### Posters

#### **P51 Compound Heterozygous MPDZ Mutations are The Underlying Cause of Mild Non-progressive Communicating Hydrocephalus**

Anne John<sup>1</sup>, Jehan Suleiman<sup>2</sup>, Aisha Al-Shamsi<sup>2</sup>, Salma Ben-Salem<sup>1</sup>, Bassam Ali<sup>1</sup>, Nesreen Al Jezawi<sup>2</sup>, Lihadh Al-Gazali<sup>2</sup>, Ranjit Vijayan<sup>3</sup>

<sup>1</sup>Department of Pathology, College of Medicine and Health Sciences, UAE University,UAE; <sup>2</sup>Department of Paediatrics, College of Medicine and Health Sciences, UAE University,UAE; <sup>3</sup>Department of Biology, College of Science, UAE University,UAE

Congenital hydrocephalus (CH) results from the accumulation of excess cerebrospinal fluid (CSF) in the brain, leading to neurological impairments. Several previously reported CH cases were shown to be caused by mutations in the L1CAM gene. In addition, a mutation in MPDZ gene has been recently reported to be responsible for CH in an autosomal recessive pattern.

In this study, an Emirati family with one child affected by CH was clinically evaluated followed by molecular analyses to reveal the causative mutation(s). Whole-exome DNA sequencing was performed on DNA isolated from the affected child and Sanger sequencing was used to establish the segregation of the identified variants. Bioinformatics and in silico analyses in addition to protein modeling were employed to confirm pathogenicity of the identified variants. Whole exome sequencing revealed two compound heterozygous variants (c.394G>A, p.G132S and c.1744C>G, p.L582V) in the MPDZ gene. Sanger sequencing showed the father to be heterozygous for the c.1744C>G variant while the mother is heterozygous for the c.394G>A variant. In silico and bioinformatics analyses suggested that both mutations are disease causing. The first variant (c.394G>A) was predicted to cause acceptor splice site change or a single amino acid change at glycine 132. The second variant (c.1744C>G) was predicted to cause a missense mutation at amino acid position 582 (p.L582V). Both variants were absent in Exome Variant Server. Protein modelling showed that the variant (serine at position 132) was limiting the flexibility of the loop which lies between L27 and PDZ-1 domains. Additionally, the mutant valine at 582 which lies between  $\beta$ C and  $\alpha$ A could disrupt the GLG loop (a conserved loop in the MPDZ structure).

The identified compound heterozygous mutations are the most likely cause of CH in the affected child.

Keywords: Congenital hydrocephalus, MPDZ, Whole exome sequencing

### Posters

#### **P53** Gonadal Mosaicism in ARID1B Gene Causes Intellectual Disability and Dysmorphic Features in Three Siblings

Pramathan Thachillath<sup>1</sup>, Aisha Al-Shamsi<sup>2</sup>, Nadia Akawi<sup>3</sup>, Nara Sobreira<sup>4</sup>, Salma Ben Salem<sup>5</sup>, Bassam Ali<sup>5</sup>, David Valle<sup>4</sup>, Anne John<sup>5</sup>, Lihadh Al-Gazali<sup>1</sup>

<sup>1</sup>Paediatrics dept, CMHS, UAEU, UAE; <sup>2</sup>Paediatrics dept, Tawam Hospital, Al Ain, UAE; <sup>3</sup>Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK; <sup>4</sup>Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Maryland, USA; <sup>5</sup>Pathology dep, CMHS, UAEU, UAE

The gene encoding the AT-rich interaction domain-containing protein 1B (ARID1B) has recently been shown to be one of the most frequently mutated genes in patients with intellectual disability (ID). The phenotypic spectrums associated with variants in this gene vary widely ranging for mild to severe non-specific ID to Coffin-Siris syndrome.

We evaluated three children from a consanguineous Emirati family affected with ID and dysmorphic features. Genomic DNA from all affected siblings was analyzed using CGH array and whole-exome sequencing (WES). Results: Based on a recessive mode of inheritance, homozygous or compound heterozygous variants shared among all three affected children could not be identified. However, further analysis revealed a heterozygous variant (c.4318C>T; p.Q1440\*) in the three affected children in an autosomal dominant ID causing gene, ARID1B. This variant was absent in peripheral blood samples obtained from both parents and unaffected siblings.

We propose that the most likely explanation for this situation is that one of the parents is a gonadal mosaic for the variant. To the best of our knowledge, this is the first report of a gonadal mosaicism inheritance of an ARID1B variant leading to familial ID recurrence.

Keywords: Intellectual disability, ARID1B, Whole exome sequencing, Gonada mosaicism

### Posters

#### P54 **A Heart With An Open Hole And Deformed Hand: Is There A Connection?**

Subbiah Sivamani<sup>1</sup>, Jaikumar Shajeev<sup>2</sup>, Kothandam Sivakumar<sup>3</sup>, Bibhas Kar<sup>1</sup>

<sup>1</sup>Centre for Genetic Studies & Research, The Madras Medical Mission, Chennai, India; <sup>2</sup>Department of Radiology, The Madras Medical Mission, Chennai, India; <sup>3</sup>Department of Pediatric Cardiology, The Madras Medical Mission, Chennai, India

Congenital heart defects occurring together with upper limb malformations as a group of dominantly inherited disorders constitute the Heart-Hand syndrome (HHS) with varied phenotypic manifestations and are broadly classified as HHS Types I-IV. To the best of our knowledge, the patient we report herein is a first case of HHS Type IV presented with large PDA and cutaneous syndactyly from India.

A 1-month-old female with complaints of interrupted feeding and forehead sweating during feeds was referred for cardiac evaluation of suspected congenital heart disease. Echocardiography, electrocardiography (ECG), radiography and physical examinations were carried. However, this patient was clinically suspected for Down syndrome and was advised for thyroid function test and karyotyping. FISH was performed to rule out mosaicism if any.

Echocardiography showed large PDA with left to right shunt. Left atrial/left ventricular (LA/LV) volume over load and severe pulmonary arterial hypertension (PAH) was noticed. ECG showed normal sinus rhythm with 120 msec PR interval and right ventricular hypertrophy. Radiograph of the right hands showed features of complete simple cutaneous syndactyly (middle and ring finger) and central type of polydactyly with probable syndactyly (index finger). Thyroid function tests revealed elevated TSH levels. Karyotype and FISH showed a normal 46,XX.

After thorough examination and the findings obtained from various investigations, a diagnosis of HHS type IV was made. The patient underwent successful PDA device closure and orthopedic surgery was planned due to syndactyly. One month after surgery, the cardiac functional class improved. Whole-exome sequencing studies are now underway to identify the definitive cause of this rare genetic disease. The management of individuals with HHS optimally involves a multidisciplinary team approach, with specialists in genetics, cardiology and orthopedics including a specialist in hand surgery.

Keywords: Heart-Hand syndrome

### Posters

#### **P55** Whole-Exome Sequencing Effectively Unveiled The Molecular Causes Underlying Single Gene Disorders Affecting Families In UAE

Makanko Komara<sup>1</sup>, Bassam Ali<sup>1</sup>, Jozef Hertecant<sup>2</sup>, Lihadh Al-Gazali<sup>1</sup>

<sup>1</sup>Department of Pathology, College of Medicine and Health Sciences, UAEU, UAE; <sup>2</sup>Department of Paediatrics, Tawam Hospital, UAE

Genetics disorders are the main cause of referral to clinical genetics laboratories in populations with high levels of inbreeding. Whole-exome sequencing has become a fundamental tool in the identification of disease causing genes. It provides coverage of more than 95% of the exons which contains 85% of disease causing mutations in single gene disorders. Identification of the genetics causes of rare recessive disorders provides important knowledge about disease mechanisms, biological pathways and may facilitate the development of novel diagnostic and therapeutic approaches.

We ascertained four families from UAE affected by single gene disorders. All patients were evaluated at the Genetic Clinic, Tawam Hospital, Al-Ain. DNA was isolated after obtaining informed written consents from the affected families. Whole exome sequencing was performed on affected individuals. In silico analysis tools were used to evaluate the consequences of the identified variants. Segregation with disease status was assessed using Sanger sequencing and real time PCR was employed to quantify mRNA when needed.

We identified pathogenic variants in NSUN2, WDR81, DYNC1H1 and PAK3 genes causing intellectual disability, disequilibrium syndrome, and malformation of cortical development and X linked Intellectual disability associated with macrocephaly in four affected families, respectively. Sanger sequencing confirmed the identified variants. In addition, in silico analysis and qPCR further supported the pathogenic nature of the variant.

Collectively, our data demonstrated that whole exome sequencing is a successful tool in identification of disease causing loci in inbred families affected by single gene disorders.

Keywords: Intellectual disability, whole exome sequencing, in-silico analysis



### Posters

#### P56 Gene Environment Interactions and some Birth Defects

Rabah Shawky  
*Ain Shams University, Egypt*

Birth defects are structural malformations present at or before birth. Established aetiologies such as chromosomal abnormalities, genetic factors and exposure to environmental teratogens contribute to a small portion of all birth defects. Unfortunately for most cases, the causes remain unknown. It is now appreciated that the more common birth defects represent complex traits with complex aetiologies. This explains why very few genes that contribute to these defects are well known. The term gene-environmental interaction implies any kind of interplay between genes (multiple genes with small effects) and environmental factors including joint or synergistic effects.

The intrauterine environment of developing fetus is determined by maternal factors such as health/disease status, lifestyle, medication, exposure to teratogens as well as maternal genotype. Certain genetic characteristics of the fetus also predispose him to developmental abnormalities.

The application of other recent technologies including Sanger sequencing, next generation sequencing and exome sequencing have increased gene discovery among patients with structural anomalies. However every technology is not without challenges and limitations.

The study of gene/ environmental interactions will lead to better understanding of the biological mechanisms and pathological processes that contribute to the development of complex birth defects.

The ultimate goal is to provide individualized medicine in terms of prevention and treatment, or to provide individualized recommendations.

Current hypothesis of interactions between some environmental factors (maternal folate nutritional status, maternal smoking and maternal hyperglycemia) and genetic pathways in the development of some birth defects (congenital heart, neural tube defects, oral clefts, etc.) will be discussed. Also the benefits of sequencing in diagnosis will be mentioned.

Keywords: Gene-environment interaction

### Posters

#### P57 Epidemiology of Muscle Diseases in The Arab World

M Fayez Alhomsi<sup>1</sup>, Amer Alhomssi<sup>1</sup>, Bassel Alhomsi<sup>2</sup>

<sup>1</sup>University Hospital Sharjah, UAE; <sup>2</sup>American University of Sharjah, UAE

Arab population is characterized by consanguinity rates in the range of 25-60%. Autosomal recessive disorders are widely spread (63%) compared to smaller proportion of dominantly inherited traits (27%). Inherited muscle diseases have been reported in Arab World.

In Jordan 73% had muscular dystrophy (MD), 50.9% had congenital muscular dystrophy, 20% had Duchenne muscular dystrophy (DMD), 16.4% had Becker muscular dystrophy (BMD), 7.3% had myotonic dystrophy, 3.6% had limb-girdle muscular dystrophy (LGMD), and 1.8% had facioscapulohumeral dystrophy. In Egypt the lifetime prevalence per 100,000 was 26.8 for muscular dystrophy, 11.49 for myotonia, 11.49 for myositis, 17.24 for systemic myopathy, and 9.57 for myasthenia gravis. In Libya, 3-year-search indentified 34 DMD patients (prevalence 6/100,000) and 19 LGMD patients (3.7/100,000). Two types of progressive MD were identified in Tunisia: typical DMD and Duchenne-like muscular dystrophy (DLMD). A very high dystrophin deletion mutation frequency is documented in Arabs compared to other ethnic groups. Frameshift deletion mechanisms are detected in 51.3% of Egyptian DMD and BMD. DLMD was mapped to chromosome 13q in Tunisian families and same locus was also reported in Algerian and Moroccan families. Autosomal recessive limb-girdle muscular dystrophies (LGMD) have a particular high frequency in Arab states especially Tunisia. LGMD2B, Miyoshi myopathy, was mapped to chromosome 2p12 in 12 families including a Tunisian family, and reported in Moroccan, Saudi, and Libyan Jewish patients. LGMD2C is the most frequent LGMD2 in Tunisia where patients share the same founder  $\gamma$ -SGCG mutation.

Autosomal dominant hyaline body myopathy is reported in four Saudi patients. The causing gene MYH7 was identified in the family and the mutation H1904L is thought to affect the slow myosin heavy chain rod domain. These and other inherited muscle diseases reported in the Arab World will be discussed at the presentation.

Keywords: Inherited myopathy, Muscular dystrophy

### Posters

#### P58 Hereditary Hearing Loss (HHL) Genes Discovery in The Qatari Population

Dragana Vuckovic<sup>1</sup>, Anna Morgan<sup>1</sup>, Khalid Abdul Hadi<sup>2</sup>, Diego Vozzi<sup>3</sup>, Paolo Gasparini<sup>3</sup>, Giorgia Giroto<sup>1</sup>, Elisa Rubinato<sup>1</sup>, Ramin Badii<sup>2</sup>, Moza K. Alkowari<sup>3</sup>, Shruti Baghat<sup>2</sup>

<sup>1</sup>University of Trieste, Italy; <sup>2</sup>Hamad Medical Corporation (HMC), Doha, Qatar; <sup>3</sup>Sidra medical research, Doha, Qatar

HHL is one of the most prevalent sensory disorders. Despite GJB2,GJB6 and the A1555G mutation play a major role worldwide, still there is a need to search for new causative genes in several population/countries such as those from the Gulf region. To overcome this lack of knowledge in the Qatari population, a 3-steps 'new gene-identification strategy' was designed. STEP1 consists in a screening by Targeted Re-Sequencing (TRS). Negative cases will undergo Whole Exome Sequencing (WES)(STEP2). STEP3 will include functional validation using Zebrafish models.

WES protocol was performed with Ion Proton (LifeTechnologies). A total of 293.903 amplicons ensuring >99% coverage of the target region were sequenced. Data were filtered according to quality value, allele frequency, pathogenicity prediction, conservation score and segregation within the family. Functional studies, including genetic characterisation through CRISPR/Cas9 and phenotypical analysis, will be performed in Zebrafish.

Eighteen Qatari families have been investigated. STEP1 characterized 61% of them. STEP2 led to the discovery of 1 new gene (BDP1-Giroto et al.,2011) and 3 candidates in families with autosomal recessive HHL. As regards these genes, the following results have been obtained: a missense mutation in KPTN was found; KPTN encodes an actin-binding protein expressed in the stereocilia, already proposed as a HHL-candidate gene (Bearer et al.,2000). In another family, two heterozygous mutations were found in PIEZO1, which encodes an ion channel that might be involved in HHL. Finally a missense mutation was detected in LAMC1, a member of the Laminin-Family, which plays an important role in hearing function. Zebrafish experiments are now in progress.

This strategy proved to be very successful by defining an accurate molecular epidemiology picture of new candidate genes for Qatari population and will be also of utmost interest to the international scientific community and to countries of the Gulf Area.

Keywords: Hereditary hearing loss, Whole exome sequencing, Targetted resequencing, Zebrafish model

### Posters

#### **P60 Genetic Analysis of Autosomal Recessive Mental Disorders Shows Complex Etiology in Consanguineous Pakistani Population**

Dragana Vuckovic<sup>1</sup>, Anna Morgan<sup>1</sup>, Khalid Abdul Hadi<sup>2</sup>, Diego Vozzi<sup>3</sup>, Paolo Gasparini<sup>3</sup>, Giorgia Giroto<sup>1</sup>, Elisa Rubinato<sup>1</sup>, Ramin Badii<sup>2</sup>, Moza K. Alkowari<sup>3</sup>, Shruti Baghat<sup>2</sup>

<sup>1</sup>University of Trieste, Italy; <sup>2</sup>Hamad Medical Corporation (HMC), Doha, Qatar; <sup>3</sup>Sidra medical research, Doha, Qatar

Mental disorder or mental illness is a complex term which is a behavioral or psychological pattern associated with disability that occurs in an individual and is not a part of normal development or culture. Mental disorders are generally classified into neurological disorders and learning disabilities or mental retardation. . Incidence of mental disorders is relatively high in Pakistan because of high consanguinity. Hallervorden-Spatz syndrome (HSS) also called neurodegeneration with brain iron accumulation (NBIA) encompasses a group of progressive extrapyramidal disorders characterized by iron accumulation in the brain. In the present study, we studied large consanguineous Pakistani family with autosomal recessive HSS having multiple affected births. Purpose of the study was to improve the understanding on protective measurements for mental disorders especially HSS.

Nucleic acid (DNA) was extracted and subjected to STS (Single tagged sequence) marker analyses for mapping of homozygosity in known genes and known loci regions using a fluorescence three primer method. All individuals showed exclusion for all known genes and loci regions. Detailed clinical examination was made for two affected of the family and showed phenotype of HSS. Further its three loops were subjected to the Genome wide scanning using SNP6.0 array for detection of homozygous regions. No shared homozygous region was found for all three loops and even for any two loops, and no match was found for compound heterozygosity. Following the sequencing of PANK2 and WDR45 genes, exome sequencing was also performed but did not find any mutation. All these analyses made the molecular genetics of MR6 very complicated and suggest several possible molecular etiologies; it could be compound heterozygous, have three different mutations or be digenic. This complexity of HSS needs advanced molecular studies like functional analyses to understand the molecular genetics of this disease phenotype.

Keywords: Hallervorden-Spatz syndrome, STS Markers

### Posters

#### P61 Role of TGF- $\beta$ and HIF-1-Alpha Signaling in T-Cell Activation

A AbdAlWahab<sup>1</sup>, Ahmed Al-shaye<sup>1</sup>, Abbas Jarrahi<sup>1</sup>, A Doudin<sup>4</sup>, Farhan Cyprian<sup>5</sup>

<sup>1</sup>College of Medicine, University of Sharjah, Sharjah, UAE; <sup>2</sup>Sharjah Institute for Medical Research, UAE; <sup>3</sup>University of Qatar, Qatar

Hypoxia-inducible factor 1-alpha (HIF-1-alpha) is a factor considered as the master transcriptional regulator of cellular response to hypoxia. The deregulation and overexpression of HIF1A by hypoxia is implicated in cancer biology. Transforming growth factor beta (TGF- $\beta$ ) is a secreted protein that controls proliferation, cellular differentiation and other functions in most cells. It is a type of cytokine which plays a role in immunity, cancer. The purpose of our experiment is to study the effect of these molecules in T cell activation.

T-lymphocytes harvested from spleens and lymph node of 6-8 weeks old, healthy, female mice. Cells were cultured in 96-well plates with RPMI 1640 media supplemented with 10% FCS, L-glutamine, HEPES, P/S and gentamycin. The T-lymphocytes were incubated at 37°C for 48 hours after treatment by TGF  $\beta$  along with activation by CD3 and CD28. Cells were incubated in normoxic and hypoxic situations. T-cell activation was investigated via flow cytometry by looking at early activation molecules such as CD44, CD62L, CD25 and Fas molecule.

Flowcytometric analysis showed down regulation of CD44 in activated CD4 positive T cells cultured in hypoxic condition, similar results were seen with CD62L. TGF- and hypoxia had no effect on Fas molecule in activated T cells though it was activated by T cell Receptor 'TCR' mediated activation. CD 25 was down regulated in both CD4 and CD8 positive lymphocytes. A synergistic effect of hypoxia and TGF- $\beta$  in down-regulating CD69 expression on CD8 T lymphocytes.

Hypoxia and TGF- $\beta$  showed a synergistic effect decreasing the T cell activity, but the individual effect of each one of these factors showed a potential induction on T cell activity. This might have a great impact in learning more about the cancer micro-environment which might lead to more targeted therapy of solid tumors.

Keywords: Hypoxia, TGF- $\beta$ , T-cell activity

### Posters

#### **P62 Association of DNA Repair Genes XRCC1 (Arg399Gln), (Arg194Trp) and XRCC3 (Thr241Met) Polymorphisms with the Risk of Breast Cancer: A Case Control Study In Egypt**

Mai Moaz<sup>1</sup>, Ragaa Ramadan<sup>2</sup>, Mostafa El Naggar<sup>3</sup>, Lubna Desouky<sup>1</sup>

<sup>1</sup>Department of Immunology and Allergy ,Medical Research Institute, Alexandria University, Egypt; <sup>2</sup>Department of Chemical Pathology, Medical Research Institute Teaching Hospital, Egypt; <sup>3</sup>Department of Chemical Pathology, Medical Research Institute Teaching Hospital, Egypt

Various DNA damage, induced by endogenous and exogenous factors, is handled through DNA repair pathways such as X-ray repair cross-complementing protein (XRCC). Genetic variations in these pathways may have a joint or additive effect on various types of cancer, including the risk of breast cancer (BC).

The aim of the study was to evaluate the association of three single-nucleotide polymorphisms (SNPs) Arg399Gln, Arg194Trp, and Thr241Met in DNA repair genes XRCC1 and XRCC3 on the risk of BC, and to assess their interaction with risk factors and prognostic markers in a case-control study in Egypt.

We detected the studied SNPs using polymerase chain reaction 'restriction enzyme polymorphism (PCR-RFLP)' in peripheral blood from 100 BC patients and 75 healthy females.

The dominant model of inheritance of Arg399Gln and Arg194Trp revealed an increase in BC risk of odds ratio (OR) of 3.56, 95% confidence interval (CI) = 1.22-10.39,  $p = 0.017$  and OR: 4.45, 95% CI = 2.35-8.45,  $p < 0.001$  respectively. However, there was no clear interaction between the studied SNPs and the known risk factors, or tumor criteria. No association between the Thr241Met genotype and BC risk was observed.

XRCC1 Arg399Gln and Arg194Trp variant genotypes are associated with an increased risk of breast cancer in Egyptian females.

Keywords: Breast cancer, XRCC1, PCR-RFLP

## Posters

### P63 Association between TollLike Receptor 4(TLR4) Polymorphisms and Breast Cancer Susceptibility in Estrogen Negative Receptor Post-Menopausal Patients

Mohammad Alanazi<sup>1</sup>, Abdullah Alamri<sup>1</sup>, Narasimha Reddy Parine<sup>1</sup>, Abdelhabib Semlali<sup>1</sup>, Maroua Jalouli<sup>2</sup>, Maha Arafah<sup>3</sup>  
<sup>1</sup>Genome Research Chair, Department of Biochemistry, College of Science King Saud University, Saudi Arabia; <sup>2</sup>Université Laval, Québec, Canada; <sup>3</sup>College of Medicine, King Saud University, Riyadh, Saudi Arabia

Breast cancer is the leading malignancy among women worldwide and is a foremost cause of cancer related death. Toll like receptors (TLRs) are a key player in regulation innate immune response that protect the host against cancer and bacterial and viral infection. Several evidences support the view that Genetic single-nucleotide polymorphisms (SNPs) of TLRs lead to the dysregulation of the defense system and consequently increasing the risk of developing cancer. In this study, we proposed to investigate the association of the common polymorphism of the TLR4 with breast cancer development arising Saudi Arabia population.

Four TLR4 polymorphisms (rs2770150, rs10759931, rs10759932 and rs4986790) were genotyped in blood samples from 127 breast cancer patients and 117 healthy controls. Relative gene expression for TLR-4 between the breast tumor and the matched normal breast tissues was evaluate by immunohistochemistry assay (n=13) using specific an anti-TLR4 antibody.

Our results demonstrate an increase in TLR4 expression in breast cancer tissues as compared to normal. We did not show any correlation between TLR4 SNPs rs10759932 and breast cancer susceptibility in the Saudi population. However, the G allele of SNP rs10759931 was found to be significantly highly frequent among patients (36.3%) compared to the control group (26.7%) suggesting that this polymorphism is strongly associated with the development of breast cancer in this ethnic population. In addition, the TLR4 polymorphism rs2770150 was shown to be highly correlated with breast cancer in patients aged over 48 years. TLR4 polymorphism rs4986790 is also associated with this malignancy in ER- (Estrogen Receptor negative) patient groups. Our data suggest that gene expression variation in TLR4 may influence the development of breast cancer and that TLR4 SNPs could be used as a biomarker for detection of this malignancy.

Keywords: Breast cancer, TLR4, biomarker

### Posters

#### **P64 Expression and Polymorphism of Toll-like Receptor 4 and Effect on NF-KB Mediated Inflammation In Colon Cancer Patients**

Mohammad Alanazi<sup>1</sup>, Maha Arafah<sup>2</sup>, Narasimha Reddy Parine<sup>1</sup>, Majid A Almadi<sup>3</sup>, Abdullah Al Amri<sup>1</sup>, Abdelhabib Semlali<sup>1</sup>, Abdulrahman Aljebreen<sup>4</sup>, Mahmoud Rouabhia<sup>5</sup>, Othman Alharbi<sup>4</sup>, Nahla Ali Azzam<sup>2</sup>

<sup>1</sup>Genome Research Chair, Department of Biochemistry, College of Science King Saud University, Saudi Arabia; <sup>2</sup>College of Medicine, King Saud University, Riyadh, Saudi Arabia; <sup>3</sup>Division of Gastroenterology, The McGill University Health Center, Canada; <sup>4</sup>Division of Gastroenterology, King Khalid University Hospital, King Saud University, Saudi Arabia; <sup>5</sup>Université Laval, Québec, Canada

Our aim was to evaluate the association between the expression and the polymorphism of TLR4/NF-KB pathways and colon cancer. Methods: TLR4 (rs4986790, rs10759932, rs10759931 and rs2770150) were genotyped in blood samples from Colorectal patients and healthy controls. TLR4 and cytokines inflammatory expression were evaluated by real time PCR on 40 matching normal and colon tissues and the protein level by Immunohistochemistry.

The highly level of TLR4 expression in colon cancer tissues is mainly due to infections by bacteria in the human colon and leads to induction of an acute secretion of inflammatory cytokines mediated by NF-KB. Also, we report here a clear evidence for an association between TLR4 rs10759931 polymorphism and susceptibility to colon cancer development. This polymorphism affects the entire population without being specific to either gender or to any age group. In contrast, the rs2770150 is associated with colon cancer in women aged over 50 years and is closely linked with the decreased levels of female sex hormones during the post-menopausal period. rs10759932 and rs 4986790 appear to have any association with colon cancer. Our data suggest that TLR4 SNPs could possibly serve as biomarkers for decision making in colon cancer treatment.

Keywords: Colon cancer, TLR4, biomarker



### Posters

#### **P65** Methylene tetrahydrofolate Reductase Polymorphisms and Preoperative Chemoradiation Response in Locally Advanced Rectal Cancer

Saloua Taleb<sup>1</sup>, Leila Beddar<sup>2</sup>, Karima Sifi<sup>2</sup>, Taha Filali<sup>2</sup>, Aicha Djemaa<sup>1</sup>, Hacem Boudaoud<sup>3</sup>, Nouredine Abadi<sup>2</sup>, Khadija Boudaoud, Karima Benmbarek<sup>2</sup>

<sup>1</sup>Department of Radiation Oncology, Faculty of Medicine, UC3, Algeria; <sup>2</sup>Laboratory of Molecular Biology and Genetics, Faculty of Medicine, UC3, Algeria; <sup>3</sup>Department of Surgery, Ain Touta Hospital, Batna, Algeria

Preoperative radiation therapy combined with chemotherapy using 5- fluoracil or capecitabine is the standard treatment for locally advanced rectal cancer. However there is a large individual variation in tolerance and therapeutic efficiency. The genetic polymorphisms represent one of the major causes in this variation. Methylene tetrahydrofolate reductase (MTHFR) may play a central role in the action of 5-FU, an inhibitor of thymidylate synthase, by converting 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate.

The aim of our study was to evaluate the C677T MTHFR polymorphism and histologic response to preoperative chemoradiation using Fluoropyrimidines in locally advanced rectal cancer.

52 patients with diagnosis of locally advanced rectal cancer were treated with preoperative concurrent Fluoropyrimidines and radiation therapy. Germ line DNA from patients was genotyped for MTHFR C677T using PCRs and RFLP. Toxicity was graded by National Cancer Institute Common Toxicity Criteria version 3.0. Therapeutic efficiency was evaluated by histopathological postoperative specimen examination. Kaplan-Meyer survival curves were defined for each polymorphism in our series.

The distribution of the three genotypes CT, CC and TT were respectively (32.6%, 48% and 19.2%). 15 patients experienced grade 3 and 4 toxicity. 677 (CT-CC) genotypes were related to a higher rate of grade 3-4 toxic events respectively (35% - 28%). T-level downstaging and a pathologic complete response (pCR) after neoadjuvant treatment was demonstrated in 60% of cases in patients with 677TT genotype, it was 41% in 677CT genotype and 56% in 677CC genotype. No association is observed between C677T polymorphism and survival (log rank= 0.02, p = 0.99).

In spite of the limited patient number, our study shows that the MTHFR 677 TT genotype can have a protective role of Fluoropyrimidines toxicity, and it can be a predictive factor in therapeutic efficiency. This study will be continued, in order to include more patients.

Keywords: Rectal cancer, MTHFR, Fluoropyrimidines

### Posters

#### **P66** Ethics and Cancer Prevention

Sonia Seddiki

*University Ahmed Ben bella Oran 1, Algeria*

Cancer is responsible for a considerable morbidity and mortality. Yet our epidemiological knowledge indicate that about 80% of cases of this disease could be prevented through changes in lifestyle issues and the environment in general. The objective of this work is to offer reflections on ethics and prevention of cancers. We found that two complementary approaches exist. One is a holistic approach to health promotion, based primarily on the adoption of behaviors favorable living well be physical, moral and social development of individuals and eliminating exposure to risks such as smoking, pollution, food etc. Screening programs are implemented under the responsibility of health professionals to reduce the risk of cancer. The field of pharmaco-prevention is still, by cons, at the stage of preliminary research. Only vaccinations have demonstrated an undeniable protective effect with regard to infections and may play a role in the occurrence of cancer. Other terms of chemoprevention by vitamin supplements and especially antihormones, have iatrogenic effects such as their use in healthy population raises serious ethical questions.

Keywords: Ethics, Cancer screening, Cancer prevention

### Posters

#### **P67 PTCH and P53 Genes Mutations in Sporadic and Radio Induced Basal Cell Carcinomas (BCC): An Algerian Population Study**

Lotfi Louhibi<sup>1</sup>, Nadhira Saidi-Mehtar<sup>1</sup>, Fouzia Benrrahal<sup>2</sup>, Meriem Abdi<sup>1</sup>, Fatima Zohra Moghtit<sup>1</sup>, Ahlem Messal<sup>1</sup>, Bernard Malfoy<sup>2</sup>, Amina Boubekeur<sup>1</sup>, Rym Abderrahmane

<sup>1</sup>University of Science and Technology of Oran, Mohamed Boudiaf, Oran, Algeria; <sup>2</sup>Plastic Surgery, University Hospital of Oran, Algeria

Mutations of p53 and PTCH genes were screened in 22 tumor samples of sporadic (SP) basal cell carcinoma (BCC) that developed in sun-exposed skin region in Algerian western population and 18 radio induced (RI) samples of BCCs developed after treatment by RX for tinea capitis also.

PTCH sporadic and RI mutations form were detected at a frequency of 22,72% and 72,22%, respectively, and for p53, frequency of mutations was 10% for sporadic form and 11% for RI form. For sporadic cases, the mutations were predominantly UV-signature transition, C→T. In both genes, the most common mutations were missense mutations, except for one which makes truncated proteins. Ptch mutations in sporadic SP form : Ser1326Phe, Pro27Ser, Pro568Leu, Leu756Phe and Gln184Stop). p53 SP form mutations : Cys176Arg, Arg156Cys, His193Glu and Leu194Phe. Analysis of Ptch RI cases shows 4 insertions (ins 10pb codon 1042; insGCG -27 TNT; insGGC -4 TNT and insG codon 1080), one duplication (dup exon8), 5 amino acid substitution (Val114Ala; Ser463Phe; Met001Lys; 2x Thr1195Ser) and 3 mutations which generates truncated proteins (Gln853Stop; Ser877Stop; Trp851Stop). p53 RI mutations form analysis gives, one deletion (del 16pb +41 Intron3) and 2 amino acid substitutions (Arg248Trp; His179Tyr).

PTCH is frequently mutated in RI form than SP and difference in the type of mutations in observed. Radio induced form lesions shows insertion and duplication in addition to missense mutations. Few mutations have been identified in p53 either a sporadic or radio-induced BCC

Results suggest that both UV and ionizing radiation affect DNA repair lesions and may significantly contribute to BCC tumorigenesis. The high rate and nature of Ptch mutations gene in RI BCC form cases could be in favor of radiation signature.

Keywords: Basal cell carcinoma, PTCH, p53, radiation

### Posters

#### **P68 Methylene tetrahydrofolate Reductase C677T Polymorphism and Digestive Cancer Risk**

Karima Sifi<sup>1</sup>, Khalida Boudaoud<sup>2</sup>, Mohamed Salah Choubar<sup>2</sup>, Nouredine Abadi<sup>3</sup>, Yasmina Chafika Amrane<sup>3</sup>, Taha Filali<sup>4</sup>, Cherifa Benlatreche<sup>2</sup>, Sabah Hanachi<sup>2</sup>, Selwa Taleb<sup>2</sup>

<sup>1</sup>Laboratory of Biology and Molecular Genetics, Faculty of Medicine, University Hospital of Constantine, Algeria;

<sup>2</sup>Radiotherapy Department of the University Hospital of Constantine, Algeria; <sup>3</sup>Anatomy Department of the University Hospital of Constantine, Algeria; <sup>4</sup>Biochemistry Laboratory of the University Hospital of Constantine, Algeria

The 5, 10 methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism. It catalyzes the irreversible conversion of 5, 10 methylenetetrahydrofolate to 5 methyltetrahydrofolate, a key substrate carbon donor for homocysteine remethylation. The MTHFR C677T polymorphism creates a thermolabile enzyme which decreases enzyme activity, appears to interfere with the phenomena of carcinogenesis by reducing the DNA methylation levels making it unstable and by monitoring the synthesis of DNA.

Numerous epidemiological studies have highlighted the important role of MTHFR in carcinogenesis.

The aim of this study was to:

- Determine the allelic and genotype frequencies of MTHFR C677T polymorphism in patients with gastric and colorectal cancers and healthy controls.
- Perform estimation of relative risk associated with this polymorphism in digestive cancers, compared to healthy controls.

#### Patients and methods

In this study, 30 patients with gastric cancer (GC), 52 patients with colorectal cancer (CRC) and 92 healthy controls, all of eastern Algeria, were genotyped for the MTHFR C677T polymorphism by using the PCR / RFLP method.

Allelic frequencies of MTHFR 677T and MTHFR 677C were 34,92 % and 65,07 % respectively in the control group, 43.75% and 56.25%, respectively, for patients with CCR and 25% and 75% respectively in patients with a GC.

The odds ratio (95% confidence interval) 677 T/T vs 677 C/C and 677 C/T vs 677C/C were 9.82 (0.91-19.54) (p<0.05) and 1.4 (0.9-2.3) (p<0.05), respectively in colorectal cancer and 1,23 ( p= 0,55 ) et 0, 62 (0, 23-1, 65) (p= 0, 20) , respectively in gastric cancer.

Our data have indicated that the C677T MTHFR polymorphism does not significantly contribute to the inherited genetic susceptibility to gastric cancer, while we have shown some evidence for possible genetic contribution of this polymorphism to the development of colorectal cancer.

Keywords: Gastric cancer, Colorectal cancer, MTHFR

### Posters

#### **P69** Heredity and Non Heredity Risk Factors: A Survey of Familial Breast Cancer Evaluation / Prevalance Among The Mexican Women

Parvathi Kumara Reddy Thavanati<sup>1</sup>, Rosa Elena Navarro Hernandez<sup>2</sup>, Maria Rosalba Ruiz Mejia<sup>3</sup>, Aurora Escoto de Dios<sup>1</sup>, Maria Elena Aguilar Aldrate<sup>4</sup>

<sup>1</sup>Institute of Human Genetics, CUCS, University of Guadalajara, Guadalajara, Mexico; <sup>2</sup>Institute of Rheumatology, CUCS, University of Guadalajara, Mexico; <sup>3</sup>Institute of Biochemistry, CUCS, University of Guadalajara, Mexico; <sup>4</sup>Public Health, CUCS, University of Guadalajara, Mexico

Higher prevalence of Breast Cancer in Mexican Women compared to other regions of the World took more importance. The present study focused to evaluate the familial risk factors of Breast Cancer + relative degenerative diseases up to third generation in the lineage of pedigree. A case control study was carried out among Proband Breast Cancer women and Healthy women. Breast Cancer risk factor were calculated by conditional logistic regression, stratified by study, age, smoking, alcohol consumption, puberty, menopausal status, conceptive use, number of sisters, parity, mortality and age when the first child born, breast feeding duration and specially on dietary habits. Breast Cancer incidence and mortality rates for particular family histories were calculated by applying age-specific risk ratios to breast cancer rates typical for more-developed countries. Majority with affected second generation of Breast Cancer (29.5%), Cervical cancer (24.2%), Pulmonary Cancer (5.9%), Diabetes Mellitus II (10.1%), Cardiopathy (9.8%) and other factors were with 20.5% (may be life styles) were at risk of Breast Cancer than the control healthy women. Among the life styles, smoking, alcohol consumption, dietary habits (premenopausal women with higher animal proteins, and red meat were associated with increased risk of breast cancer and less found high intakes of polyunsaturated fatty acids-PUFA, beta carotene, soya proteins, total soya products) played a major role among Propositus Breast Cancer incidence than control. Family history of different types of cancer + some % of degenerative diseases (hereditary) will be a risk factor for breast cancer among Mexican Women along with such as childbearing history, breast feeding etc.,. (Non-Heredity) Women with second generation with a history of breast cancer or at some degenerative diseases possibly are at increased risk of the disease, most will never develop breast cancer, and most who do will be aged 50 when their cancer is diagnosed.

Keywords: Breast cancer. Case-control study

### Posters

#### **P70** **Dissecting Hypoxia Regulated Non-Coding RNAs in Breast Cancer**

Hani Choudhry

*Department of Biochemistry, Faculty of Science, Center of Innovation in Personalized Medicine, Saudi Arabia*

Hypoxia is a hallmark of most solid tumours and associated with poor clinical outcome. In hypoxic condition, cells induce hypoxia-inducible factor (HIF) that regulates expression of hundreds of genes to allow cells to adapt and survive in low level of oxygen. To date, little is known about the role and function of many non-coding RNAs in hypoxia.

We performed a comprehensive analysis on hypoxia transcription landscape and epigenetic markers of transcriptional activation in MCF-7 breast cancer cells under hypoxia (1% O<sub>2</sub>) using next generation sequencing. Analyses revealed that all classes of non-coding RNA are profoundly regulated by hypoxia including piwiRNA, miRNA, tRNA, and sn/snoRNA. Analysis revealed downregulation of snRNAs and tRNAs in hypoxia, whereas miRNAs, antisense transcripts and lncRNAs are globally upregulated in hypoxia. Large number of lncRNAs is found overexpressed under hypoxia and associated with HIF binding, suggesting direct transcriptional regulation of lncRNAs by HIF. NEAT1 is among the most hypoxia induced lncRNA and a direct transcriptional target of HIF-2 $\alpha$ . We confirmed the hypoxic upregulation of NEAT1 in 13 breast cancer cell lines and in tumour xenografts models treated with bevacizumab. NEAT1 increases the formation of nuclear paraspeckles bodies and contributes to increase cell proliferation, cell survival, and inhibit apoptosis. In addition, NEAT1 is required to retain hypoxia induced hyper edited Junctional Adhesion Molecule A (JAM-A) mRNA in nucleus to inhibit its translation. In a large breast cancers cohort (n=2000), high expression of NEAT1 is linked with poor prognosis and with different clinicopathological features.

Our results extend the knowledge of the hypoxic transcriptional response into the spectrum of non-coding transcripts. These findings provide novel mechanisms of transcriptional regulation in hypoxic tumours through non-coding RNAs and open new avenues to find novel pathways and targets to develop therapies for breast cancer.

Keywords: Hypoxia, NEAT1, Breast cancer

### Posters

#### P71 The Alternatives in Biodosimetry

Ahlem Messal

*Department of Applied Molecular Genetics (CMG), University of Science and Technology, Algeria*

The main objective of Biological Dosimetry is its applicability in radioprotection. The analysis of dicentric chromosome observed in metaphase cells arrested by Colcemid is the most reliable method for dose-assessment. However, with this technique cells exposed to high doses show a delay or impossibility to reach mitosis, and the limit of the technique is up to 5-6 Gy. For higher doses the analysis chromosome aberrations observed in chromosomes prematurely condensed from interphase cells G2 is being proposed as an alternative.

In present study, twelve different experimental conditions were analysed, with three different approaches. We proved that when Premature Chromosome Condensation with Calyculin-A (PCC-CA) is used jointly with Colcemid, if only metaphase cells are considered similar frequencies of dicentrics are obtained respect those obtained using the conventional mitotic arrest with Colcemid.

The results here presented seem to indicate that when PCC-CA is used if metaphase cells are considered similar dose-effect curves will be obtained by both methods.

Keywords: Dosimetry, dose-effect curve, Premature Chromosome Condensation with Calyculin-A

### Posters

#### **P72** Dissection of The Germline Component of Cancer Susceptibility Across Tumors and Individuals

Jan Korbell<sup>1</sup>, Xavier Estivill<sup>2</sup>

<sup>1</sup>European Molecular Biology Laboratory (EMBL), Heidelberg, Germany; <sup>2</sup>Sidra Medical Research Centre, Qatar

Cancer risk has mainly been investigated in genome-wide association scans (GWAS) of large cohorts, targeting common variants or known risk variants included on genotyping arrays. Conversely, cancer genome sequencing data has mainly investigated the landscape of somatic mutations, including mutational spectra and their impact on drug susceptibility and molecular states such as transcriptomes. Rare germline variation is not accessible to classical array-based GWAS but it can be effectively studied by new analysis approaches applied to existing whole-genome sequencing (WGS) or whole-exome sequencing (WES) datasets. The International Cancer Genome Consortium (ICGC) PanCancer dataset generated by the Pancancer Analysis of Whole Genomes (PCAWG) study aims to provide a comprehensive dataset of somatic and germline variants across ~2,800 cancer patients across 20 different cancer types. I will provide an update on the current status, aims and preliminary results of the PACWG-8 working group on the germline cancer genome. PCAWG-8 is currently in the process of devising approaches to reconstructing the germline genome genotypes and haplotypes for ~2,800 cancer patients, with available WGS data. These data are used to define germline risk factors in coding and non-coding regions, and to examine how somatic mutation patterns and profiles of gene expression associate with germline genotypes. This research should provide new insights into cancer risk mechanisms, and help establish commonalities and differences in molecular processes leading to cancer in different tumor entities studied in PCAWG.

Xavier Estivill and Jan Korbell and the Pancancer Analysis of Whole Genomes (PCAWG) germline working group

Keywords: Whole genome sequencing, Whole exome sequencing, Database



### Posters

#### **P73 Central Nervous System Primitive Neuroectodermal Tumors and Diabetes Comorbidity in Arabian Gulf Population**

M Fayez Alhomsy, Amer Al Homssi  
*University Hospital Sharjah, UAE*

More than two hundred (209) cases of central nervous system primitive neuroectodermal tumors (CNS-PNET) are identified in our pathology archives over a period of sixteen years. Files of these patients are reviewed to check co-morbidity with diabetes mellitus (DM).

Three subtypes of CNS-PNET with specific cytogenetic findings are usually identified. Both karyotypic analysis and the fluorescence in situ hybridization (FISH) procedure on paraffin-embedded tissues are used looking for the presence of *i(17q)*, and deletions of 22. Medullocytoma is characterized by areas of 'lipomatous differentiation', low proliferative potential, and manifestation in adults. Atypical teratoid/rhabdoid tumor (ATT/RT) is characterized by the presence of rhabdoid cell differentiation and triad immunohistochemical analysis of epithelial membrane antigen (EMA), vimentin, and smooth muscle actin (SMA). Cytogenetic studies show that the most frequent cytogenetic abnormality in medulloblastomas is isochromosome 17q, and in ATT/RT is deletion in chromosome 22. At the onset of the symptoms of CNS-PNET fourteen patients had type 1 DM, two patients had maturity onset diabetes of the young (MODY), and one patient had type 2 DM. The overall incidence of DM in this group of patients is (17/209) 8.1%.

Although this incidence may appear lower than expected, the prevalence throughout the later years may become much higher as the incidence and prevalence rates of DM in the Arabian Gulf population are in excess of 23-27%. This behooves us to conduct a collaborative study with other Arabian Gulf Countries (GCC) and other Middle Eastern Countries at large.

Keywords: CNS-PET, Diabetes

### Posters

#### **P74** Cytotoxic Effect of *Fagonia Indica* Grown in UAE Against HELA Cancer Cell Line in Vitro

Haya Alnims, Hamda Shaddad  
*University of Modern Sciences, Dubai, UAE*

*Fagonia indica* (Family Zygophyllaceae) is a small spiny under- shrub, mostly found in the desert of Asia and Africa. It is used in folk medicine for cancer as well as most of the disorders considered to be due to poisons. The cytotoxic activity of plant extract (Hexan) was assessed against human Cervical cancer (Hela) cell lines by using the MTT assay. eight concentrations (2, 3, 10, 100, 125, 150, 175 and 300 µg/mL) of plant extract were assessed through one incubation time period ( 24h) for Hela cell line. The results revealed that the eight concentrations of plant extract showed anti-tumor properties in a concentrations-dependent manner. Among these concentrations, 150µl/ml was the most effective in producing percentage of growth inhibition (PGI) in Hela cancer cell line

Keywords: Cytotoxic, *Fagonia indica*

### Posters

#### **P75** Molecular and Hematological Characterization of acquired Alpha Thalassemia among Sudanese Leukemic Patients

Leena Mirghani, Babiker Mohamed  
*Aineel University, Faculty of Medical Lab.Sciences, Sudan*

Acquired alpha thalassemia (hemoglobin H (HbH) disease) is a rare complication of neoplastic chronic myeloid disorders especially Myelodysplastic syndrome and other types of leukemia. The association between alpha thalassemia and leukemia type or prognosis is defined by the presence of HbH inclusion which indicated by down regulation of alpha globin gene expression.

This study aimed to determine the frequency of the acquired alpha thalassemia (HbH disease) among Sudanese leukemic patients and studying the hematological and molecular characteristics features of this disorder.

This descriptive study include 135 Sudanese leukemic patients having a different type of leukemias, male and female with various age groups was enrolled in different hematological and molecular tests. A total of 129 samples from Sudanese leukemic patients enrolled in this study for quantitation of alpha\beta ratio, HbH preparation and CBC. The frequency of HbH inclusions among the study population was 27. % positive sample, the positive HbH preparation among each type of leukemia showed a higher frequency in AML (40.6%) followed by (35.0%) in CML while showing lower results in lymphoid leukemias (22.0% in ALL and 18.5% in CLL). The correlation was statistically significant with AML and CML.

The molecular analysis showed that there was a reduction in alpha \beta globin synthesis ratios which associated with the hematologic changes and the presence of HbH inclusion in leukemic patients (mean  $0.11 \pm SD$ )

The finding of the present study showed that the frequency of HbH inclusion among leukemic patients was 27.9% of the total population. There was a statistical significant correlation between the type of leukemia and the frequency of HbH inclusions.

Keywords: Alpha thalassemia, HbH inclusions, Leukemia

### Posters

#### **P76 Counterplay between Vitamin D and Busulphan Metabolism in The Preconditioning for Stem Cells Transplantation**

Moustapha Hassan<sup>1</sup>, Wenyi Zheng<sup>1</sup>, Ibrahim El-Serafi<sup>2</sup>, Ahmed El-Serafi<sup>3</sup>

<sup>1</sup>Department of Laboratory Medicine, Karolinska Institute, Sweden; <sup>2</sup>Faculty of Medicine, Port-Said University, Egypt;

<sup>3</sup>University of Sharjah, UAE

Vitamin D is a mysterious molecule which seems to have a role in many tissues. As exposure to the sun is the main producer of this vitamin, it is not surprising that modern life style affects the vitamin level. Hereby we evaluated the level of vitamin D in the blood of patients undergoing the preconditioning regimen prior to stem cell transplantation with busulphan. The latter is a cytostatic drug that has a very narrow therapeutic range and thus requires intensive monitoring. The correlation between vitamin D and busulphan accumulation in the body has never been described before.

Venous blood samples from 51 patients were collected. The level of Bu in plasma was estimated using by HPLC/GC after drug extraction. The area under the curve was determined by measuring the plasma concentrations at different time points by using the software WinNonlin. Vit D was measured using ELISA technique. student t-test was used to determine the statistical significance. p-value less than 0.05 in two tail test was considered as significant.

Patients with low area under the curve for the drug had the highest level of the vitamin. This correlation was very clear in children less than 5 years old. Patients were classified according to the underlying disease and showed variable levels of vitamin D. The inverse relationship between the area under the curve and the vitamin level was clear in neuroblastoma while absent in thalassemia.

Vitamin D may have an effect on the metabolism of busulfan. We explain our results by the induction of liver enzymes which affects the drug metabolism. We recommend the evaluation of vitamin D before the administration of busulphan.

Keywords: Vitamin D, Busulfan, Stem cell transplantation

### Posters

#### **P77 Genetic Variants in The 53BP1 Gene and Breast Cancer Risk**

Abdu Adam<sup>1</sup>, Awatif Siddig Salih<sup>2</sup>

<sup>1</sup>*UAE University, UAE;* <sup>2</sup>*Qassim University, Saudi Arabia*

TP53BP1 is a key component of radiation-induced DNA damage repair. The purpose of this study was to evaluate the significance of a known common single nucleotide polymorphism in this gene (rs560191) in patients with breast cancer. Recent data indicate that several polymorphisms of key regulators from the DNA damage repair pathway (i.e. 53BP1) are associated with cancer development susceptibility.

In the single locus analyses, none of the polymorphisms achieved significant difference in the genotype distributions between the patients and the controls ( $P = 0.38$  and  $P = 0.16$  for Glu353Asp and Gly421Ser respectively). Multivariate logistic regression analyses revealed that a non-significantly increased risk of breast cancer was associated with the variant genotypes of P53BP1 Gly412Ser, adjusted OR = 1.39 (95% CI 0.65-3.00) for 412 Gly/Ser – 1.76 (95% CI 0.80–3.90) for 412 Ser/Ser. Also for 353Glu/Asp and 353 Asp/Asp genotype, were not associated with breast cancer risk adjusted OR = 1.57 (95% CI 0.74-3.31) and 1.60(0.57- 4.52) respectively. In the subgroup analyses, we found that the variant genotype of P53BP1 412 Ser/Ser is associated with almost increased risk of breast cancer with patients who are older than 50 years  $P = 0.08$  [adjusted OR = 4.00

In this study, we found that P53BP1Ser/Ser genotype carrier in the subgroup of women 50 years and older and those who have P53BP1Ser alleles in patients were at high risk compared to control group in the same age. In relation to age, the genotypic and allelic frequencies of P53BP1Glu353Asp locus revealed no association with breast cancer. In the literature, the association of P53BP1 polymorphisms and age was not available.

Keywords: Breast cancer, p53BP1

### Posters

#### **P78** FOXP3 Gene Promoter Polymorphism in Breast Cancer Patients in Basrah City/Iraq

Mohamad Alhajaj, Taif Al Battat

*Basrah University, Iraq*

The research was designed to investigate a polymorphism (rs3761548) and incidence of breast cancer in Basrah City in the south of Iraq. Genetic polymorphism was evaluated in 100 blood samples collected from female breast cancer patients from many hospitals (Basrah City), and 100 controls by allelic -specific PCR. We noticed that the genotype frequency was 63% and 57% for CC homozygote, 26% and 14% for CA heterozygote and 11% and 33% for AA homozygote in control and patient respectively. It was also found by statistical analysis that there is a positive association for homozygous AA (OR=3,9851 ,95%CI=1.8778 to 8.4569 ) in relation to breast cancer susceptibility .

Keywords: Breast cancer, FOXP3

### Posters

#### P80 A Genetic Overview of 21 Y-STR Markers in UAE Population

Mohammad Alenizi<sup>1</sup>, Venkata Lakshmi<sup>2</sup>, Muhammad Nazir<sup>2</sup>, Sheikha Hassan Sanqoor<sup>3</sup>

<sup>1</sup>General Department of Criminal Evidences Identification Department, Kuwait; <sup>2</sup>College of Biotechnology, University of Modern Sciences, Dubai, UAE; <sup>3</sup>Gen. Dep. of Forensic Science and Criminology, Dubai Police, UAE

This study assessed Y-STR (Short tandem repeats) population variation in the UAE that could provide relevant genetic diversity and forensic information for the Emirates population. This study analyzed 278 unrelated, male individuals from UAE populations for 23 Y STR markers. Blood samples with informed consent, were collected from UAE male individuals and placed on FTA® cards (Whatman, UK) following the lab's standard operating protocol. Amplification of 23 Y-STR loci was performed on a GeneAmp PCR System 9700 thermal cyclers (Life Technologies) using the reagents in the PowerPlex®Y23 System (Promega Corporation, Madison, WI) and followed the manufacturer's recommended protocol. The detection of amplified fragments was performed on Applied Biosystems 3500xL Genetic Analyzer using POP-41 polymer and a 36-cm 3500xL 24-capillary array. Data were analyzed with GeneMapper® ID-X Software v1.4 software (Life Technologies). Population based analyses were performed using the open source R statistical computing program, which include; number of alleles per marker per population, allele frequencies, and haplotype counts. The results suggested that the UAE population tends to show a higher degree of haplotype sharing between its individuals compared to other populations and the distribution of Y STR variability can provide the information about geographic and ethnic diversity for different populations.

Keywords: STR, Population genetics

### Posters

#### **P81** The Association of Single Nucleotide Polymorphisms at the PON1 Gene with Susceptibility to Breast Cancer in Iranian Patients

Shirin Shahbazi

*Tarbiat Modares University, Iran*

Paraoxonase 1 (PON1) is an enzyme that destroys oxidised-lipids. It is composed of 354 amino acids and is encoded by the PON1 gene located at 7q21.3. The exonic Q192R polymorphism of PON1 affects enzyme activity, varying by over 40 fold between individuals. Several studies have described a connection between Q192R and increased risk for breast cancer.

In a case-control design, we assessed the association of PON1-Q192R with the risk of breast cancer. Sixty-eight breast cancer patients and 83 healthy women without family history of breast cancer were recruited to the study. Genotyping was performed by ARMS-PCR using a set of four primers. PCR product size of common primers was 354 bp. Amplification of A allele specific primers and G allele specific primers result in a 239 bp and 168 bp fragments, respectively. Statistical analysis was done by SPSS V16-software. Odds ratio (OR) was evaluated and the 95% confidence interval (CI) was used to estimate the precision of the OR.

The accuracy of the ARMS assay was confirmed by DNA sequencing of randomly selected representative samples. The allele frequency of G allele was determined 0.78 and 0.73 in cases and controls, respectively. Prevalence of the QQ genotype was 60.3% in cases and 55.5% in controls. In comparison with the QQ genotype, the QR genotype was not significantly associated with breast cancer risk (OR 0.89, 95% CI 0.45 to 1.77), whereas the RR genotype was associated with a reduced risk (OR 0.48, 95% CI 0.11 to 1.98). PON1 plays prominent role in various diseases such as atherosclerosis. Less is known about the effect of the Q192R SNP of PON1 on breast cancer and studies have been conflicting. Here, we show that Q192R might contribute to the lower risk of breast cancer.

Keywords: Breast cancer, PON1, Case-control study, ARMS assay



### Posters

#### **P82 Development Of Biological Assays to Detect Cancer Biomarkers and Tumor Sensitivity: A New Era In Setting Up Preventive- And Personalized- Medicine**

Firouz Darroudi

*College of North Atlantic-Qatar, Qatar*

Different cytogenetic assays were developed using human peripheral blood lymphocytes and tumors to detect biomarkers for cancer of different origins, as well as to detect chemo- and radiation- sensitivity of tumors and cancer patients.

G1 and G2 assays in metaphases, micronuclei in binucleated cells, premature chromosome condensation (PCC) in interphase of normal cells and those derived from tumor biopsies, and multi-color fluorescence in situ hybridization (FISH) by using whole genome chromosome painting assay were applied in this study.

Results obtained using a large number of cancer patients revealed these assays have the potential to be used at a very low cost and in a short period of time for monitoring studies of a large number of cohorts to search for cancer-prone individuals. G2 assay and micronuclei could successfully be implemented to detect Xeroderma pigmentosum, Retinoblastoma, Ataxia telangiectasia, Artemis, Breast cancer, Wilms tumor, Colorectal, polyposis coli and Roberts cancer patients.

In addition, G2 radio-sensitivity assay could discriminate between Aplastic- and Fanconi- anemia patients; and could design accurately a better (life-saving) radio- and chemo-therapy regimen for these patients.

The analysis of PCC and multi-color FISH techniques in primary cervical carcinoma at different stages of progression revealed for the first time chromosome-karyotype directly prepared from cervical tumor biopsies in less than 2 hours after surgery. A positive trend was found between stage advancement of cervical tumors and higher frequencies of numerical and structural aberrations.

The combined assay has the potential to detect cancer biomarker(s) and it can also be used to elucidate the sensitivity of tumor as well as lymphocytes of patients to radio- and/or chemo-therapy treatment regimen.

The result obtained are clearly indicating a new line of medical research program with the potential to pave the way toward generating preventive- and personalized- medicine for cancer patients.

Keywords: Biomarkers, FISH

### Posters

#### **P83 Identification of a Novel HLA-A Allele, HLA-A\*01:195, in a UAE National**

Habiba Alsafar<sup>1</sup>, Wael Abdrabou<sup>1</sup>, Ini-Isabee Witzel<sup>1</sup>, Guan Tay<sup>2</sup>, Agnieszka Paduch<sup>3</sup>

<sup>1</sup>Department of Biomedical Engineering, Khalifa University, UAE; <sup>2</sup>Centre for Forensic Science, University of Western Australia, Crawley, Western Australia; <sup>3</sup>Transplant Diagnostics, Thermo Fisher Scientific, Hennigsdorf, Germany

The Human Leukocyte Antigen (HLA) genes are the most polymorphic genes in the human genome. The three major HLA class I genes, HLA-A, -B and -C, play a key role in histocompatibility. While conducting a study of the MHC complex to provide new insights into mutations that may predispose to autoimmune disease in the population of United Arab Emirates (UAE), a novel variant of the HLA-A\*01 allele was discovered.

Genomic DNA was extracted from saliva samples collected from UAE nationals. Exons 2, 3 and 4 of the HLA-A, -B and -C loci were amplified using the (ABI) GeneAmp PCR 9700 system and sequenced using the SeCore HLA Kit (Thermo Fisher). Capillary gel electrophoresis was carried out on the ABI 3500 Genetic Analyzer. Sequences were analyzed using the uTYPE software and the online tools, SIFT and I-Mutant, were used to predict the effect of the amino acid substitution on the function and structure of the novel protein.

A novel polymorphic site in exon 3 of HLA-A locus was identified. The new single nucleotide polymorphism (442A>G, Ile124Val) distinguishes this new allele from its closest match, the relatively common HLA-A\*01:01:01:01 allele. The mutation results in a missense mutation that changes the Isoleucine at codon 124 of the  $\alpha 1$  chain of the mature HLA protein to Valine. The I124V substitution is predicted to have deleterious effect on HLA-A protein function with a probability for Valine at this site of  $p=0.03$ . The change is also predicted to have a destabilizing effect on its structure with a free energy change ( $\Delta G$ ) value of - 1.15 Kcal/mol for the novel amino acid.

The novel HLA-A\*01 allele was accepted by GenBank and was assigned Accession Number KT220195. The allele was officially designated as HLA-A\*01:195 by the WHO Nomenclature Committee.

Keywords:HLA

### Posters

#### **P84 Novel Compound Heterozygous Mutations In ENO3 Gene Cause reduced beta enolase Activity And Are Associated with Facial Weakness and Exercise Intolerance in Three Siblings**

Lihadh Al-Gazali<sup>1</sup>, Shozeb Haider<sup>2</sup>, Fedah Emad<sup>1</sup>, Anne John<sup>3</sup>, Barira Islam<sup>2</sup>, Jozef Hertecant<sup>4</sup>, Bassam Ali<sup>3</sup>, Ahmed Alghafri<sup>3</sup>

<sup>1</sup>Department of Paediatrics, College of Medicine and Health Sciences, UAE; <sup>2</sup>UCL School of Pharmacy, London, UK; <sup>3</sup>Department of Pathology, College of Medicine and Health Sciences, United Arab Emirates; <sup>4</sup>Department of Paediatrics, Tawam Hospital, Al-Ain, United Arab Emirates

Beta-enolase deficiency is a rare autosomal recessive glycogen storage disorder characterized by general muscle weakness and exercise induced myalgia. Mutations in the ENO3 gene have been shown to cause this type of glycogen storage disease which was named type 13 with only three reported cases in the literature.

In this study, we clinically evaluated three siblings of an Emirati family with facial weakness and exercise intolerance. Exome sequencing was used to identify the causative gene and mutations followed by Sanger sequencing to confirm segregation in the family. Beta-enolase activities of the bacterially expressed wild type and mutant proteins were measured using colorimetric/ fluorometric assay kit. Protein conservation and structural analysis were performed in silico on the identified mutations.

Novel double heterozygous mutations were detected in the three affected siblings [c.1204G>A (p.R403H) and c.786-787insTCA (p.S263dup)] at exons 8 and 11 of the ENO3 gene, respectively. The parents were found to be heterozygous for one of the two mutations; the duplication mutation was inherited from the father and the substitution missense mutation was inherited from the mother. Pathogenicity was supported by bioinformatics analyses showing that R403H and S263dup affect conserved amino acid residues lying in close proximity to important domains involved in enzyme activation. In addition, the bacterially expressed mutant proteins exhibited lower beta-enolase enzymatic activities compared to wild type [46.5% for R403H (p-value > 0.005) and 36.9% for S263dup (p-value > 0.05)] providing further evidence on their pathogenicity.

We identified two novel compound heterozygous mutations in the ENO3 gene underlying the rare autosomal condition, glycogen storage disorder type 13. We suggest this condition should be added to the differential diagnosis of facial weakness in childhood.

Keywords: Glycogen storage disorder, ENO3

### Posters

#### **P85** A Study of the Influence of Single Nucleotide Gene Polymorphism on the Risk of Hypertension

Naglaa Soliman, Neveen Hemimi  
*Dubai Medical College for Girls, UAE*

Large number of genes possesses alleles that may affect blood pressure in humans. Various studies have reported the linkage of hypertension to many gene polymorphisms including genes of endothelial nitric oxide synthase (eNOS), angiotensinogen (AGT), lipoprotein lipase (LPL), and methyl tetrahydrofolate reductase (MTHFR), but we couldn't find a study of combined effect of these gene polymorphisms on risk of hypertension. Aim of the study: In the present study we aimed to examine and compare the association of hypertension with 5 single nucleotide polymorphisms (SNPs); eNOS rs1799983, AGT rs699, LPL rs320, MTHFR rs180113338 and MTHFR rs1801131.

The SNPs were genotyped in 60 hypertensive and 66 control subjects using polymerase chain reaction and restriction fragment polymorphism followed by agarose gel electrophoresis. Results: eNOS rs1799983 and AGTrs699 were found to be significantly associated with hypertension  $p < 0.05$ , OR (95% CI) 2.7(1.27-5.60); and 2.3 (1.00-5.10) respectively. The other SNPs have shown a tendency to increase the risk with OR between 1.5 and 2.2 with no statistical significance. The risk of hypertension was significantly elevated with combined polymorphism of eNOS rs1799983 with other SNPs as Rs1801131 OR 2.2 (0.70-2.69), rs699 OR 2.6 (0.3-22.99), rs320 OR 4.2 (1.88-9.41) and with rs1801133 38 OR 4.8 (1.19-19.27).

We concluded that combined appearance of risky alleles may allow determining the genetic profile predictive of hypertension.

Keywords: Hypertension, PCR-RFLP

### Posters

#### **P86 Association of LL-1B Polymorphism and Aggressive Periodontitis in The Algerian Population**

Khalida Hachmaoui<sup>1</sup>, Boubaker Boukerzaza<sup>2</sup>, Abdallah Boudjema<sup>3</sup>, Fatima Zohra Benaissa<sup>2</sup>, Hayet Drabla-Ouahrani<sup>2</sup>, Kawther Nourelhouda Boukortt<sup>3</sup>, Nadja Saidi-Ouahrani<sup>3</sup>

<sup>1</sup> Service de parodontologie Département de chirurgie dentaire EPSP d'Oran, Oran, Algeria; <sup>2</sup>Service de parodontologie Département de chirurgie dentaire CHU de Sétif, Oran, Algeria.; <sup>3</sup>Laboratoire de Génétique Moléculaire et Cellulaire, Université des Sciences et de la Technologie d'Oran-Mohamed BOUDIAF-USTOMB-, Oran, Algeria.

Periodontitis is a pathological multifactorial. It is recognized that microbial factors cannot be held solely responsible for periodontitis. The two major causes are pathogens and the host's genetic heritage. Genetic factors in part explain the clinical variability in periodontitis; however, a genetic basis has not been clearly defined. Search of susceptibility to the disease genotype is the subject of several studies on different genes related to the immune system. Among these genes those of the IL-1 cytokine that plays an important role in the pathogenesis of periodontitis. Our approach is the "case-control" study of IL1B Snp: C + 3954T (rs1143634T) gene polymorphism. The purpose of this study is the investigation of a possible association between IL-1B gene polymorphism and the risk of aggressive periodontitis in Algerian. We have achieved real-time PCR using Taq Man technology. Our sample consists of 188 individuals, including 60 DNA belonging to patients with periodontitis (cases) and 128 without periodontitis (controls). Significant differences were found in the frequencies of the minor alleles of cases of aggressive periodontitis compared to healthy controls  $p < 0.05$ . The statistical analysis of genotype showed a probable association between this polymorphism and periodontitis in our sample study. Gene polymorphism studied seems to be associated with a predisposition to aggressive periodontitis in the Algerian population.

Keywords: Periodontitis, IL1B

### Posters

#### **P87 Association of APOA5 Rs662799 and Rs3135506 Polymorphisms With Arterial Hypertension In Moroccan Patients**

Sanaa Ouatou<sup>1</sup>, Mohammed El Khasmi<sup>2</sup>, Hicham Charoute<sup>3</sup>, Hassan Rouba<sup>3</sup>, Abdelhamid Barakat<sup>2</sup>

<sup>1</sup>Institut Pasteur Casablanca Maroc, Morocco; <sup>2</sup>Laboratoire de Physiologie et Genetique Moleculaire, Faculte des Sciences Ben; <sup>3</sup>Laboratoire de Genetique Moleculaire et Humaine, Departement de Recherche

Arterial hypertension (AHT) is one of major public health problem in the world, it will affect more than 1.56 billion adults worldwide in 2025. Hypertensive individuals have higher risk to develop coronary artery disease (CAD), cerebrovascular disease and heart failure than normotensive persons. AHT is a polygenic and multifactorial disease resulting from combination between genetics and environment factors. Apolipoprotein A5 (APOA5) gene, related to the metabolism of triglycerides in several different ethnic groups. The goal of the study is to investigate the association between the APOA5 polymorphisms and haplotypes with Arterial Hypertension in Moroccan patients.

The study was performed in 283 subjects, 149 patients with AHT and 134 controls. All subjects were genotyped for the APOA5 -1131 T C (rs662799), 56C G (rs3135506) and c.553G T (rs2075291) polymorphisms. All statistical analyses were performed using STATA software, version 11.0. and PLINK software, version 1.07.

There was a strong association between 1131T C and 56C G polymorphisms with AHT. The -1131T C and 56C G polymorphisms were significantly associated with increased systolic blood pressure (SBP) and triglycerides (TG) levels. There were 4 haplotypes with a frequency higher than 5%, constructed from APOA5 polymorphisms, with the following order: 1131T C, 56C G and c.553G T. Haplotype H1 (TCG) was associated with decreased risk of AHT, whereas the haplotypes H2 (CCG) and H4 (CGG) were significantly associated with an increased risk of AHT. Carriers of H1 haplotype had a lower SBP and DBP and TG. In contrast, significant elevated SBP, DBP and TG were found in H4 haplotypes carriers.

Our data demonstrate for the first time that several common SNPs in the APOA5 gene and their haplotypes are closely associated with modifications of blood pressure and serum lipid parameters in the AHT patient.

Keywords: Hypertension, APOA5, haplotype

### Posters

#### **P88** Associations of common SNPs in the SORT1, GCKR, LPL, APOA1, CETP, LDLR, APO genes with lipid trait levels in an Algerian Population Sample

Houssam Boulenouar<sup>1</sup>, Aline Meirhaeghe<sup>2</sup>, Nadhira Nadhira<sup>1</sup>, Hadjira Ouhaibi-Djellouli<sup>3</sup>, Leila Houti<sup>4</sup>, Imane Hamani-Medjaoui<sup>5</sup>, Djabaria Naïma Meroufel<sup>1</sup>, Sarah Aicha Lardjam-Hetraf<sup>1</sup>, Louisa Goumid<sup>2</sup>, Philippe Amouyel<sup>1</sup>, Philippe Amouyel<sup>2</sup>, Xavier Hermant<sup>1,2</sup>, Sounnia Mediene-Benchekor<sup>1</sup>

<sup>1</sup>Laboratoire de Génétique Moléculaire et Cellulaire, Université des Sciences et de Technologie d'Oran Mohamed Boudiaf, Algeria; <sup>2</sup>Institut Pasteur de Lille; Université Lille Nord de France, France; <sup>3</sup>Département de Biotechnologie, Faculté des Sciences de la Nature et de la Vie, Université d'Oran, Algeria; <sup>4</sup>Laboratoire des Systèmes d'Information en Santé, Université d'Oran, Oran, Algeria; <sup>5</sup>Caisse Nationale des Assurances Sociales des travailleurs salariés, Clinique Spécialisée en Orthopédie et Rééducation des Victimes des Accidents de Travail, Algeria

Genome-wide association studies have identified many lipid-associated loci primarily in European and Asian populations. In view of the differences between ethnic groups in terms of the frequency and impact of these variants, our objective was to evaluate the relationships between seven lipid-associated variants (considered individually and in combination) and serum triglyceride, total cholesterol, HDL- and LDL-cholesterol levels in an Algerian population sample (ISOR study, n=751). Methods: We selected eight SNPs located within or near the following genes: SORT1, GCKR, LPL, APOA1, CETP, LDLR, APOE and MLXIP for which we had a statistical power greater than 0.80 for at least one of the four lipid parameters in the ISOR study. Genotyping was performed using KASPar technology. Genetic variants were considered both individually and combined.

Three SNPs (in SORT1, CETP and GCKR) were individually associated with lipid level variations. Moreover, the combined risk allele scores for total cholesterol, triglyceride and LDL-C levels (encompassing between three and six SNPs) were associated with their corresponding lipid traits. Conclusion: Our study is the first to show that some of the lipid-associated loci in European populations are associated with lipid traits in Algerians. However, for most of the tested lipid-associated loci, we found that effect sizes observed here in an Algerian population differed from those reported in the literature for populations of European descent. Although our results will have to be confirmed in other North African populations, this study contributes to a better understanding of genetic susceptibility to lipid traits in Algeria.

### Posters

#### **P89 Mapping Genetic Research Among Non-communicable Disease Publications in Selected Arab Countries: First Step Towards A Guided Research Agenda**

Shahd Othman<sup>1</sup>, Soha Yazbek<sup>2</sup>, Abla Sibai<sup>1</sup>, Zeina Jamaluddine<sup>2</sup>

<sup>1</sup>*Epidemiology and Population Health, American University of Beirut, Beirut, Lebanon;* <sup>2</sup>*Medical Laboratory Sciences, American University of Beirut, Beirut, Lebanon*

In the Arab world, the response rate to non-communicable diseases (NCD), particularly policy response and implementation has been weak, despite the extensive epidemiological evidence highlighting the alarmingly increased prevalence of chronic diseases. Generating genetic information is key to promote efficient disease management strategies. We undertook a scoping review to generate a profile of the undertaken research on genetics of NCD publications in selected Arab countries. The purpose of this article is to examine and analyze the extent, range, and nature of published research, in order to identify the gaps in NCD-genetics research and inform policy action for NCD prevention and control.

The scoping review was conducted based on Arksey and O'Malley five stages methodological framework.

The search identified 569 articles that focus on NCD-genetics research in the selected Arab countries for the past 13 years (Jan 2000-Dec 2013). Across all the investigated countries, the most abundant research design conducted was descriptive and clinically focused, rather than etiologically focused ( $P < 0.05$ ). Country specific carrier and risk screening is not among the top researched. Genetic component of certain highly heritable diseases; diabetes, obesity, hypertension, chronic lung dysfunction and metabolic syndrome, are under investigated.

This scoping review identified many gaps for further research in the context of bioinformatics and GWAS. Research has to be redirected towards NCDs with the highest morbidity, heritability and health burden within each country. A focused research plan to include community genetics is required for its proper integration in the Arab community.

Keywords: Non-communicable diseases, Community genetics



### Posters

#### P90 NAT2 Phenotyping and Genotyping Among Emiratis

Yousef M. Abdulrazzaq<sup>1</sup>, Bassam R. Ali<sup>2</sup>, Mohammad Majed AlAhmad, Anne John<sup>2</sup>, Salim Bastaki<sup>3</sup>, Naheed Amir<sup>3</sup>  
<sup>1</sup>Department of Pediatrics, College of Medicine and Health Sciences, UAE University, UAE; <sup>2</sup>Department of Pathology, College of Medicine and Health Sciences, UAE University, UAE; <sup>3</sup>Department of Pharmacology, College of Medicine and Health Sciences, UAE University, UAE

Genetic polymorphisms in N-acetyltransferase-2 (NAT2) may modify the risk associated with carcinogen exposure, disease, drug response and toxicity. Limited studies have been carried out on NAT-2 polymorphisms among Emiratis and thus this study is to determine the alleles and genotypes frequencies and their correlation with acetylation phenotyping in Emiratis.

Five hundred subjects have been enrolled based on the maximum variability in data with confidence interval CI=5%. The subjects were asked to consume 300ml of a caffeinated soft drink or a cup of coffee and provide a buccal swap and a spot urine sample 2 hours later. Caffeine metabolites have been measured using HPLC to determine the phenotype status.

DNA isolation protocol has been carried out using Isohelix DNA isolation kit. NAT2 genotyping has been carried out by PCR-RFLP analysis. SPSS version 19 has been used for data entry and Spearman's rho statistical test was used for analysis.

The subjects' ages ranged from 16 to 50 years. Out of all subjects; 285 (50.5%) are the results of consanguineous marriages, 65 (22.8%) of them with first degree relative.

We found that (82.2%) of the subjects were slow metabolizers and (16.4%) were intermediate and (1.4%) were fast acetylators. Moreover, (78.2%) of our subjects were homozygote for mutant alleles genotyping, (17.6%) were heterozygote and (4.2%) were homozygous for the wild type genotyping.

The mutant alleles' frequency was 0.87 with allele 5 frequency=0.334, allele 6=0.105, allele 7=0.272 and allele 14=0.159. The wild type allele frequency was found to be 0.13. There is a significant correlation between phenotype and genotypes with 0.103 value (P value = 0.022; 95% CI of differences using Spearman's rho statistical test). There are a high percentage of slow acetylators among Emiratis which is directly related to the presence of mutant alleles in NAT2 gene.

Keywords:NAT2, Acetylators, PCR-RFLP

### Posters

#### P91 Allele Frequency of Angiotensin-converting Enzyme Insertion/deletion Polymorphism in Emirati Population

Ahmed Hassoun<sup>1</sup>, Wael Abdrabou<sup>2</sup>, Aurelie Mawart<sup>2</sup>, Guan Tay<sup>3</sup>, Hiba Alblooshi<sup>3</sup>, Habiba Al Safar<sup>2</sup>, Naushad Rais<sup>4</sup>  
<sup>1</sup>Dubai Diabetes Centre, Dubai Health Authority, UAE; <sup>2</sup>Faculty of Biomedical Engineering, Khalifa University, UAE; <sup>3</sup>Centre for Forensic Science, University of Western Australia, Perth, Australia; <sup>4</sup>School of Life Sciences, Manipal University, Dubai, UAE

Angiotensin-Converting Enzyme (ACE) is a metalloproteinase that catalyzes Angiotensin I into Angiotensin II. Insertion/Deletion is the most studied polymorphism of ACE and it had been linked to diseases such as Type 2 Diabetes and hypertension. In this study, we analyze the genotype distribution and allele frequency of ACE I/D among Emirati population and compare our results with data from different populations around the world.

Genomic DNA was extracted from 200 unrelated healthy saliva samples of an Emirati population (100 females and 100 males). ACE I/D polymorphism genotype was performed through PCR based method followed by gel electrophoresis while a meta-analysis was conducted to collect ACE genotype data from other populations worldwide for comparison purposes. Differences amongst populations were analyzed using a Pearson's X2 test.

Genotype distribution for Emirati population are II = 11%, ID = 46.5% and DD = 42.5% with allele frequencies (I) = 0.34 and (D) = 0.66. Our comparison of genotype distribution with other population highlights some similarity of Emirati population with some Arab populations (Kuwaitis, Sudanese, Syrians, Lebanese ( $p > 0.2$ ), Bahrainis ( $p = 0.2$ ), and Israelis ( $p = 0.09$ )), African populations (Somalis ( $p = 0.152$ ) and Nigerians ( $p > 0.6$ )), European Mediterranean populations (Italians, Greeks and Spanish ( $p > 0.2$ )) and finally American populations ( $p = 0.5$ ).

Our Emirati population shows high heterogeneity that could be explained by genetic mixture with African, European and Asian population through its history. I/D polymorphism of ACE seems not enough to explain prevalence disease in UAE population.

Keywords: ACE, Population genetics

### Posters

#### **P92** Next Generation Sequencing Identified a Novel GNPTG Mutation Underlying Mucopolidosis III Gamma in a Large Consanguineous Pakistani Family

Muhammad Naeem, Muhammad Aman

*Medical Genetics Research Lab, Quaid-i-Azam University, Islamabad, Pakistan*

Mucopolidosis III gamma (ML III gamma) is a rare autosomal recessive disorder characterized by radiographic evidence of mild to moderate dysostosis multiplex, progressive joint stiffness and pain, scoliosis and normal to mildly impaired cognitive development. Cardiac valve involvement and respiratory complications can be significant. ML III gamma is caused by mutations in the GNPTG, which encodes the gamma subunit of the enzyme N-acetylglucosamine-1-phosphotransferase. The current study was aimed to identify the underlying cause of mucopolidosis phenotype in a large consanguineous Pakistani family.

We ascertained seven individuals affected with ML III gamma from a Pakistani family. After obtaining informed consent, genomic DNA was isolated from all patients and five normal individuals of the family. Linkage study was performed by whole genome SNP genotyping in three affected and two normal individuals of the family using Affymetrix Human SNP Array 6.0. In order to identify the causative mutation, whole exome sequencing of genomic DNA from one affected individual was performed on Illumina HiSeq2000 platform (Illumina, USA) using SureSelect V4 kit (Agilent Technologies, USA).

The affected individuals showed clinical features of MLIII gamma, including joint stiffness, vertebral scoliosis and bilateral corneal clouding. Cardiac abnormalities were identified in one individual. Lung function, intelligence and an abdominal ultrasound were normal in all affected individuals. Whole genome SNP genotyping mapped the disease locus to chromosome 16p13.3. Whole exome sequencing identified a novel 4-bp deletion mutation in the GNPTG that was confirmed by Sanger sequencing. The mutation segregated in the family in agreement with autosomal recessive pattern.

We identified a novel mutation in the GNPTG as the underlying cause of MLIII gamma in a Pakistani family expanding the mutation spectrum and genotype phenotype correlation. This study supports the role of next generation sequencing technologies for the molecular diagnosis of rare inherited disorders.

Keywords: Mucopolidosis, GNPTG, Whole exome sequencing

### Posters

#### **P93 Impact of Apolipoprotein E Polymorphism In General Population and In Patients of Peripheral Arterial Disease In Constantine City**

Benlatreche Cherifa<sup>1</sup>, Ziada Hadia<sup>2</sup>, Khodja Djamel<sup>2</sup>, Boumendjel Sabrina<sup>1</sup>, Ouldjaoui Ahmed<sup>1</sup>, Sifi Karima<sup>1</sup>, Abadi Nordine<sup>1</sup>

<sup>1</sup>Biochemistry Service, Hospital Ibn Badis, Faculty of Medicine, Algeria; <sup>2</sup>Laboratory of Biology and Molecular Genetic, University of Constantine, Algeria

Apolipoprotein E has been one of the most studied genetic polymorphism, particularly for its effects on lipid profiles. Several epidemiological studies have identified that plasma concentrations of low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) are important predictors of myocardial infarction and coronary heart disease. The objective of this study was to evaluate the genetic polymorphism of apolipoprotein E and its effect on lipids profiles in normal population and in peripheral arterial disease.

This study was carried out on a total of 539 samples including 509 normal and 30 subjects with peripheral arterial disease in Constantine. The apoE DNA fragment was amplified by polymerase chain reaction (PCR). The PCR products were digested with restriction enzyme HhaI. The fragments of enzymatic restriction were separated by electrophoresis in polyacrylamide gel.

Mean level of lipid, as well as genetic of Apolipoprotein E were determined. The subjects having the genotype  $\epsilon 3/\epsilon 4$  compared with  $\epsilon 3/\epsilon 3$  had statistically significantly higher mean cholesterol ( $1.95 \pm 0.41$  mg/dl vs  $1.77 \pm 0.31$  mg/dl  $p < 0.01$ ), LDL-C ( $1.24 \pm 0.37$  mg/dl), vs ( $1.15 \pm 0.36$  mg/dl,  $p < 0.01$ ), TG ( $1.35 \pm 1.13$  vs  $1.15 \pm 0.57$  mg/dl  $p < 0.05$ ) and no differences in HDL cholesterol. Whereas the subjects who carries the genotype  $\epsilon 2/\epsilon 3$  have significantly lower mean of cholesterol and LDL ( $1.35 \pm 0.27$  vs  $1.77 \pm 0.31$  and  $0.85 \pm 0.22$  vs  $1.15 \pm 0.36$  respectively). No evidence of an association between apolipoprotein E polymorphism and peripheral arterial disease was observed. The apoE allele frequencies of patients and controls were 3.4% vs. 5.0% for  $\epsilon 2$ , 86.6% vs. 84.3% for  $\epsilon 3$ , and 10% vs. 10.7% for  $\epsilon 4$ .

These results indicate that apoE polymorphism has an influence on lipid profiles and no evidence of an association with peripheral arterial disease was observed.

Keywords: Apolipoprotein E, Lipoproteins, Peripheral artery disease

## Posters

### P94 Gangliosidosis GM1

Nasrin Ghasemi<sup>1</sup>, Yusef Hafeghati<sup>2</sup>, Pooneh Nikuei<sup>3</sup>

<sup>1</sup>Medical Genetic Department, Recurrent Abortion Research Center, Yazd, Iran; <sup>2</sup>Department of Genetic, Sarem Hospital, Tehran, Iran; <sup>3</sup>Hormozgan University of Medical Sciences, Iran

GM1 gangliosidosis is an inherited disorder that progressively destroys nerve cells in the brain and spinal cord. This disease is estimated to occur in 1 in 100,000 to 200,000 newborns.

The patient is a 4 years old girl. She was good till 7 months and from that time her disease began with convulsion, severe growth deficit, neurodevelopmental delay, hypotonia and later spasticity.

The finding in physical examination was coarse fascial features, flaring alae nasia, frontal bossing, long philtrum and prominent maxilla and hepatosplenomegaly in abdomen. In laboratory tests she had anemia with normal thyroid function tests, normal blood electrolytes and normal lactate and pyruvate. MRI showed hypersignal in both periventricular and cerebral white matter. Based on our findings the patient was investigated for storage disorders and enzyme activity showed that B-galactosidase enzyme activity in the leucocytes was severely reduced. Based on this report and clinical symptoms the diagnosis was GM1-gangliosidosis. Result of molecular analysis of GLB1 gene showed a homozygous splice mutation in intron 13 of GLB1 gene (c.1348-2A>G).

This disorder has an autosomal recessive inheritance pattern. Mutation in the  $\beta$ -galactosidase gene results in this disease. The pathology of the disease begins with the inability to cleave the terminal galactose from ganglioside and mucopolysaccharide, then accumulation of these products within lysosomes and then the storage disease. The diagnosis is confirmed by the assay of  $\beta$ -galactosidase in the peripheral leukocytes or in cultured skin fibroblasts. Prenatal diagnosis has been established based on the appearance of cultured amniotic fluid cells.

Keywords: Gangliosidosis, GLB1

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PAHGC 2016 Secretariat  
Meeting Minds Experts, United Arab Emirates  
Tel: +9714 4270492, Fax: +97144270493  
Website: [www.meetingmindsdubai.com](http://www.meetingmindsdubai.com)