CENTRE FOR ARAB GENOMIC STUDIES
A Division of Sheikh Hamdan Award for Medical Sciences

2nd PAN ARAB HUMAN GENETICS CONFERENCE

ABSTRACT BOOK

20 - 22
November 2007
Dubai, United Arab Emirates

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Scientific Program

Wednesday 21 November 2007

08.00 – 09.30	Registration
Session 1	**Leaders in Genomics and Healthcare**
09.30 – 10.00	**The Human Variome Project and Pilot Projects** Prof. Richard Cotton, The Human Variome Project
10.00 – 10.30	**Integration of Genomic Sciences and Genomic Medicine** Prof. Edison Liu, The Human Genome Organisation
10.30 – 11.00	**Newborn Screening in the Region** Dr. Danuta Krotoski, National Institutes of Health, USA
11.00 – 11.30	**Priorities, Publication and Credit** Dr. Myles Axton, Nature Genetics, USA
11.30 – 12.00	Coffee Break
Session 2	**Complex and Recessive Disorders in the Arab World**
12.00 – 12.30	**Genetic Disorders in Arab Populations** Dr. Ghazi O. Tadmouri, Centre for Arab Genomic Studies, UAE
12.30 – 13.00	**Advances in the Genetics of Type 2 Diabetes Mellitus** Prof. Riad Bayoumi, Sultan Qaboos University, Oman
13.00 – 13.30	**Delineation of the Clinical and Molecular Basis Underlying Several New Recessive Disorders in the UAE** Prof. Lihadh Al-Gazali, UAE University, UAE
13.30 – 14.30	Lunch Break
Session 3	**From Phenotypes to Genotypes**
14.30 – 14.50	**Mutation in WNT10A is Associated with an Autosomal Recessive Ectodermal Dysplasia: The Odonto-Onycho-Dermal Dysplasia** Prof. Andre Megarbane, Saint Joseph University, Lebanon
14.50 – 15.10	**Anhydrotic Ectodermal Dysplasia in Omani Families** Dr. Anna Rajab, Ministry of Health, Oman
15.10 – 15.30	**A Novel Approach for the Study of the Genetics of Hypertension in**

Arabs: Heritability and Linkage Analysis Results of "Oman Family Study"
Prof. Mohammad O. Hassan, Sultan Qaboos University, Oman

15.30 – 15.50 **A Whole-Genome Scan in a Large Family with Leukodystrophy and Oligodontia Reveals Linkage to 10q22**
Dr. Eliane Chouery, Saint Joseph University, Lebanon

15.50 – 16.10 Coffee Break

16.10 – 16.30 **Microarray as an Efficient Modern Molecular Tool in the Detection of Submicroscopic Genetic Abnormalities in Multiple Congenital Anomalies: Diagnosis and Prevention**
Dr. Sabitha Murthy, Al Wasl Hospital, United Arab Emirates

16.30 – 16.50 **Dominant Effect of Smoking on Airway Epithelium Gene Expression Profiles Among Individuals of European, African, Southeast Asian and Arabian Ancestries**
Prof. Lotfi Chouchane, Weill Cornell Medical College, Qatar

16.50 – 17.10 **Independent Introduction of Two Lactase Persistence Alleles into Human Populations Reflect Different History of Adaptation to Milk Culture**
Dr. Nabil S. Enattah, University of Helsinki, Finland

Thursday 22 November 2007

Session 4	**Bioethics and Human Genetics**
09.30 – 10.00	**International Bioethics and Human Genetics. The activities of UNESCO** Prof. Henk ten Have, UNESCO
10.00 – 10.20	**Ethics of Mutation Databases: Correctness in Reporting Genetic Variation and its Effects** Prof. Richard Cotton, The Human Variome Project
10.20 – 10.40	**Genetic Counseling in the Muslim World: The Challenges** Dr. Aida Al Aqeel, King Faisal Specialist Hospital and Research Centre, Saudi Arabia
10.40 – 11.00	**Ethical Concerns to the use of Pre-implantation Genetic Diagnosis in the Gulf Cooperative Council States** Dr. Hamza A. Eskandarani, King Faisal University, Saudi Arabia
11.00 – 11.20	**What is the Impact of Genetic Counseling and Prenatal Diagnosis in Genetic Diseases Prevention in an Arab Muslim Population?** Prof. Habiba Bouhamed Chaabouni, Charles Nicolle Hospital, Tunisia
11.20 – 11.40	**Prevention of Genetic Diseases: Understanding Families and Communities hold the Key for Success** Dr. Anna Rajab, Ministry of Health, Oman
11.40 – 12.00	Coffee Break
Session 5	**National Startegies for the Prevention of Genetic Disorders in the Region**
12.00 – 12.20	**Bahrain National Hereditary Diseases Strategy (1984-2007)** Dr. Shaikha Al-Arrayed, Salmaniya Medical Complex, Bahrain
12.20 – 12.40	**National Strategy for the Prevention of Genetic and Congenital Disorders in Jordan** Prof. Hanan Hamamy, National Center for Diabetes, Endocrinology and Genetics, Jordan
12.40 – 13.00	**Newborn Screening for Inborn Errors of Metabolism-Combining Molecular and Biochemical Testing: A Saudi Perspective** Dr. Moeen Al-Sayed, King Faisal Specialist Hospital and Research Center, Saudi Arabia
13.00 – 13.20	**Newborn Screening in Lebanon: 12 Years Experience**

Dr. Issam Khneisser, Saint Joseph University, Lebanon

13.20 – 13.40 **Genotype-Phenotype Correlation in Gaucher Disease: Strategy for Prevention and Therapy in Egypt**
Prof. Rabah Shawky, Ain Shams University, Egypt

13.40 – 14.45 Lunch Break

Session 6 **Fast Track Reports**

14.45 – 15.00 **ER Retention and Degradation of Mutated Proteins is a Common Mechanism in Numerous Loss-of-Function Recessive Diseases**
Dr. Bassam R. Ali, UAE University, United Arab Emirates

15.00 – 15.15 **Succesfull Preimplantation Diagnosis in a Family Affected with Zellweger Syndrome**
Dr. Moeen Al-Sayed, King Faisal Specialist Hospital and Research Center, Saudi Arabia

15.15 – 15.30 **Evaluation of Cell Free Fetal DNA in Maternal Plasma of Early and Late Onset Pre-Eclampsia Patients**
Dr. M.A. El Bassuoni, Menoufiyia University, Egypt

15.30 – 15.45 **Molecular Analysis of F8 in Lebanese Hemophilia A Patients: Report on 23 Novel Mutations and Phenotype-Genotype Correlation**
Dr. Claudia D. Khayat, Hotel Dieu de France Hospital, Lebanon

15.45 – 16.00 **Most Encountered Genetic Disorders in Egypt: Classification and Registry**
Dr. M. El-Ruby, National Research Centre, Egypt

16.00 – 16.30 Coffee Break

Closure

16.30 – 17.00 **Announcing the Dubai Declaration**

Keynote Speaker Profiles

Prof. Richard Cotton
President, Human Variome Project

Richard Cotton AM BAgSc., Ph.D, D.Sc. (Melbourne) initiated the Mutation Research Centre, now renamed the Genomic Disorders Research Centre, in January, 1996 (www.genomic.unimelb.edu.au). He has always been interested in the biochemical genetics of human disease and has recently focussed on mutation. Amongst his more notable scientific achievements are the conception, planning and execution of the fundamental experiment, which proved that when two immunoglobulin producing cells were fused, the immunoglobulin of both parental cells were produced in the hybrid. This laid the experimental and theoretical foundation for the widely used monoclonal antibody technique. He also conceived the widely used tetrohydrobiopterin (BH4) load test to identify the serious variants of PKU, but BH4 is currently being trialed in heart disease. He is particularly interested in improving mutation detection technologies to make them cheaper and simpler, so that they can be more widely applied, and holds several patents in the area. A recent development has been a method to detect DNA damaging compounds. He has written two books entitled "Mutation Detection", initiated the journal entitled "Human Mutation", and in 1991 initiated bi-yearly international workshops on Mutation Detection and in 1998 bi-yearly HUGO Mutation Detection Courses. In 1996 he has also started a worldwide initiative (The HUGO Mutation Detection Database Initiative, recently formed into the Human Genome Variation Society (HGVS) website: www.hgvs.org.) to capture and distribute lists of mutations. In June 2006, he convened a Meeting, co-sponsored by WHO, which initiated the Human Variome Project (www.humanvariomeproject.org). He can be contacted at (Telephone) +61 3 9288 2980 and Fax +61 3 9288 2989 and Email cotton@unimelb.edu.au.

Dr. Edison Liu
President, Human Genome Organisation

Dr. Edison Liu was born in Hong Kong, China, and emigrated to the United States in 1957. He received his bachelor's degree (Phi Beta Kappa) in chemistry and psychology from Stanford University where he remained to complete his M.D. in 1978. This was followed by internship and residency in internal medicine at Washington University, St. Louis, and clinical cancer fellowships at Stanford University (Oncology), and at the University of California at San Francisco (Hematology). He then pursued post-doctoral studies as a Damon-Runyan Cancer Research Fellow at the University of California at San Francisco in the laboratory of Dr. J. Michael Bishop identifying transforming genes in human leukemic states. In 1987, he joined the faculty of Medicine at the University of North Carolina at Chapel Hill. There, he developed programs in leukemia and breast cancer research centering on molecular epidemiology and cell signaling. In 2001, Dr. Liu assumed the position of Executive Director, Genome Institute of Singapore which is a flagship programme of the Biomedical Sciences Initiative of Singapore. At the GIS, he is building an international research institute of 300 individuals focused on integrating genomic sciences with cell and medical biology. His scientific investigations have spanned molecular epidemiology to molecular biochemistry of human oncogenes and his current scientific research investigates the dynamics of whole genome gene transcription that explains biological states in cancer.

Henk A.M.J. ten Have
Director, Division of Ethics of Science and Technology, UNESCO

Henk ten Have is Director of the Division of Ethics of Sciences and Technology at UNESCO, Paris, France. He has studied medicine and philosophy at Leiden University, the Netherlands. He received his medical degree in 1976 from Leiden University and his philosophy degree in 1983. He worked as researcher in the Pathology Laboratory, University of Leiden (1976-1977), as practising physician in the Municipal Health Services, City of Rotterdam (1978-1979), and as Professor of Philosophy in the Faculty of Medicine and Faculty of Health Sciences, University of Limburg, Maastricht (1982-1991). Since 1991 he has been Professor of Medical Ethics and Director of the Department of Ethics, Philosophy and History of Medicine in the University Medical Centre Nijmegen, the Netherlands. Since September 2003 he joined UNESCO as Director. He is involved in many public debates concerning euthanasia, drug addiction, genetics, choices in health care and resource allocation. His research has focused on ethical issues in palliative care. He has been coordinator of the European Commission funded Project, 'Palliative Care Ethics'. Also, he serves on numerous editorial boards. He has been editor-in-chief of Medicine, Health Care and Philosophy. He has been co-founder and secretary of the European Society for Philosophy of Medicine and Health Care. He published Medische Ethiek (1998; revised edition 2003), a textbook for medical curricula (also translated in Lithuanian language). His other recent books include Palliative care in Europe: Concepts and Policies (Amsterdam, the Netherlands; IOS Press; 2001), Bioethics in a European Perspective (Dordrecht, the Netherlands; Kluwer Academic Publishers; 2001), and The Ethics of Palliative Care: European Perspectives (Buckingham, UK; Open University Press; 2002). In 2004 he has published (with co-editor Ruth Purtillo) the book Ethics and Alzheimer Disease (Johns Hopkins University Press, Baltimore) His most recent publication is a book on euthanasia (Death and Medical Power: An Ethical Analysis of Dutch Euthanasia Practice. Open University Press, 2005). In UNESCO he is involved in a wide range of international activities in bio-ethics, such as the promotion of the Universal Declaration of Bioethics and Human Rights as well as capacity building (in particular promoting ethics teaching and assisting in the establishment of ethics committees) in developing countries. He is also responsible for international activities in environmental ethics, science ethics (exploring the ethics of science, and especially Codes of Conduct for Scientists) and technology ethics (ethics of nanotechnologies and ethics of space technologies).

Dr. Danuta Krotoski
Acting Associate Director, Prevention Research and International Programs (PRIP), NICHD, National Institutes of Health

Danuta Krotoski is the Acting Associate Director for Prevention Research and International Programs at the National Institute of Child Health and Human Development (NICHD) at the US National Institutes of Health. In this capacity she coordinates the Institutes portfolios in prevention and international research and chairs the NICHD HIV/AIDS Coordinating Committee. In addition, Dr. Krotoski serves as the co-chair of the US National Children's Study International Interest Group and is working with the WHO to develop recommendations for core protocols for longitudinal cohort studies in developing countries. A geneticist by training, Dr. Krotoski has been instrumental in developing the Institute's activities on newborn screening in the Middle East and North Africa and serves on the MENA Newborn Screening Steering Committee. Prior to assuming this position, Dr. Krotoski served as the Director of Fellowships and Workshops at the Human Frontier Science Program in Strasbourg, France. Dr. Krotoski is a developmental biologist and received her Ph.D. at Tulane University. She was a postdoctoral fellow and then staff member at the Developmental Biology Center, University of California Irvine. She originally came to the NIH as the Program Director for Developmental Neurobiology, Limb Development and Teratology in the Genetics and Teratology at NICHD and then became Director of the Basic Rehabilitation Research and Career Development Program at the National Center for Medical Rehabilitation Research at NICHD. Dr. Krotoski also served as Program Officer for Fellowships at the Fogarty International Center.

Dr. Myles Axton
Editor, Nature Genetics

Myles Axton is the editor of Nature Genetics. He was a university lecturer in molecular and cellular biology at the University of Oxford and a Fellow of Balliol College from 1995 to 2003. He obtained his degree in genetics at Cambridge in 1985, and his doctorate at Imperial College in 1990, and between 1990 and 1995 did postdoctoral research at Dundee and at MIT's Whitehead Institute. Myles's research made use of the advanced genetics of Drosophila to study genome stability by examining the roles of cell cycle regulators in life cycle transitions. His interests broadened into human genetics, genomics and systems biology through lecturing and from tutoring biochemists, zoologists and medical students from primary research papers. Helping to establish Oxford's innovative research MSc. in Integrative Biosciences led Myles to realize the importance of the integrative overview of biomedical research. As a full time professional editor he is now in a position to use this perspective to help coordinate research in genetics.

Keynote Lecture Presentations

K1

Priorities, Publication and Credit

Axton M.
Nature Genetics, New York, United States of America; m.axton@NATURENY.com

Nature Genetics publishes the very highest quality research in genetics. It encompasses genetic and functional genomic studies on human traits and on other model organisms, including mouse, fly, nematode and yeast. Current emphasis is on the genetic basis for common and complex diseases and on the functional mechanism, architecture and evolution of gene networks, studied by experimental perturbation. I will discuss the work of the journal's editors- from the lab visits we make to solicit the best papers- through to the presenting the work to the public via press release. I will talk about how we make decisions, set standards and use referee's advice. The idea of "microattribution" is an extension of the normal scientific practice of citing original references. When requiring authors to deposit data in public databases, I believe that journals, databases and funders should ensure that quantitative credit for the use of every data entry will accrue to the relevant members of the data-producing and annotating teams.

K2

The Human Variome Project and Pilot Projects

Cotton R.G.H. and the Human Variome Project Consortium
Genomic Disorders Research Centre & Dept of Medicine, The University of Melbourne, St. Vincent's Hospital, Fitzroy VIC 3065, Australia; cotton@unimelb.edu.au

The lack of systematic collection of mutations led to a meeting in Montreal in 1994 of some of the world's leading geneticists, which concluded that as experts in genes are the best curators, the collection of mutations should be achieved via a federation of Locus Specific DataBase (LSDB) curators. This would lead to a standard of curation not possible in central databases (OMIM/HGMD). This led to the formation of the HUGO-Mutation Database Initiative (HUGO – MDI; Cotton 2000) and then to the Human Genome Variation Society (HGVS; Horaitis and Cotton 2004, www.hgvs.org). Delegates of the highest possible level from various organizations related to genetic health and funding agencies agreed to launch the Human Variome Project (HVP) at a meeting in Melbourne June 20-23, 2006 (Ring et al 2006, www.humanvariomeproject.org). In simple terms, the project aims to systematically collect human gene variation with associated phenotype information and make it available to those who need it. This will involve global collaboration with a number of major interacting projects developed, funded and carried out by working groups and others. The scale of the project requires considerable coordination and funding. The delegates generated 96 recommendations necessary, but not necessarily sufficient, to carry out the HVP and these have recently been published copyright free in Nature Genetics (Cotton et al 2007) along with an Editorial in the same issue. Funding bodies have been approached to establish the coordinating office and develop projects related to the recommendations. There are a number of projects in progress or planned, which will define the recommended direction for all genes and countries to review and adapt to their situation. This includes collection of data from clinics and diagnostic labs and its transfer via LSDBs to central databases, ethical aspects, transfer of LSDBs to NCBI, an others.

References

Cotton et al 2007. Recommendations of the 2006 Human Variome Project Meeting. Nat. Genet. 39:436-439.

Editorial. (2007) What is the Human Variome Project? Nat. Genet. - 39, 423.

Horaitis O. and Cotton R.G.H. The Challenge of Documenting Mutation Across the Genome: the Human Genome Variation Society Approach (2004) Hum Mutat. 23:447-452.

Ring, H.Z., Kwok, P.Y. & Cotton, R.G. Human Variome Project: an international collaboration to catalogue human genetic variation. Pharmacogenomics 7, 969-72 (2006).

K3

Ethics of Mutation Databases: Correctness in Reporting Genetic Variation and its Effects

Cotton R.G.H.
Genomic Disorders Research Centre & Dept of Medicine, The University of Melbourne, St. Vincent's Hospital, Fitzroy VIC 3065, Australia; cotton@unimelb.edu.au

The reporting of genetic variation, referred to as a mutation in the clinic, and its effect, or lack of effect, is important to inform decisions in the clinic regarding prognosis, family planning and therapy. It also assists research and diagnostic strategies. However, on the one hand, there are reasons to be sensitive to the views of those who carry a deleterious mutation and on the other the views of society in need to diagnose, counsel and treat others who depend on prior information held in the literature. Discussion of ethical guidelines in human genetics and other areas has been general and difficult to decide what is applicable in the mutation database area. For this reason there has been an effort to develop practical guidelines relevant particularly to locus specific databases (LSDBs). Twelve principles have been derived on which to base activity (Cotton et. al. 2005). Currently the Chair of the Human Variome Project Ethics Working Group Professor Sue Povey, an LSDB curator, is developing a protocol for curators to put into practice on a daily basis. The practical guidelines will be discussed in this presentation.

References

Cotton, R.G., Sallee, C. & Knoppers, B.M. Locus-specific databases: from ethical principles to practice. Hum Mutat 26, 489-93 (2005).

K4

Strengthening Newborn Screening in the Middle East and North Africa

Krotoski D., Engelson G., Hanson J., Namaste S., Howell R.R.
National Institute of Child Health and Human Development, National Institutes of Health, US Department of Health and Human Services. Bethesda, MD, United States of America; krotoskd@mail.nih.gov

Newborn screening (NBS) has received increased global interest with the identification of genes related to developmental disabilities and technological advancements are enabling us to identify interventions that can ameliorate or treat a number of genetic disorders. In addition, our increased understanding of vulnerable periods during children's development has placed a greater emphasis on interventions that will prevent subsequent disease and disability. Screening of newborns for genetic and metabolic conditions provides an opportunity to identify affected children timely manner so that effective intervention can be used, where they are available. There has been great interest in NBS for genetic and metabolic conditions in countries of the Middle East and North Africa due to a number of factors. With decreasing infant mortality, genetic disease and other congenital disorders are becoming an increasingly larger public health issue. In addition, reports from the region indicate that there is a high rate of consanguineous marriages in the population resulting in the expression of rare autosomal recessive disorders. Further, there is a growing recognition of the value of NBS and the role it plays in preventing or ameliorating mental retardation, physical disability, neurological damage and even death in conditions that are amenable to screening. Finally there is particular interest in disorders for which diagnosis and treatment is simple and relatively inexpensive. To address the regional interest in development of newborn screening programs, the National Institute of Child Heath and Human Development of the US National Institute of Health together with the Ministry of Health of the Kingdom of Morocco and other partners organized a conference entitled *Strengthening Newborn Screening in the Middle East and North Africa* in November 2006 in Marrakech Morocco. The meeting participants, representing most of the countries of the region, developed the *Marrakech Declaration*, which concluded that all countries in the Middle East and North Africa are encouraged to develop policies and the necessary support to establish systematic national newborn screening programs that should screen for at least one condition. The *Declaration* recommended establishing effective lines of communication among NBS activities in the region linking them with experts in other countries through annual meetings, a dedicated website, and the development of training modules. A Steering Committee has been established that has developed a strategy for implementing the recommendations of the *Marrakech Declaration* that will be outlined in this presentation.

K5

Genomics Sciences and Genomic Medicine

Liu E.T.
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Genomic medicine involves the provision of medical care that uses the power of genomic knowledge and technologies to resolve complex problems. New technologies in sequencing, cloning, and genotyping have enabled this advance. The new challenge will be the assembly and management of this high volume of data with dimensional complexity. Genomic medicine therefore means computational medicine as well. We will describe how genomic approaches are changing our understanding of cancer, as a model system. Our work, at the Genome Institute of Singapore, in transcriptional profiling has led to transcription factor binding site dynamics, and human variations in those binding sites. We employ a strategy of using genomic data to reconstruct systems maps of critical regulatory networks. This integrative approach permits modeling of complex interactions and allowed us to quickly uncover complex mechanisms of drug action. Coupled with the dramatic expansion of disease gene discovery in population studies, we now find that rather than a few genes, hundreds of genes may be involved in the genesis of a single complex disease. Harnessing complexity will be our next great challenge.

K6

Intenational Bioethics and Human Genetics. The Activities of UNESCO

ten Have H.
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The ethics program of UNESCO has started in the early 1990s with the request of the Member States to develop global ethical standards in regard to the Human Genome Project. The International Bioethics Committee (IBC) composed of 36 independent experts from all regions has been established in 1993 in order to advise the Director-General in ethical matters. The IBC drafted the Universal Declaration on the Human Genome and Human Rights that was adopted by the Member States of UNESCO in 1997 and by the United Nations in 1998. This Declaration was followed by a more specific request relating to the collection, processing, use and storage of human genetic data. The International Declaration on Human Genetic Data has been adopted in 2003. Subsequently a much broader mandate was given in order to identify universal bioethics principles in general. This resulted in the Universal Declaration on Bioethics and Human Rights, unanimously adopted in 2005. This last Declaration is the first global statement in the area of bioethics to which governments have committed themselves. The challenge now is to translate it into practical activities in the Member States, such as ethics committees, ethics education, public debate and legislation.

Lecture Presentations

L1

Mutation in WNT10A is Associated with an Autosomal Recessive Ectodermal Dysplasia: The Odonto-Onycho-Dermal Dysplasia

Adaimy L., Chouery E., Megarbane H., Mroueh S., Delague V., Nicolas E., Belguith H., de Mazancourt P., Megarbane A.
Medical Genetics Unit, Faculty of Medicine, University Saint Joseph, Beirut, Lebanon; megarbane@usj.edu.lb

Odonto-onycho-dermal dysplasia is a rare autosomal recessive syndrome in which the presenting phenotype is dry hair, severe hypodontia, smooth tongue with marked reduction of fungiform and filiform papillae, onychodysplasia, keratoderma and hyperhidrosis of palms and soles, and hyperkeratosis of the skin. We studied 3 Lebanese consanguineous Muslim Shiite families including six individuals affected with odonto-onycho-dermal dysplasia. Using a homozygosity mapping strategy, we assigned the disease locus to an approximately 9 cM region at chromosome 2q35-q36.2, located between markers rs16853834 and D2S353 (AFM296VH9), with a maximum multipoint LOD score of 5.7. Screening of candidate genes in this region led us to identify the same c.697G>T (p.Glu233X) homozygous nonsense mutation in exon 3 of the WNT10A gene, in all patients. At the protein level, the mutation is predicted to result in a premature truncated protein of 232 aa instead of 417 aa. This is the first report of a human phenotype resulting from a mutation in WNT10A gene, and the first demonstration of an ectodermal dysplasia caused by an altered WNT signaling pathway, expanding the list of Wnt-related diseases.

L2

Genetic Counseling in the Muslim World: The Challenges

Al-Aqeel A.I.
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Genetic counseling is the process in which an individual or a family obtains information and advice about a genetic condition that may affect the individual, his progeny, his relatives, or the family as a whole. Based on this knowledge he can take the pertinent decision regarding marriage, reproduction, abortion and health management. Genetic counseling includes five themes, medical management, risk determination, risk options, reproductive decision making, and .support services. Genetic counseling involves a partnership of physicians, genetic counselors, and genetics support groups. The majority of clinical geneticists subscribe to the principle of non-directive ness: information about risks, natural history, treatment, and outcome are presented in a balanced and neutral manner, but decisions about reproduction are left to the family. In the Muslim World and in the Kingdom of Saudi Arabia (KSA) it involves many challenges, as it has to be carried within the context of religion and culture, according to Islamic ethical and cultural background of the individual with community-based genetic counseling in one's own language. We are at a time of unprecedented increase in knowledge of rapidly changing technology. Such biotechnology especially when it involves human subjects raises complex ethical, legal, social and religious issues. A WHO expert consultation concluded that "genetics advances will only be acceptable if their application is carried out ethically, with due regard to autonomy, justice, education and the beliefs and resources of each nation and community". Public health authorities are increasingly concerned by the high rate of births with genetic disorders especially in developing countries where Muslims are a majority. Therefore it is imperative to scrutinize the available methods of prevention and management of genetic disorders. Islam is a religion which encompasses the secular with the spiritual, the mundane with the celestial and hence forms the basis of the ethical, moral and even juridical attitudes and laws towards any problem or situation. Islamic teachings carry a great deal of instructions for health promotion and disease prevention including hereditary and genetic disorders, therefore we will discuss how these teachings play an important role in the diagnostic, management and preventive measures including: genomic research; population genetic screening, including premarital screening, pre-implantation genetic diagnosis, newborn screening; assisted reproduction technology; stem cell therapy and genetic counseling.

L3

Bahrain National Hereditary Diseases Strategy (1984-2007)

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The hereditary disease program started in Bahrain in 1984. In 1991, a National Committee for prevention of Genetic disease was formed to plan the control program of genetic diseases in the country. The strategic goals were to reduce the incidence of hereditary diseases in Bahrain, and to improve the standard of management and treatment of patients suffering from these diseases. These efforts continued for the past 25 years. It had tremendous effect in reducing the prevalence of Genetic Blood Diseases among the newborns, from 20 per thousand to 5 per thousand with 75% reduction. Consanguinity rate also declined gradually due to increase awareness about genetic diseases. The total consanguinity rate and the first cousin marriages rate in 1990 were 39% and 24%, respectively, while it became 11% and 7.8% in 2007 with 66% decline. The prevention strategy depended on Health Education, Screening and Counseling programs. Screening for hemoglobinopathies included sickle cell disease and thalassemia, was undertaken on the following categories of the population: Antenatal mothers, Premarital Couples, Newborns, and School students. The other measures taken included: registration of genetic and congenital disorders and improving and updating the laboratory services, as a cytogenetic lab was established in 1999 and a molecular genetic laboratory started in 2000. These are some of the efforts performed to reach our goals. By evaluating the effect of implementing such strategy, we found it to be successful, but more efforts are needed to reduce the rate of other genetic diseases, and to improve services for patients.

L4

Delineation of the Clinical and Molecular Basis Underlying Several New Recessive Disorders in the UAE

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*Departments of *Paediatrics and **Pathology, FMHS, UAE University, Al Ain, United Arab Emirates; algazali@hotmail.com*

The population of the UAE is characterized by high level of consanguinity and large family size leading to increase in the frequency of autosomal recessive disorders. High proportion of these recessive disorders is new or previously un-described in the literature. This often leads to difficulty in providing diagnosis and genetic counseling for affected families. We present several new autosomal recessive disorders diagnosed in the UAE and discuss their clinical manifestations together with their molecular characterization. It is anticipated that many of these disorders are also present in other parts of the Arab world and therefore our findings are likely to be helpful for the diagnosis, genetic counseling and prevention of their occurrence.

L5

Newborn Screening for Inborn Errors of Metabolism-Combining Molecular and Biochemical Testing: A Saudi Perspective

Al-Sayed M.
King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; moeen@kfshrc.edu.sa

Screening for inborn errors of metabolism relies mainly on biochemical assays that detect the presence of an abnormal metabolite or the excess of a normal metabolite. For the past thirty years screening programs for inborn errors of metabolism have been carried out largely using the bacterial inhibition assays (BIA) using dry blood spots (DBS) collected on special filter paper as introduced by Dr. Robert Guthrie. These programs focused on a small number of diseases such as phenylketonuria (PKU) and maple syrup urine disease and involved one test for each disease. Tandem Mass Spectrometry (MS/MS) introduced in early1990s has been a major advance in this field. It provides an automated high throughput, specific, and broad-spectrum approach to screening for over 20 metabolic disorders, including those covered by BIA tests. As a consequence, this technology has been adopted by many centers and several screening programs have started to appear across the globe. While biochemical analysis provides a rapid diagnostic tool, it can do little to prevent the disease from reoccurring in the affected families and their close relatives. Prenatal diagnosis in sometimes difficult or unreliable using biochemical methods and carrier/premarital testing is not possible. Genetic counseling is often limited because genotype-phenotype correlation cannot be provided. Furthermore, certain diseases show similar biochemical profiles with MS/MS and differentiation can only be accurately provided by molecular analysis. Taking in consideration the advances in molecular diagnostic tools over the last decade, combining molecular analysis with biochemical testing can overcome these shortcomings. DNA can be easily extracted from dried blood spots using whole genomic amplification or other techniques. This can then be subjected to pre-designed automated high throughput molecular assays for rapid detection of pathogenic mutations. Turning to the local arena, inborn errors of metabolism are quite common in Saudi Arabia and the surrounding gulf countries. Contributing factors include extensive consanguinity, relative homogeneity of the gene pool and large family size. Often a small number of pathogenic founder mutations are responsible for any given metabolic/genetic disease in the region. This presentation will give an overview of the diseases where founder mutations have been identified mostly by our institution. We will focus on the practicality, rationale, and advantages of combing molecular analysis with biochemical screening for inborn errors of metabolism in Saudi Arabia.

L6

Successful Pre-implantation Diagnosis in a Family Affected with Zellweger Syndrome

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Zellweger syndrome is the prototype and the most severe of Zellweger Syndrome spectrum (ZSS). ZSS is a group of clinically and genetically heterogeneous disorders, caused by defects in at least 12 PEX genes involved in normal peroxisome assembly. Patients affected with this syndrome have severe neurological dysfunction including hypotonia, seizures, severe mental retardation, and characteristic craniofacial dysmorphism. Severe growth failure is the rule and death occurs in most patients within the first year of life. ZS is commonly observed in Saudi Arabia among other autosomal recessive diseases partially due to extensive consanguinity. Given the lethality of the condition and considering psychosocial and cultural issues, we opted for a preventive approach in a Saudi family affected with ZS by screening for mutations in PEX genes followed by pre-implantation diagnosis (PGD). Index case in the family underwent mutation screening for PEX genes. This was followed by PGD using whole genomic amplification PCR and sequencing. A new mutation in PEX 26 gene was identified in this family. Following PGD, a singleton pregnancy ensued after transfer of two normal embryos. A healthy baby girl was born and postnatal DNA testing revealed a normal homozygous genotype. We report successful prevention of ZS in a Saudi family by PGD following identification of a new mutation in PEX 26 gene.

L7

ER Retention and Degradation of Mutated Proteins is a Common Mechanism in Numerous Loss-of-Function Recessive Diseases

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More than a third of all cellular proteins are targeted to the endoplasmic reticulum (ER) as a first step in their trafficking along the secretory pathway to their final destinations. Within the ER lumen, nascent proteins enter into folding pathways assisted by the large number of molecular chaperones present in this organelle. The processes of protein folding, assembly into multi-subunit complexes and export out of the ER are subjected to a stringent quality control system to ensure that only properly folded and assembled proteins are transported out of the ER. Malfolded proteins and orphan subunits of protein complexes are rejected by the ER quality control machinery and as a result are re-translocated to cytosol for degradation by the ubiquitin/proteasome systems. These processes have been named ERAD and have been implicated in the cellular mechanisms of at least 30 loss-of-function recessive monogenic diseases including cystic fibrosis and emphysema. Due to the high stringency of ERAD and the large number of cellular proteins that has to pass this quality control system (~10,000), we reasoned that many more loss-of-function diseases will result from ER retention and degradation. We therefore, utilized bioinformatics and data mining approaches to identify novel ERAD disease candidates. We found that at least 45% of all known human disease proteins have an ER targeting signal and we identified many ERAD candidate diseases. We validated our bioinformatics approach experimentally by establishing that ERAD is indeed responsible for the loss-of-function of ROR2 in Robinow syndrome, a recessive disorder prevalent in several Middle Eastern countries. Further research is ongoing to establish the mechanisms of other recessive disorders found in Arab populations. The importance of establishing the mechanisms of genetic diseases has recently been highlighted by the possibility of utilizing ERAD as a target for the treatment of those diseases.

L8

Advances in the Genetics of Type 2 Diabetes Mellitus

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Genome-wide association (GWA) studies developed by several research groups, have provided a powerful approach to the identification of genes involved in type 2 diabetes, during 2007. Case-control comparisons of thousands of patients and controls using 500K Mapping Array sets, identified 8 new genes and replicated results of 4 previously identified genes. The new genes include the Zinc Transporter SLC30A8, the Insulin Degrading Enzyme, IDE; the Homeo-box protein, HHEX; Kinesin Interacting Factor, KIF11; Exostosin 2, EXT2; Fat Mass and Obesity Associated, FTO; CDK5 Regulatory Subunit Associated Protein 1 like 1, CDKAL1; Cyclin Dependent Kinase Inhibitor 2A, Isoform 4 and Inhibitor B, CDKN2A and CDKN2B. Other previously identified genes such as PPARG, KCNJ11, TCF7L2 and IGF2BP2, were confirmed. The function of most of these genes is being worked out with a promise of prevention and therapeutic applications of profound effects. However, these associations explain only a portion of the disease risk in Caucasians. In the Arab population of Oman, using linkage analysis, we identified 5 novel loci involved in the glucose homeostasis-obesity phenotypes, that do not overlap the above loci. This adds further to the heterogeneity of the complex traits controlling susceptibility to type 2 diabetes.

L9

What is the Impact of Genetic Counseling and Prenatal Diagnosis in Genetic Diseases Prevention in an Arab Muslim Population?

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Genetic counseling remains the best and the most efficient action for genetic diseases prevention. Based on families' education, and sometimes followed by prenatal or preimplantation diagnosis, genetic counseling is relevant by reducing the incidence of hereditary and congenital disorders. The development of medical care, the accumulation of laboratory techniques and the legality of pregnancy termination will help largely to decrease the severity and the frequency of inherited diseases. In daily practice we are sometimes surprised by parents' attitude. After genetic counseling, why do parents decide to stop reproduction despite the availability of prenatal testing or the absence of recurrence risk? While, some other parents at very high risk continue to have children. To reply to such questions we surveyed during three years couples who were referred to the genetic center for genetic counseling. We considered only couples at risk of affected children. We evaluated the impact of genetic counseling on parents' attitude by analyzing two parameters, the occurrence of pregnancies and the acceptance of prenatal screening and prenatal diagnosis. These parameters were correlated to parents' characteristics: age, socioeconomic situation, education level; to the number and children health status and to the kind and severity of the disease. We analyzed simultaneously the same parameters in the group of couples who were referred for prenatal diagnosis during this period. The aim of the presentation is to evaluate the real impact of genetic counseling and prenatal diagnosis on genetic diseases prevention in an Arab Muslim country and to determine how to increase the acceptability of the role of genetic counseling in welfare family. Legislation for genetic counseling: In areas with high risk of genetic diseases for example where consanguinity rate is increased , it would be necessary to establish genetic counseling facility as obligatory. In premarital stage each partner have to be informed about risk for his progeniture. Each couple will be of course responsible of his decision making. Legislation for pregnancy termination in countries where it is accepted have to be established taking account of the community culture.

L10

Dominant Effect of Smoking on Airway Epithelium Gene Expression Profiles Among Individuals of European, African, Southeast Asian and Arabian Ancestries

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Cigarette smoking is the major cause of airway disorders throughout the world, and we hypothesized that the environmental stress of smoking induces a predictable airway epithelial gene expression profile, regardless of genomic variability among individuals of different ancestries. Expression profiles of airway epithelium obtained by fiberoptic bronchoscopy were assessed in 27 smokers and 23 non-smokers using Affymetrix microarrays. K-nearest neighbor (K=5) class prediction (smoker vs non smoker) analysis was used to obtain a gene expression "predictor set" from New York individuals of European and African ancestry. The predictor set was then assessed for its ability to identify smoking status of individuals of Southeast Asian (Nepalese, Indian, Pakistani and Bangladeshi) and Arab (Qatari and Palestinian) ancestry residing in Qatar. The European/African ancestry predictor set, comprised of 186 probe sets with an average (+/- SE) predictor strength of 1.02 +/- 0.02, was validated as 100% of blinded samples from the source population were correctly identified for smoking status. Strikingly, the same predictor set correctly predicted 80% of the samples from individuals of Southeast Asian and Arab ancestry. The data demonstrates that the gene expression changes of the airway epithelium of smokers is so universal (i.e., smoking is such a dominant environmental stress), that a predictor set of the expression profile of 186 genes accurately identifies smokers from non-smokers among a diverse world-wide population, despite disparate ancestral origins and concomitant disparate genomes.

L11

A Whole-Genome Scan in a Large Family with Leukodystrophy and Oligodontia Reveals Linkage to 10q22

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We previously reported a large inbred Syrian pedigree with an autosomal recessive neurodegenerative disorder. The clinical picture of the six affected children was oligodontia, and a degenerative neurological condition with onset around age 12, characterized by progressive ataxia and pyramidal signs. Corresponding abnormalities in the white matter and cortical atrophy were detected by MRI. A whole-genome screening using 390 microsatellite markers was completed but showed no evidence of linkage to any chromosomal region, a finding most probably attributed to the multigenerational pedigree of that family. A genomewide linkage analysis, using the GeneChip Mapping NspI Affymetrix array containing 260 000 SNPs with a mean intermarker distance of 10Kb was then undertaken. Data were analyzed with the Agilent GeneSpring GT software. Maximum multipoint lod scores of 5.66 (NPL score = 7.65) was detected on chromosome 10q22 region. Haplotype analysis enabled mapping of the disease loci to a region of 8.7 cM. This genomic interval contains 88 known genes including the Prosaposin gene (*PSAP)* responsible of metachromatic leukodystrophy which was excluded. Sequencing of some other logical genes are pending. We conclude that genome-wide linkage analysis by using high density SNPs markers is a very powerful assay compared to the standard 10 cM microsatellites markers. Cloning of the gene responsible of this new disorder will improve the understanding of the link between teeth and brain.

L12

Most Encountered Genetic Disorders in Egypt: Classification and Registry

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Diseases with genetic bases have been a major health problem to every society. Heavy economic, social and health burdens are imposed on the afflicted family as well as the society. In general genetic diseases are relatively prevalent among the Arab population, and are a significant cause of morbidity and mortality in this population. Incidence of congenital malformations among Egyptians ranges from 1,16 to 3,17 %. This is probably due to the high consanguinity rate (20 – 40 %) among Egyptians. Early diagnosis of various genetic disorders and malformations with proper intervention (medical, hormonal, dietary, and interventional by stimulation of motor & cognitive development) will reduce the burdens of genetic disorders at the individual, familial and community levels. A comprehensive classification system is necessary for genetic diseases in order to provide a framework in which to scientifically study the etiology, pathogenesis and treatment of diseases in an orderly fashion. In addition, such system gives clinical geneticists a way to organize the health care needs of their patients. Classifications of various disorders were reviewed, to determine which classification to follow. We revised classifications adopted by Ismail (1996), Rimoin et al. (2002), ICD-10 – CM (2003), and ICF (2004). However these classifications were based on the etiological diagnosis, pathological diagnosis, phenotypic diagnosis and / or mode of inheritance. Therefore, we established our own classification of genetic disorders, as a modification of the previous mentioned classifications. The main purpose of our classification is to include four major descriptive categories (axes), that geneticists consider to identify the genetic disorders. These axes are the phenotypic axis, the etiologic axis, the differential diagnosis axis, and the referral axis, which includes patients seeking genetic counseling. The Final Report of the study (1/7/2004 – 30/6/ 2007) included 3417 cases, of which 2686 cases (78.6 %) were referred from private sectors, self-referral and universities; while 731 cases (21.4 %) cases were referred from the selected hospitals and primary health care centers (PHCCs) of Ministry of Health and Population. Each patient was subjected to meticulous clinical examination, pedigree construction, anthropometric measurements, and differential diagnosis. We established an integrated classification for the genetic disorders referred to Genetic Clinic of NRC. This classification considers the etiological, phenotypic, differential diagnosis and referral categories (axes), and is entitled “Genetic/Diagnostic/Referral Classification”. It includes 18 disease groups. The results, discussion, and recommendations will be presented.

L13

Independent Introduction of Two Lactase Persistence Alleles into Human Populations Reflect Different History of Adaptation to Milk Culture

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The T-13910 variant located in the enhancer element of the lactase gene correlates perfectly with lactase persistence (LP) in Eurasian populations whereas it is almost nonexistent among some global populations showing high prevalence of LP implying the presence of additional still unknown LP variants. Here, we report identification of two new mutations among Saudis, also known to have high prevalence of LP. The variants represent a compound LP allele that is driven to a high prevalence among Middle East population(s) and correlates well with the prevalence of LP. Our functional analyses in vitro show that both SNPs of the compound allele are required for the enhancer effect, most probably mediated through the binding of the hepatic nuclear factor 1 alpha. High selection coefficient s~0.04 for LP phenotype was found for both Caucasian T-13910 and Arab alleles. We also show that the Caucasian T-13910 and the earlier identified East African G-13907 LP allele share the same ancestral background allele and most likely share the same history, probably related to the same cattle domestication event. Contrary, the compound Arab allele shows a different, highly divergent ancestral haplotype. This would imply that these two major global LP alleles have arisen independently, the latter perhaps in response to camel milk consumption. This result would support the convergent evolution of the LP in diverse populations, most probably reflecting different history of adaptation to milk culture.

L14

Ethical Concerns to the use of Pre-implantation Genetic Diagnosis in the Gulf Cooperative Council States

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Assisted reproductive technology (ART) makes pre-implantation genetic diagnosis possible, allowing embryos to be screened genetically before placement in the uterus, by analyzing the DNA from a single cell after amplification by polymerase chain reaction and/or the use of fluorescence in situ hybridization (FISH) technique. However, ethical objections have been raised against genetic screening of embryos, giving the practice an uncertain ethical and legal status. The ethical objections fall into two main categories: one set focuses on embryo status and the manipulations of embryos that PGD entails, and the other set sees major ethical problems in genetic selection because of its eugenic implications. Therefore, we have surveyed the possible presence and compliance to any legislation to the PGD practice in the existing fifty IVF centers in the GCC States. The PGD techniques, mainly FISH analyses, are practiced in three centers in Saudi Arabia only even though many IVF centers are contemplating the PGD program. This is because of the high cost of tests and the sophisticated technology involved in such program, and the poor returns of the investment. In general, however there are deficiencies in the legislation which regulates the PGD practice. Such shortcoming has led many centers to support the notion that selection of embryos to avoid serious genetic disease in the offspring is no more eugenic than medically approved abortion after prenatal diagnosis.

L15

National Strategy for the Prevention of Genetic and Congenital Disorders in Jordan

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Jordan is faced with major challenges in providing comprehensive and up-to-date health services in a rapidly advancing field such as genetics. With the achievements made in the control of communicable and nutritional disorders, the infant mortality rate in Jordan has declined to 22/1000 live births, which results in an increased proportion of deaths due to genetic and congenital disorders. Effective evidence-based strategies for the prevention and control of common genetic and congenital disorders at the community level include a combination of basic public health measures, and the education and involvement of the primary health care network. A strategic action plan for the prevention of genetic and congenital disorders in Jordan for the period 2006-2010 was jointly prepared and is being implemented by the MOH, WHO and NCDEG. The overall goal would be to monitor yearly the frequencies of affected births of genetic and congenital disorders and to achieve a progressive decline in the national rates of genetic and congenital disorders. The plan includes national programs for premarital screening, newborn screening, public and professional education, establishing a national birth defects registry, and introducing new technology.

L16

A Novel Approach for the Study of the Genetics of Hypertension in Arabs: Heritability and Linkage Analysis Results of "Oman Family Study"

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The complexity of the interaction of genetic susceptibility and environmental determinants of hypertension, require novel approaches to linkage analysis. To determine heritability and run linkage analysis for the primary cardiac and haemodynamic components of blood pressure under resting and stress conditions. 24-hour and beat-to-beat BP, cardiac and haemodynamic parameters (impedance cardiography) were obtained in 1124 subjects, from 5 large multigenerational and consanguineous Arab pedigrees aged 16- 90.years. Mental and physical stress were evoked by Stroop colour and ice immersion tests, respectively. Heritability analysis was carried out using variance decomposition method (SOLAR software). Linkage analysis was carried out using the 400 cM Marshfield marker map. Heritability values (H2R) for daytime SBP and DBP were 0.28 and 0.38, respectively. They were higher than those obtained during sleep (0.20 and 0.17). H2R for resting R-R intervals during ice immersion and Stroop were 0.32, 0.36 and 0.40, respectively. Stroke volume, Cardiac output, cardiac contractility, left ventricular ejection time showed similar linear increases with the respective stress tests. Linkage analysis revealed 13 loci for cardiac and BP phenotypes only during Stroop colour testing in chromosomes 1, 3, and 8, with clusters of SBP, DBP and RRI at two Loci in chromosome 12. One locus for sleep BP was in chromosome 8. The dissection of blood pressure into its primary components together with the use of mental stress in a unique pedigrees structure provided a robust model for the detection of genetic loci of hypertension. Heritability and gene Loci controlling BP can best be revealed under mental stress and during sleep.

L17

Genotype-Phenotype Correlation in Gaucher Disease: Strategy for Prevention and Therapy in Egypt

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Gaucher disease (CGD) is the most common inherited lysosomal storage disorder. It results from deficiency of the enzyme glucocerebrosidase necessary to break down glucucerebroside leading to its accumulation in macrophage lysosomes referred to as Gaucher cells. During the period from Jan 95-Oct 2006, 49 patients with GD were diagnosed. Mean age was 2.5 years. Investigations included CBC, bone marrow aspirate, liver biopsy, plain x-ray of long bones and chest, abdominal ultrasonography, echocardiography, measurement of plasma chitotriosidase and B-glucosidase activity in peripheral leucocytes. Molecular diagnosis was done for 17 patients. Screening for GD was done in 5 families and prenatal diagnosis was done in 3 families using CVS. Enzyme replacement therapy (ERT) using recombinant imiglucerase (cerezyme) in a dose of 60u/kg/2w. was given to patients. Follow up protocol was done. Most of our patients belonged to type III (29), followed by type I (15) and type II (5). All patients presented by pallor & hepatosplenomegaly. In addition type II presented by neurological manifestations & type III by ophthalmoplegia and convulsions. Some patients demonstrated atypical presentation as extensive pulmonary infiltrate, cardiomyopathy, bone disease or malignancy. There is reduction in weight, height, Hb level and platelet cont. Chitotriosidase was high while enzyme level was decreased. The most common mutation was L444P. A new mutation was detected. Family screening demonstrated GD in 5 sibs & prenatal diagnosis demonstrated normal fetuses. Using ERT there was improvement in weight, height, Hb level, platelet count, with reduction in liver span and splenic length. However response to ERT was variable in different patients even with same phenotype or Genotype. Some patients needed larger doses. Supportive therapy is also important to improve quality of life.

L18

Molecular Analysis of F8 in Lebanese Hemophilia a Patients: Report on 23 Novel Mutations and Phenotype-Genotype Correlation

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Hemophilia A (HA) is an X-linked recessive hereditary bleeding disorder affecting one in 5000 men, resulting from mutations in the F8 gene. Our objective was to identify the spectrum of mutations of the F8 gene responsible of the HA in Lebanese patients, and perform a genotype/phenotype correlation in the patients' cohort. A cohort of 76 HA patients from 52 unrelated families was studied. The tested individuals were screened for intron 22 and intron 1 inversion by PCR. In the absence of mutations in both introns, a dHPLC screening followed by a DNA sequencing of all coding region was performed. When patients presented novel mutations, 100 control chromosomes were tested in order to exclude common polymorphisms. Large deletion was confirmed by MLPA technique. The mRNA was specifically studied whenever a splice site mutation was detected. In addition, studies of the putative biochemical function and FVIII 3D structures were conducted. Twenty three novel mutations were identified in this study: 12 missense, 3 nonsense, 2 splice site, 5 small deletions, and one large deletion. A history of inhibitor found in 8 over 75 patients correlated with large deletion, intron 22 inversion, and nonsense mutations. We were able to identify all causative mutations. This knowledge is very important, particularly because it represents a huge step for genetic counseling.

L19

Newborn Screening in Lebanon: 12 Years Experience

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The estimated yearly newborn load in Lebanon is around 70,000 for a population estimated at 4.5 millions. The rate of consanguinity remains relatively high at about 11%. There is no publicly-funded mandatory newborn screening program. In 1996, a private university-based newborn screening center was established covering 4 diseases: congenital hypothyroidism, phenylketonuria, congenital galactosemia, and G6PD deficiency. Since then, this program has screened an average of 12,000 newborn babies a year. In 2006, the center started using a tandem mass spectrometry machine, which allows the expansion of the spectrum of screened diseases to several metabolic disorders. The Newborn Screening Quality Assurance Program organized by the CDC supervises the laboratory results. The "Laboratory Quality Improvement MS/MS Working Group" analyzes all raw data to evaluate performance. Among 135,000 newborns screened, 760 (56/10000) were G6PD deficient cases, 87 congenital hypothyroidism (6/10000), 14 cases of phenylketonuria (1/10000) and 5 cases of congenial galactosemia (0.3/10000). Only 8000 samples have so far been analyzed on MS/MS, in which one case of tyrosinemia, one case of methylmalonic aciduria and one case of CPT1 deficiency were detected. The PPV for the use of tandem mass spectrometry was 0.58. The gravity of metabolic diseases detected with a relatively high PPV justifies the expansion of the screening spectrum.

L20

Microarray as an Efficient Modern Molecular Tool in the Detection of Submicroscopic Genetic Abnormalities in Multiple Congenital Anomalies: Diagnosis and Prevention

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Birth of a child with multiple congenital anomalies (MCA) is a personal tragedy to the child and his/her family, and a great challenge in routine pediatric practice. 25% of all pediatric admissions are due to MCA, and most of them (about 50%) are of unknown etiology. Because of the complex clinical presentation, a precise clinical diagnosis of these patients is usually very challenging. About 30% of all MCAs are known to have a definite underlying genetic cause, majority of them being chromosomal abnormalities. Genetic diagnosis of patients with MCA is thus mainly based on chromosomal studies. With the advancement in technology and availability of new diagnostic methods, it is becoming increasingly evident that a number of patients classified as idiopathic or having unknown etiology, actually do have some underlying submicroscopic genetic alterations which are probably missed due to the limitations of microscopic resolution (5-10 Mb). Array based comparative genomic hybridization (Array-CGH) is one of the most advanced genetic diagnostic tool that enables the detection of novel microdeletions and/or duplication in patients with unexplained mental retardation and/or multiple congenital anomalies (MR/MCA). Multiple congenital anomalies are one of the major causes of concern in the Arab population. 33% of the referrals at our Genetic Center are of patients with MCA. We at our center have been able to identify several new submicroscopic chromosomal abnormalities in some of our patients with MR/MCA who had normal chromosomes by routine chromosomal analysis. Further analysis by microarray (oligo array-CGH), which enables a very high resolution detection (5-50 kb), revealed the specific underlying genetic abnormality. These abnormalities are novel and not reported earlier. This advanced molecular diagnostic method is becoming convincingly acceptable because of its power of unfolding a wealth of hidden information. Literature suggests that it has opened a totally new dimension in genetic diagnosis and medical practice. It is increasingly helping the patients and clinicians in a better understanding of the underlying genetic cause leading to this serious clinical condition, delineation of genotype-phenotype correlation, thus finally enabling an efficient patient care and counseling. Clinical applications of array-CGH and its importance in health care in the Arab population will be discussed.

L21

Prevention of Genetic Diseases: Understanding Families and Communities Hold the Key for Success

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The comprehensive health care systems and improvements in the quality of life in Golf Cooperation Council (GCC) Countries have resulted in better survival of children born with disadvantages. This has led to a progressive increase in the prevalence of genetic diseases and disabled in the community. Understanding social beliefs, respect of the traditions set up in Islamic community and understanding psychological difficulties faced by families affected by genetic disease is essential for planning care and prevention. In most circumstances, it is possible to discuss prevention after establishing a relationship with the family during the process of clinical assessment, investigation and non-directive genetic counseling. Experience in the Sultanate of Oman now shows that couples at risk of genetic disorders, who have been informed of the risk, seek all acceptable means to maximize their chances of having healthy children. A professional setting where geneticists, health educators, counselors and community support groups, all work together as a team in a friendly and positive manner create a solid base for successful prevention.

L22

Anhydrotic Ectodermal Dysplasia in Omani Families

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Hypohidrotic (anhidrotic) ectodermal dysplasia (HED), a genetic disorder characterized by defective development of hair, teeth, and eccrine sweat glands, is usually inherited as an X-linked recessive trait mapped to the X-linked ectodermal dysplasia locus, EDA, at Xq12-q13.1. The existence of an autosomal recessive form of the disorder had been proposed but subsequently had been challenged by the hypothesis that the phenotype of severely affected daughters born to unaffected mothers in these rare families may be due to marked skewing of X inactivation. Consanguineous Omani families with possible autosomal recessive HED have been identified on the basis of the presence of severely affected male and female siblings and unaffected parents. Homozygous mutation in the EDAR gene on chromosome 2, and mutation of the EDA gene on the X chromosome were found in Omani families. The recognition of non-allelic genetic heterogeneity and molecular genetic testing are crucial for genetic counseling.

L23

Genetic Disorders in Arab Populations

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Genetic disorders are chronic in nature and often require lifelong management with no definitive cure. In the Arab World, several disorders, including chromosomal (Down syndrome, Turner syndrome), single-gene (sickle-cell disease, thalassemia, glucose-6-phosphate dehydrogenase deficiency, hemophilia, inborn errors of metabolism) and multifactorial disorders (coronary artery disease, arteriosclerosis, diabetes mellitus, hypertension, obesity) are common. Some of these disorders have assumed epidemic proportions as in the cases of sickle cell disease, alpha-thalassemia, hypertension, and diabetes mellitus. Generally, genetic disorders are a leading cause of spontaneous abortion, neonatal death, increased morbidity and mortality in children and adults as well. They are a significant health care and psychosocial burden for the patient, the family, the healthcare system and the community as a whole. Since 2004, the Centre for Arab Genomic Studies (CAGS) aimed at determining the scale of genetic disorders in the Arab World. Overall, data available at CAGS indicate the presence of nearly 850 genetic disorders in Arab populations. The majority of these disorders include congenital malformations and chromosomal abnormalities followed by endocrine, nutritional, and metabolic disorders. Autosomal recessive inheritance occurs in about two-third of the cases, thus, emphasizing the impact of consanguineous marriages on the genetic morbidity of the populations in the region. Moreover, the genetic pathologies of nearly 250 genetic disorders remain unknown. Hence, the genetic characterization for these disorders will surely bring fresh insights to our understanding of the human genome.

L24

Evaluation of Cell Free Fetal DNA in Maternal Plasma of Early and Late Onset Pre-Eclampsia Patients

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Pre-eclampsia a severe disorder of unknown etiology remains a major cause of fetal and maternal mortality. Because of heterogeneous nature of this disorder, it could be sub-classified into two distinct forms termed early and late onset to better understand the cause. These two forms are defined as the development of symptoms before or after 34 weeks of pregnancy respectively. Cell free fetal DNA (cff DNA) concentration in maternal plasma may have diagnostic importance on pre-eclamptic pregnancy. By its nature, genetic marker has the characteristics of being completely derived reflecting fetal counterpart of pre-eclapmsia. The present study was conducted to evaluate cff DNA concentration in maternal plasma of early and late onset pre-eclampsia patients, correlate it with disease severity, fetal umbilical Doppler velocimetry and fetal birth weight. Thirty seven primigravida pregnant women manifested with pre-eclampsia were recruited. Patients were classified according the gestational age by first trimester ultrasound into *Group I* early onset having symptom before 34 wks of pregnancy (n=13) and *Group II* late onset having symptoms after 34 wks (n=14). Two groups *Group III* and IV n=20 of respective gestational age matched control. Blood was collected plasma was separated. Patients and controls were subjected to full antenatal examination, abdomen Ultra sonography, urine analysis, serum protein level, plasma DNA extraction and quantitative PCR amplification for both the *(SRY*) gene sequence on the Y chromosome (SRY-3317T) TaqMan probe and *beta-globin* gene by using of Light Cycler Real-Time PCR System. Cff DNA levels were highly significant elevated in the early preeclampsia studied group when compared to corresponding control group mean level 1040.6± 383.2 vs 98.2±.18.8 GE/ml ($P < 0.001$). Significant elevation was revealed when comparing cff DNA in late onset preeclampsia group with their matched control mean level 554.5±196.0 vs 100.1±18.04 GE/ml ($P < 0.05$). Meanwhile, high significance was shown between early and late onset preeclampsia ($P < 0.001$). Most obviously Quantities of fetal circulating DNA in early rather than late onset preeclampsia group were significantly negative correlated with fetal birth and fetal umbilical blood flow($r= -0.44, -0.520$ respectively ($P < 0.05$). Evaluation of cff DNA in Maternal plasma is a valuable marker in preeclampsia and its associated fetal outcome particularly in early onset cases. To be widely applicable Nucleic acid marker are needed that are equally relevant for male and female fetuses. Future studies seeking to understand the value of cff DNA evaluation in preeclampsia should clearly separated into early and late onset cases in order to avoid reaching conclusion based on cases from only one subtype being studied.

Poster Presentations

P1

Modification of Tongue Guard for Speech and Functional Rehabilitation in Children with Down Syndrome

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Down Syndrome is the first chromosomal disorder to be defined, and the most common cause of mental retardation. Mental retardation in Down syndrome ranges from severe to low average range. The single most characteristic feature of Down syndrome in newborn and infants is hypotonia. This hypotonia is reflected in particular on facial expression and oral dysfunctions causing lack of mastication, deglutition and speech. The present study introduces a modification of classical tongue guard to be used by children with Down Syndrome aiming to develop better speech environment and improve motoricity of tongue and orofacial muscles in these children. This study was carried out on a group of twenty two children affected with Down aged between five and eight years. Ten of the selected samples were taken as control group while the other twelve children were considered subjects for the study. The subject group were given the modified tongue guard “mobile tongue retractor ” to be used for a period of six months in the rate of two hours daily divided into four equal cessions . Both groups are free from any hearing defect and both of them attended the interdisciplinary oral consultation sessions. Assessment was made for the following: Lip position and mouth posture, tongue position, occlusion and speech. Statistical analysis of the obtained results should improvement in all muscular parameters (mouth posture, tongue position and occlusion). These parameters showed statistically significant differences between the subject and the control group. On the other hand, hypernasality showed slight improvement, but less than the muscular parameters.

P2

Prevalence Rates of Congenital Anomalies in Giza, Egypt (2005-2007): Establishment of Population Bases Registry

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Much remains to be learned about the prevalence and etiology of congenital anomalies. Despite recent advances in genetics and reproductive biology, nearly two thirds of birth defects are of unknown etiology. In the present study, a population-based birth defect monitoring system was initiated based on data from two hospitals and two maternity centers in Giza. Data on cases were coded according to the four-digit malformation codes of the International Classification of Diseases, Tenth Revision (ICD-10). This study presents rates of congenital anomalies occurring among the 70,574 live born in Giza during the period from July 2005 till April 2007. Five hundred eighty cases with congenital anomalies (CAs) were identified, with a rate of 8.2 /1000. Of the 580 reported cases of CAs, 90 cases were identified with isolated CAs (15.5 %) and 490 with multiple CAs (84.5 %). The central nervous system was the most frequently affected (2.64 /1000), followed by musculoskeletal system and limb anomalies (2.14/1000), congenital heart defects (0.78/1000) and genitourinary tract anomalies (0.75/1000). Congenital anomalies of chromosomal origin were documented in 64 cases (0.91/1000). Males had a higher rate of congenital abnormalities than females (4.6/1000 versus 3.4/1000). Consanguinity was documented in 54.3% of the cases with 43.3% first cousins. The data from this study of congenital anomalies in Giza, Egypt may be used as the baseline information to establish a population-based registry of birth defects in the area for proper health care and planning.

P3

A Registry for 4749 Cases with Genetic Disorders Associated with Orodental Anomalies

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Genetic disorders have been a major health problem to every society. Orodental diseases impose an economic, social and health impact on the family as well on the society. Egypt has a high rate of heritable genetic diseases (nearly 10%) and also a high rate of associated orodental anomalies. This situation can be utilized to study how the genomic defects cause the disease and consequently search for novel dental preventive and treatment modalities. Prevention and early intervention for orodental diseases will improve the overall health status of individual as well as the society and will alleviate the economic and psychological burden on the family and the community. The objectives of the work was to establish a data base for orodental anomalies in genetic disorders by registry of 4749 case during the last five years, thus emphasizing on congenital and developmental anomalies of the mouth to aid in the diagnosis since it has been recognized as being associated with genetic disorders and to help in early intervention, to reduce the burden of orodental diseases at the individual, family and community levels. To establish a registry for genetic diseases associated with orodental and craniofacial abnormalities: (1) A special computer program for registry of cases referred to the oro-dental department was constructed to establish a data base for the orodental anomalies in the genetic disorders. (2) 4749 cases were filled on sheets to facilitate the registry on the computer program. (3) Statistical analysis to this data was done and the percentage of the most common anomalies in each diagnosis was recorded.

P4

Detection of Mitochondrial Abnormalities for Various Mitochondriopathies at the Shafallah Genetics Center

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Mitochondrial diseases are clinically a heterogeneous group of disorders that give rise to dysfunction of the mitochondrial respiratory chain. They can be due to mutations of the mitochondrial DNA (mtDNA) or the nuclear genome. There are many mitochondrial disorders prevalent in the Arab world such as MELAS, LHON, CPEO, Mitochondrial myopathies and Leigh syndrome (LS). There is no reason to assume that diseases caused by mutations of the mitochondrial genome are more common in the Middle East. However, consanguineous marriage patterns mean that mitochondrial syndromes caused by nuclear genes inherited in autosomal recessive manner should be more common. For this reason, the Shafallah Genetics Medical Center will be active in mapping nuclear genes associated with mitochondrial abnormalities and studying nuclear-mitochondrial interactions. The center is capable of conducting various diagnostic assays to detect mtDNA abnormalities. These include: i) Sequencing the full mtDNA genome; ii) detection of mtDNA deletion(s), which is usually performed on DNA extracted from skeletal muscles; iii) measurement of relative mtDNA content by real time PCR and iv) assessment of mtDNA oxidative stress status either in blood or urine samples.

P5

Haptoglobin Gene Polymorphisms in Kuwaiti and Nigerian Sickle Cell Disease Patients

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Haptoglobin (Hp) is a sialoglycoprotein with hemoglobin-binding capacity that plays a key role in preventing the toxic effects of free hemoglobin (Hb) liberated in hemolytic states like sickle cell disease (SCD). There are 3 major functional Hp phenotypes: Hp 1-1, Hp 2-2 and the heterozygous 1-2. Hp 1-1 is the most effective in binding Hb, while 2-2 is the least and 1-2 is intermediate. Hp 2-2 is a recognized genetic risk factor for atherosclerosis, while 1-1 protects against vascular complications of diabetes mellitus. Its role in the pathophysiology of SCD has not been documented. We have carried out Hp genotyping in 30 Kuwaiti and 31 Nigerian SCD patients using a PCR technique. The Hp genotype results are as follows:

Hp Genotype	Nigerian (n=31)	Kuwaiti (n=30)
2-2	3 (9.7%)	16 (53.3%)
1-2	15 (48.4%)	12 (40.0%)
1-1	13 (41.9%)	2 (6.7%)

The frequency of the Hp-2 allele is 0.34 among the Nigerian and 0.73 in Kuwaiti patients. Hp polymorphism is therefore a significant discriminating factor in the two groups. While the differences probably reflect the ethnic backgrounds of the patients, it will be interesting to see if the genotype has any correlation with different SCD phenotypes e.g. frequent severe vaso-occlusive crisis, osteonecrosis and brain infarcts. This is the focus of ongoing research.

P6

Thalassemia Intermedia Due to a Novel Mutation in the Second Intervening Sequence of the Beta-Globin Gene

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We describe a new β-thalassemia mutation in the β-globin gene of an 8 year-old Moroccan boy. This homozygous mutation produces a phenotype of thalassemia intermedia and is associated with the Mediterranean haplotype IX. We discuss the pathophysiological consequences of this mutation located near the 3' end of the β-globin IVS II.

P7

A Genodermatosis : A View from Saudi Arabia

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It is estimated that there are more than 2000 named dermatological diseases. The pattern of dermatological diseases is different from one place to another being influenced by many factors like the environment, and the social and economic status. It has been also estimated that 300 of the dermatological diseases are caused by genetic disorders. Some of them are common and some are rare. The definition of ‘‘rare’’ in diseases is different. A disease is considered rare in United States, when it occurs in less than 200,000 individuals, while In Europe, a disease is considered as rare when it affects 1 person per 2,000. However a rare disease in a given area might be fairly common in the other areas. Due to large family size and consanguinity, genodermatoses are more common in developing countries. Due to less public health education, there are some myths and misconceptions that surround the genodermatoses, and hence perpetuate the sufferings of affected patients. In this presentation, few examples of uncommon genodermatoses like Kinder syndrome, hereditary hypotrichosis simplex, and multiple hereditary trichoepithelioms (MHT) will be presented, together with a proposed strategy to fight this major public health problem.

P8

Service Indicators for a Regional Hemoglobinopathy Preventive Program in Dohuk-Iraq

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β-Thalassemia major and sickle cell disease are important health problems in Dohuk Governorate at the extreme north of Iraq, which made instituting proper preventive programs a necessity. Accordingly, and as a prerequisite for such a program, the Governorate was mapped for these hemoglobin disorders, the service indicators of the preventive program were assessed, and the β-thalassemia mutations were characterized. A total of 591 couples (1182 individuals) attending the health centers for premarital checks were screened. 44 (3.7%) were found to be carriers of β-thalassemia, 14 (1.2%) of the sickle cell gene, and one (0.1%) of δβ-thalassemia. Three couples (5/1000) were found to be at risk of having children affected by β-thalassemia major. While the estimated number of affected children expected with a major hemoglobinopathy was 39 per year. The β-thalassemia defects of 213 chromosomes were characterized using ARMS and reverse hybridization techniques and it was found that the most prevalent mutation was the IVSII.1 (G>A; 22.1%), followed by Codon 44 (-C; 14.1%) and IVS I.1 (G>A; 10.3%). The above findings stress the importance of a regional preventive program, and will help set the stage for initiating such a program for these hemoglobinopathies based on premarital screening, counseling and prenatal diagnosis.

P9

Pre-Marital Genetics Screening: The Saudi Experience

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Saudi Arabian cultures are tribal and heavily consanguineous. Marriage between cousins has been part of the culture for millennia leading to “founder” effect and a large number of autosomal recessive diseases. Informed premarital screening for genetic blood disorders, thalassemia, and sickle cell anemia (which is not linked to any type of enforced prevention of marriage) has been mandatory in KSA for the past three years, after it was approved by a Fatwa. In the year 2004 and 2005, screening of almost a quarter a million people from 130 Ministry of Health primary health care centers were carried out. 2,003 and 2,441 cases of incompatibility were identified respectively; of which Sickle Cell traits of 4.19% and 4.21%; Sickle Cell cases of 0.27% and 0.25%; β thalassemia minor of 3.2% and 3.24%; β thalassemia major of 0.08% and 0.06%, were identified. This screening has subsequently led to a decrease in consanguineous marriages in the screened population of 9.2% and 11.6% for the years 2004 and 2005 respectively. However, the system is not yet able to follow-up on all incompatible cases

P10

Pre-implantation Genetic Diagnosis (PGD) for Genetic and Metabolic Disorders in Saudi Arabia

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Saudi Arabian culture is highly consanguineous, with the first cousin marriages accounting for 60-70% of all marriages. Given the difficulties in management of genetic disorders, preventive measures for the suffering families from autosomal recessive disorders by doing pre-implantation genetic diagnosis is undertaken. Almost20 cases are successfully prevented by PGD. The first of these disorders is Sanjad-Sakati Syndrome (SSS), OMIM# 24140, which is characterized by congenital hypoparathyroidism, growth and mental retardation with a unique 12bp deletion. The second is Niemann Pick Disease type B (NPD-B), OMIM# 257200, (acid sphingomylinase (ASM) deficiency) with more than 70 mutations have been reported in (SMPD1) gene, which presents with severe phenotype in Saudi Arabia. Four unique mutations are found in our Saudi families. A family with (W533R) mutation in the (SPMDI) gene suffering from a severe phenotype underwent PGD. The third disorder is Morquio's disease (MPSIV), OMIM # 253000, with severe classic phenotype with N-acetyl galactosamine-6-sulftase deficiency (MPSIV-A). More than 20 different mutations in (GALNS) gene have been reported in (MPSIV-A). A family with three affected siblings with severe classic (MPIV-A) with detected W195C mutation in the (GALNS) gene underwent PGD. In all these three families PGD was undertaken using fluorescent PCR (F-PCR) and/or nested PCR with sequencing on a single cell. A singleton pregnancy ensures after transfer of one heterozygous and one normal embryo and prenatal diagnosis by CVS confirmed a normal pregnancy. This is the first report of successful PGD in different genetic disorders in Saudi Arabia.

P11

Premarital Counseling Services in the Kingdom of Bahrain: 1985-2007

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Premarital counseling started in Bahrain in 1985 in the Genetic Clinic at Salmaniya Medical Center. In 1993, a voluntary premarital counseling service was established in all health centers. The main objective of premarital counseling is to reduce hereditary disorders especially the common hemoglobinopathies in Bahrain i.e., sickle cell disease and thalassemias. The other objectives is provide counseling regarding high-risk behaviors, including those related to HIV, Hepatitis B, and other infectious diseases. To promote awareness regarding reproductive health, family planning, and healthy lifestyles, and to provide immunizations medical, social, and psychological support when needed. More recently a law (Government Gazette: Issue 2640, 23rd June 2004) has been passed by the Bahrain Government which requires that all Bahraini couples, who are planning to marry, undergo mandatory premarital counseling. The development of this law included wide consultation with all stakeholders to ensure that socio-cultural mores, theological issues and aspects of human rights had been considered. During 2005 and 2006, after the implementation of the law 9107, 8711 clients attended the clinic, respectively. Out of these, 1% and 1.2% presented with SCD and 12.9% and 14% were carriers for SCD. Beta thalassemia major prevalence was reported in 0.2% and 0.3% of clients, while 2.6% and 3% were carriers for beta thalassemia. In addition, G6PD-deficiency was reported in 22% and 25% of clients, respectively. These frequency figures were similar to those obtained from the student screening program. The presentation will discuss the degree of satisfaction of the clients and their opinion to improve this service. With these measures, we hope to contribute toward reducing the number of affected newborns and thereby reducing their morbidity and mortality rates.

P12

Metformin and the Genetic Variations of Organic Cation Transporters

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Metformin is a biguanide used as an oral hypoglycaemic agent in the treatment of type 2 diabetes mellitus (DM). According to the United Kingdom Prospective Diabetes Study, metformin is the drug of choice for the treatment of overweight newly diagnosed type 2 diabetics. Metformin is excreted into urine almost entirely in an unchanged form. The renal clearance of metformin is much higher than the glomerular filtration rate in humans suggesting a significant contribution of tubular secretion in addition to filtration. Organic cation transporters (OCT) have been suggested to mediate tubular secretion of metformin, and studies have shown that metformin is a superior substrate for the OCT2 rather than OCT1 which is mainly expressed in the renal basolateral membrane. However, other studies have shown the involvement of OCT1 in the disposition of metformin, which is primarily expressed in the liver. Studies showed that human genetic variants of these transporters can explain some of metformin pharmacokinetic variability. The aim of the present study is to (1) investigate the factors affecting metformin plasma concentrations and (2) to investigate the correlation between the genetic variations in OCT1 and OCT2 and metformin plasma concentration in a single ethnic diabetic group (UAE population). A cross sectional study, fasting blood sugar, lactate, serum creatinine, glycated haemoglobin, metformin level, and DNA samples will be collected from participating type 2 diabetic patients. Genetic variations of the drug transporter genes lead to accumulation of metformin in the plasma, therefore, contribute to inter-individual differences in response to metformin therapy, and adverse effects.

P13

Assessment of the Frequency of a Novel MRE11 Mutation Responsible of the Rare Ataxia Telangiectasia-Like Disorder in Saudi Population

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Ataxia telangiectasia-like disorder (ATLD) is a very rare variant of ataxia telangiectasia (AT). MRE11 mutations are the underlying cause of ATLD. Recently an MRE11 mutation was described in 10 ATLD Saudi Arabian patients from three unrelated families. Clinically the patients had early onset, slowly progressive, ataxia plus ocular apraxia phenotype with an absence of immune deficiency. Genetically, the patients were homozygous for a novel missense mutation, a G to C change at nucleotide 630 of the MRE11 gene. The resulting amino acid change at position 210 (Trp to Cys) results in a destabilization of the Mre11–Rad50–Nbs1 (MRN) complex required to activate pathways involved in cell cycle checkpoints activation, DNA repair and the onset of apoptosis following genotoxic stress. The high number of Saudi ATLD patients with this particular mutation in MRE11 would suggest noticeable frequency in the general population of Saudi Arabia. The aim of the present study was to assess the allelic frequency of this mutation in Saudi population. A cohort of 220 Saudi national were studied. The 630G>C mutation were genotyped by direct sequencing. The 440 alleles were all wild-type (G/G). This might suggest that the mutation is limited to geographically isolated families as the 10 patients were all from the detached central region of Saudi Arabia. Larger studies with members from different Saudi regions are required to estimate the frequency of this mutation in Saudi Arabia. Supported by KFSH&RC grants 2000 031 and 2040 025.

P14

Down Syndrome Studies in Oman

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The birth prevalence of Down syndrome (DS) seems to be high in Middle Eastern States. Here, we present the first relevant study of DS in the Sultanate of Oman. From 2000 to 2006, the ascertainment of DS can be considered almost complete. Analysis yielded an unusually high prevalence of 1: 383 among live births (sex ratio 1.3). In almost 90% of cases, the cytogenetic diagnosis was performed within 6 months after birth. Based on a case-control study, increased maternal age was identified as a significant risk factor for DS, but not sufficient to explain its high prevalence. In all informative cases (N = 95) the non-disjunction error occurred during oogenesis. Consanguineous marriages were higher among parents of DS children than in the Omani population in general. The identification of additional risk factors is a challenge and of great relevance with respect to primary prevention and adequate genetic services.

P15

Termination of Pregnancy for Prevention of Genetic Disease: An Islamic Perspective

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Termination of pregnancy (TOP) is always a difficult decision to make on parents and physicians irrespective of the religious belief. Being not a mere medical choice, TOP has complex ethical, moral, and legal considerations and leaves parents with enormous psychological burdens that are sometimes intolerable. On the other hand, ending the life of an embryo is the only option for preventing many genetic disorders and will likely remain to be the most effective way of prevention in various genetic conditions. Honoring humans and observing the rights for the fetus, parents, and society constitute the basis for the approach to the Islamic ruling in this issue. The dignity and respect for the fetal life should be observed and protected; without a legitimate reasoning form an Islamic jurisprudence standpoint, ending the life of a fetus is generally forbidden and is considered an assault and a sinful act. In this presentation, we review the stages of embryo development according to the Holy Quran and Sunna; the time of breathing the soul into embryo as an important landmark in relation to TOP is addressed. We also review the position of the major Fiqh Schools on TOP and the stands of the main Ifta Councils in the Islamic World. Furthermore, we attend to the different opinions of contemporary scholars in this matter.

P16

Molecular Genetics in Brain Primitive Neuroectodermal Tumors

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Of more than two hundred cases of primitive neuroectodermal tumors (PNET) of central nervous system diagnosed three relevant subtypes of PNET with specific cytogenetic findings are usually identified. These are medulloblastoma, lipidized medulloblastoma (liponeurocytoma) and atypical teratoid/rhabdoid tumor (ATT/RT). Genetic features in these tumors can be studied by conventional cytogenetic, molecular cytogenetic and molecular genetic in correlation with prognosis in these tumors. 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. Labeled Streptavidin-Biotin method is used to demonstrate the presence of epithelium membrane antigen, cytokeratine, vimentin, desmin, smooth-muscle Actin, S-100 protein, neurofilament protein, glial fibrillary acidic protein, synaptophysin, alpha fetoprotein, placental alkaline phosphatase, and human chorionic gonadotropin using antibodies on paraffin embedded tissues. Over a period of sixteen years more than 200 cases of CNS-PNET are identified. 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. This retrospective study makes use of more than 200 cases of CNS-PNET, and enables identification of these subtypes to help predict more accurately their histological behavior and their clinical outcome, based on their morphological, immunohistochemical, and cytogenetic profiles.

P17

Variations of G Protein-Coupled Receptor 40 Gene and its Association with Type 2 Diabetes Mellitus in Omanis

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Recently, a G protein-coupled receptor 40 (GPR40) gene has been highlighted as a new gene that may be associated to type 2 diabetes mellitus (T2DM). It was shown that the GPR40 receptor is expressed predominantly in the pancreatic β-cells and that it mediates an amplifying effect of free fatty acids on glucose-induced insulin secretion. For this, this study aimed to examine the coding and promoter regions of the GPR40 gene for variations by sequencing and to assess whether identified variants were associated with T2DM in Omanis. Genotyping of the GPR40 gene were performed for 89 T2DM samples and 40 control samples. One single nucleotide polymorphism (SNP) was found in the coding region (G/A) and two consecutive SNPs in the promoter region (T/C and G/A). For each SNP, allelic and genotypic frequencies were calculated. The results indicated that allele A of the G/A SNPs in the coding region as well as the promoter region was the common allele in both groups. For the T/C SNP in the promoter region, allelic frequencies of 0.57 and 0.43 were calculated for the T and C alleles respectively in T2DM group. The control group had a frequency of 0.6 for allele T and 0.4 for allele C. Genotype frequencies, for each SNP, were used to test for any associations with type 2 diabetes. None of the three SNPs found in this study was associated with T2DM in Omanis. Haplotype reconstruction and analysis were performed for the promoter SNPs. The results showed no significant difference in haplotype frequencies between the two tested groups. From these results we concluded that variations in the promoter and coding regions of the GPR40 gene found in Omani individuals do not appear to be associated with type 2 diabetes.

P18

Neonatal Cord Blood Screening with HPLC - Towards Comprehensive and Improved Patient Care of Sickle Cell Disease in Oman

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Oman is a country with a population comprising of a wide range of ethnic groups, high rates of consanguinity and increased incidences of inter-cousin marriages. There is an increased prevalence of hemoglobinopathies which is of growing importance as knowledge of a population structure can be a unique aid in planning genetic services. The aim of this study was to establish neonatal cord blood screening in the Sultanate of Oman, in an effort to determine the prevalence of hemoglobinopathies by a cost-effective method. High performance liquid chromatography [HPLC] is a powerful tool to screen newborns for hemoglobinopathies. Neonatal screening includes cord blood samples collection, screening, and follow up of all newborns with abnormal results. A total of 7837 consecutive cord blood samples were screened for presence of possible hemoglobinopathies by HPLC using Biorad Variant II program between April 2005 & March 2007. Complete blood counts [CBC] were also obtained on Cell Dyn 4000 automated blood cell counter. All samples were then processed to isolate and store mononuclear leukocytes for subsequent molecular diagnostics. The findings indicated a 47.07% incidence of α–thalassemia, based on low mean cell volume [MCV] & mean cell hemoglobin [MCH] on the CBC and significant amounts of Hb Barts on HPLC. The overall incidence of other hemoglobinopathies was 9.87%, with 5.47% incidence of sickle hemoglobin. On HPLC, D-window, E-window and C-window were present in 0.93%, 0.77% and 0.06% of the samples respectively. Since HPLC cannot diagnose beta thalassemia major at birth, in samples with HbA below 10%, the beta globin gene was directly sequenced including the promoter, all exons and introns in these samples. Amongst 206(2.62%) samples sequenced, beta thalassemia trait was confirmed in 201 cases and 5 cases were found to be homozygous for beta thalassemia major. Additionally, direct sequencing of all abnormal samples with HbS [n=429], HbD [n=73], HbE [n=42], and HbC [n=5] was also performed on ABI Prism 3100 genetic analyzer to assign the correct genotype status to these subjects and use the same to validate the HPLC results. The significantly high incidence of hemoglobinopathies in newborns in the Sultanate of Oman emphasizes the value of neonatal cord blood screening to be implemented as the first step in the national strategy towards total management of hemoglobinopathies including early diagnosis, comprehensive clinical care and counseling of the affected families. The results of this large study wound indicate that using HPLC [<2 USD/sample] is a cost effective method. Moreover, prescreening of both parents and selecting only samples of neonatal cord blood from newborns with either parent having an underlying genetic trait for hemoglobinopathy would result in the a huge cost saving to the tune of over 90% as compared to universal neonatal cord blood screening and can be recommended as a highly cost-effective method targeted to screen only the abnormal samples.

P19

FamGUARD: Paving a Way for Molecular Services in Oman

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Genetic services provision is a global issue; even in high-income countries, costs exceed available resources. Oman has greater problems; the infrastructure for genetic services is less; genetic illnesses (especially autosomal recessives) are common; genetic epidemiology is scanty. To address this, a strategic project, FamGUARD (Family and Genetic Understanding of Autosomal Recessive Diseases), supported by H M Sultan Qaboos' Research fund, was designed. Clinical information, pedigrees and blood samples were collected from families with multiple affected individuals. In all families, homozygosity testing was performed using whole genome analysis by Single Nucleotide Polymorphisms (SNP) testing, followed by local microsatellite-based linkage. Within the identified loci, disease-specific mutation analysis was attempted in candidate genes. Several loci were identified with LOD scores above 3.7 for AR disorders, including hereditary spastic paraplegia, late infantile seizures, Bardet-Biedl syndrome, dilated cardiomyopathy and neonatal hepatic failure. Mutations characterized are being analyzed for etiological significance. This model for molecular investigation, with earlier use of whole genome analysis in informative families, has produced significant scientific results as well as mapping data which might be used to initiate more focused genetic counseling.

P20

Another Locus for Hereditary Spastic Paraplegia (SPG35) Maps to Chromosome 16q21-q23.

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Hereditary spastic paraplegias (HSPs) are clinically and genetically heterogeneous neurodegenerative disorders in which the main clinical feature is upper motor neuron degeneration leading to progressive spasticity and weakness of the lower limbs. To date, 14 autosomal recessive HSP loci have been mapped. A large consanguineous Omani family in which an autosomal recessive form of HSP is segregating was ascertained. Age of onset varied from 6-11yrs; two individuals also had seizures. Following exclusion of known ARHSP loci, gene chip SNP analysis was performed on all affected individuals using the Affymetrix 250K STY chip to map the relevant disease loci. All 7 affected individuals shared a 20.4Mb (3.25cM) region of homozygosity located on chromosome 16q21-q23.1, defined by SNP markers rs149428 and rs9929635 with a peak multipoint LOD score of 4.86. Two candidate genes, dynein cytoplasmic 1 light intermediate chain 2 (DYNC1LI2) and vacuolar protein sorting 4 homolog A (VPS4A) were sequenced but no disease causing mutations were identified. We have located the chromosomal location of a new form of HSP (SPG35) and defined the clinical features; the disease causing gene has not yet been identified.

P21

A Dysmorphic Girl with Acrocephaly, Seizures, Long Fingers and Cherry Red Spots: A New Association?

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A dysmorphic 10- month old girl referred with chronic generalized tonic clonic convulsion resistant to sodium valproate, but completely controlled with carbamazepine.. The girl was acrocephalic with flat occiput and has epicanthic fold and bilateral mild convergent squint. The parents were able to identify at birth that their daughter has similar appearance to her previously died siblings. At the age of 10 month she didn't have any visible tooth. Her fingers were long and spindle in shape. All of her growth parameters were just below the third centiles for age and sex .Her weight was 7 kg, length was 63cm, and her head circumference was 40 cm. The rest of the examination was normal. She didn't have congenital heart defect or abdominal organomegaly. Her muscle tone and tendon reflexes were normal. Fundoscopi examination showed bilateral macular cherry red spots. Cetavlon test for mucopolysachridosis was negative. Abdominal sonography revealed normal finding CT scan of the brain was normal. Chromosome analysis was normal. Serum and urine chromatography showed no abnormal amino acids. Chromosomal analysis showed normal female karyotype. The patient may have a new clinical association or clinical syndrome that occurred in familial pattern suggesting autosomal recessive inheritance.

P22

Genetic Polymorphism of Drug-Metabolizing Enzymes (Pharmacogomics) in Qatari Population

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It is clear that one drug can not fit all and one dose does not suit all. The importance of understanding "individuality" in drug response and associated benefits (avoiding drug toxicity, increasing drug efficacy, fine tuning the drug towards its target) has aroused great interest in recent years. The field of "Pharmacogenetics" (genetic basis of inter individual and interethnic variations in drug metabolism) is revitalized and even expanded towards "Pharmacogenomics" (aiming at right drug to the right patient at right dose) because advances in human genome project allow a present vision of personalized prescription of drugs according to the genetic make up of a given patient. In this context, a ground molecular epidemiological screening work was performed in healthy Qatari population where there is paucity of information. Towards understanding the molecular basis of pharmacogenetic polymorphism of enzyme loci in ethnic Qataris, we analyzed the sequence variations in CYP2B6, CYP2C9, and CYP2C19 gene loci of phase I drug biotransformation and GSTM1 and GSTT1 gene loci of phase II pathway in one hundred (200 chromosomes) available DNA bank from healthy ethnic Qatari volunteers. Genotyping of known alleles of CYP2C9, CYP2C19 and CYP2B6 genes were explored through TaqMan SNP assay system. A multiplex PCR method was used to detect the deletional alleles of GSTM1 and GSTT1 genes. Our data suggest a specific frequency spectrum of variations in ethnic Qataris, with values intermediate between Caucasians and Asian-Indians for both GST loci but a similar one to Caucasians for all CYP loci explored. Nevertheless high prevalence of homozygotes likely reflect the high consanguinity rate, particularly for CYP2B6*9 alleles. Relevance of these findings will be discussed in the context of breast cancer treatment.

P23

Genetic Polymorphic Profile of Qatari Population for Fifteen Autosomal Loci

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Diversity profile of 15 short tandem repeat (STR) loci was evaluated using AmpFISTR Identifier kit (Applied Biosystems) in DNA from 120 healthy native Qataris after informed consent. All the 16 markers (including the Amelogenin gender differenciator) were amplified by PCR using the commercially available "Identifier primer set" in a multiplexed reaction. Size separation of the PCR products was carried out by electrophoresis on a 3100 genetic analyser (Applied Biosystems) including positive and negative controls as well the size standards. Allele identification and tabulation was performed using Genemapper v3.2 software. Statistical analyses including determination of the matching probability, power of discrimination (PD), polymorphism information content, power of paternity exclusion (PE), and typical paternity index were performed using the software PowerStats (Promega Corporation, Madison, Wisconsin). The discriminating power of a locus, which represents the probability that two randomly chosen subjects do not have the same genotype, was calculated as 1-Pi, and the combined discriminating power of the 15 loci as 1 - (Π Pi), where Pi is the sum of the squares of frequencies of all genotypes at a given locus. The higher the discriminating power of a locus, the more efficient it is in discriminating between members of the population. The power of paternity exclusion, defined as the fraction of individuals who would not have the same DNA profile, was calculated from the following formula: PE=h2 (1-2hH2), where h is heterozygote frequency and H is homozygote frequency. The higher the PE value, more the non-fathers are excluded. The combined power of paternity exclusion was calculated as 1 – Π(1- PEi). The typical paternity index was calculated as (H+h)/2H. Overall genotype distribution adhered to expectations from Hardy-Weinberg equilibrium by three independent testings for all markers (0.00333). No significant linkage disequilibrium (LD) was noted between any pair of loci after Bonferroni correction (0.000476). We found that the most discriminating locus in the study population was D2S1338 (PD=0.969), while the least informative locus was TPOX (PD=0.821). Individual power of exclusion values ranged from 0.322 (TPOX) to 0.762 (FGA). They indicated low degrees of exclusionary power for the loci when used individually. However, combined power of discrimination and combined power of exclusion were both estimated to be greater than 0.9999 for the Qatar population sample, thereby demonstrating the forensic utility / individual identification of a multilocus-based analysis.

P24

The Genetic Basis of Nonsyndromic Deafness in Saudi Arabia

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Congenital sensorineural hearing impairment affects approximately 1/1000 children in western countries. About 60% of all cases of sensorineural deafness are estimated to be of genetic origin, mainly with autosomal recessive inheritance. More than 400 genes are involved in the hearing process, and over 130 genes are identified that cause hereditary deafness (HD). Mutations in the Connexin GJB2 and GJB6 genes account for 50% of non-syndromic HD in various populations. A project has been launched in Saudi Arabia since 2005 to identify the most common loci for nonsyndromic hearing loss aiming to (1) collect 1000 individuals affected by HD→ 823 patients/family members enrolled, (2) screen all individuals for mutations in the Connexin genes→ Analysis in 500 individuals → GJB2 and GJB6 account for ~5% of HD, and (3) select families with the strongest histories for linkage analysis → 96 families (2 or more affected) and 27 families (3 or more affected). Fifteen families so far linkage conducted. The initial results indicate that Connexin genes play a minor role (~5%) in HD in Saudi Arabia. Two loci were identified through linkage analysis, a novel mutation in USH1G and a previously reported mutation in the MYO7A. Our methods for characterization of HD are robust and the application of this knowledge to newborn and pre-marital screening will have a major impact upon early intervention and prevention of HD in Saudi Arabia.

P25

Permanent Neonatal Diabetes Experience from Southern Region of Saudi Arabia

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Neonatal diabetes (both transient and permanent) is very rare with an estimated incidence ranging from 1:400,000 to 1:500,000 neonates. It can be isolated, part of an association, or part of a syndrome (e.g., Wolcott-Rallison Syndrome). In this paper we are reporting the association between Permanent Neonatal Diabetes Mellitus (PNDM) and Central hypothyroidism, hemolytic anemia, and microcephaly (with brain dysgenesis) with a total of five cases over a period of four years (2001 to 2005), reflecting higher incidence (1:50,000).

P26

Saudi's Perception of Premarital Screening and Consanguinity

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Saudi Arabia has been ranked among countries with high consanguinity and inbreeding levels, thus giving rise to Autosomal recessive genetic disorders, mainly genetic blood disorders. Therefore, the premarital screening program was introduced in 2004 to help in the prevention of common genetic blood disorders in the country. With the aim of examine the perception of young Saudi adults towards the program and the practice of consanguinity in the country. 108 questionnaires were distributed to the targeted public, followed by semi-structured interviews with ten participants. The outcome of the study revealed a general acceptance and awareness of the premarital screening program alongside some basic information on hereditary diseases. But this did not necessarily indicate proper understanding of the services provided by the program, as several misconceptions were expressed. It was abundantly clear from the findings that consanguineous marriages are commonly practiced in the country. Reasons given for this common practice were manly associated with the Bedouin culture and the social structure of the Saudi community with some reference to financial issues. It is evident from the results of this study that extra information and educational campaigns need to be provided for the public explaining the reasons for premarital screening and relationship between consanguineous marriages and genetic disorders, to tackle any misunderstanding and to improve the standard of health services, with consideration given to the cultural and social behavior of the Saudi community.

P27

Novel ASL Mutations Underlying Argininosuccinic Aciduria in Saudi Arabia

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Argininosuccinic aciduria (ASA) is common in Saudi Arabia as a consequence of extensive consanguinity. It is the most common urea cycle disorder identified by the Metabolic Screening Laboratory of our Institution. Affected patients are confirmed biochemically by Tandem Mass Spectrometry, which whilst sensitive, cannot be used for carrier detection. Establishment of the range and incidence of mutations underlying ASA in this population were not previously established. We utilized Whole Genome Amplification, PCR and direct sequencing to identify the molecular lesions underlying ASA. A missense mutation (Q354X) that accounts for 50% of Saudi patients with ASA was recently reported by our institution. In this study we report a further four novel mutations (D115Y, G157R, R186W and G361X) found in Saudi patients with ASA. The missense and one nonsense mutation were confirmed by their absence in ~300 chromosomes from the normal population. Cross species conservation of amino acid residues was observed in some but not all instances. Where parental and other familial DNA samples were available, segregation of the mutation in an autosomal recessive pattern of inheritance was confirmed. Together the five mutations described above cover ~90% of ASA patients in Saudi Arabia. This coverage provides efficient molecular diagnosis of ASA in the Saudi population and lays the foundation for preventative measures including inductive screening in extended families, counseling, and regional pre-marital screening.

P28

Knowledge and Beliefs of Saudi Parents About their Child's Genetic Condition

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This study was initiated based on the importance of understanding the cultural background of a society when it comes to developing and implementing a healthcare service such as genetic counseling. The study explored the knowledge and beliefs of Saudi parents towards genetic diseases and conditions using a selective sample from within the Saudi population, a population scarcely studied in such a context. Data were collected using semi-structural interviews from 15 Saudi parents of children with a genetic condition. The data provided a general idea of culturally-shaped beliefs held by Saudi parents with regard to genetic disease causation. Two major themes emerged from the analyzed interview transcripts with regard to disease causation: scientific knowledge and lay beliefs. The findings showed that personally-held beliefs fluctuate throughout time and are affected by several influential factors revolving around three main domains: health-related issues, divine intervention, and the evil eye. The study's findings also revealed factors used by Saudi parents to support or use as counter-evidence against the hereditary explanation offered by healthcare professionals of their children's condition.

P29

Mice with Altered Expression of α-Actinin-4 Exhibit Distinct Morphologic Patterns of Glomerular Disease

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Mutations in ACTN4, encoding the actin-binding protein α-actinin-4, cause a form of familial Focal Segmental Glomerulosclerosis (FSGS). We developed two strains of transgenic mice, one strain carrying a human disease-associated mutation in murine Actn4, and another strain that does not express α-actinin-4 protein. Using light and electron microscopy, and immunogold staining, we examined kidneys from these mice at various ages. Nearly all adult homozygous Actn4 mutant (KI) and Actn4 null (KO) mice developed collapsing glomerulopathy. KI mice also exhibited prominent actin and α--actinin-4-containing cytoplasmic electron densities that were not consistently seen in wild type (WT), heterozygous Actn4 mutant (HET), or KO mice. HET mice (the genetically faithful model of human ACTN4-mediated disease) did not develop glomerulosclerosis, but did exhibit focal glomerular hypertrophy and mild glomerular ultrastructural changes in the older mice

P30

Detection of Y Chromosome Micro-Deletions of Idiopathic Azoospermic and Severely Oligozoospermic Infertile Men in Iraqi Population

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Infertility is a world wide health problem involving both male and female. Infertility due to male factor, is considered as a major contributor in the prevalence picture (10- 30%). In this study, fifty-two cases of idiopathic oligospermic and azoospermic infertile Iraqi males were selected. Case selection was based on case history, Semen analysis, clinical examination, endocrinological and cytogenetic study. Sequence Tagged Sites (STS) primers were used and tested on each subject DNA by multiplex PCR. These were; SY84, SY86 (AZFa); SY127, SY134 (AZFb); SY254, SY255 (AZFc) and SY14 (SRY) as an internal control. Seven of the fifty-two cases (13.4 %) showed deletion of at least one of the STS markers; five cases of which had a complete AZFc deletion (two of which were brothers) and two cases had a partial AZFc deletion. Two cases of the complete AZFc deletions were further overlapped by Partial AZFb deletions. The overall results have indicated that there is a relative high prevalence rate of AZF microdeletions within the Iraqi population. AZFc deletion is performing as the major type (50%) in comparison with other deletions. All AZF deletions represent high expressivity and penetrance rate. AZF interval deletions in family history negative cases indicate that it was de novo deletion.

P31

The Molecular Basis of Chronic Granulomatous Disease in Oman

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Chronic granulomatous disease (CGD) is a rare immunodeficiency disorder characterized by life threatening infections. It results from mutations in any of the four genes CYBB (gp91phox), CYBA (p22phox), NCF-1(p47phox), and NCF-2 (p67phox). The aim of this study was to characterize the molecular basis of CGD in Omani patients. CGD was suspected in 13 patients from 8 families by clinical examination and investigated biochemically (Nitroblue tetrazolium test), and by flowcytometry (Dihydrorhodamine test (DHR).Using direct DNA sequencing, GeneScan and allele-specific PCR technologies we analyzed the genetic variations of NCF-1 complex comprising functional and pseudogenes. Only one patient presented X-linked inheritance pattern, who incidentally also had McLeod's Syndrome. He was demonstrated to have a large deletion of approximately 600 kb involving both CYBB gene and the McLeod's gene (XK). Amongst the remaining 12 patients of autosomal recessive transmission, we were able to identify mutations in the NCF-1 gene, (the most common form of autosomal recessive CGD) in 6 patients. In four kindred from one family we found the homozygous G784A mutation (Gly262Ser) in Exon 8 of the NCF-1 gene. Additionally, two patients had homozygous ΔGT mutations in the functional NCF-1 gene. Thus, amongst 8 families studied, we were able to identify the underlying molecular basis of CGD in four (54%). Despite extensive analysis of all the four major genes of the NADPH-oxidase, we could not define the molecular basis of CGD in 6 patients from the remaining 4 families. The study must be extended towards the analysis of two other genes namely (NCF-4 and Rap1A) in order to decipher the causal locus and associated mutations.

P32

Variable Genetic Structure of the NCF-1 Gene Complex in Omani Population/Patients Complicates Diagnosis of Autosomal p47phox Chronic Granulomatous Disease

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Chronic granulomatous disease (CGD) is an inherited disorder characterized by life threatening infections due to defective phagocytosis by leucocytes. Approximately a quarter of the CGD patients have mutations in NCF-1 gene encoding p47phox. However, due to extreme homology between a single functional NCF-1 gene and two linked pseudogenes on the same chromosome, detection of carriers of CGD by conventional PCR and DNA sequencing is not possible. The only difference between them is a GT deletion at the beginning of exon 2.The common mutation in CGD patients is a GT deletion in the same position further complicating the analysis. Gene-scan method exploits the difference in GT(pseudogene) to GTGT(functional) ratio of NCF-1 complex to assess the genetic variation/ arrangement of this locus. The aim of this study was to use Gene-Scan method to diagnose CGD patients and carriers of ΔGT mutation in the functional NCF-1 gene. GeneScan was performed by ABI 3100 genetic analyzer and results analyzed using GeneScan program 3.1(ABI Applied Biosystems). The ratio of pseudogene-to gene in control Omani population revealed three groups of subjects. 149(74%) showed 2:1 ratio, 49 (24%) 1:1; and 4(2%) 1:2 ratio. Amongst the patients from two studied families a ratio of 5:1 was observed while obligate carriers had ratios of 2: 1 and 1: 1. In conclusion, GeneScan ,although simple and accurate in defining the structure of the NCF-1 gene complex, the presence of atypical pseudogenes with GTGT sequence (likely arising from homologous cross-over between pseudogene and functional NCF-1 gene) in Omani subjects (affected or not for CGD), interpretation of GeneScan data for diagnosis of patients or carriers warrant extreme caution and is not that straightforward. Nevertheless by careful DNA studies of informative families, Genescan has a proven utility and has allowed us to define the haplotypes in conjunction with other linked markers, and thereby allow diagnosis of carriers and patients.

P33

The Impact of Genome Informatics on Next-generation Personalized Diagnostics and Medicines

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The advent of 2nd generation, low-cost, DNA sequencing technologies is leading to dramatic increases in the rate of genome data generation. The utilization of these new technologies to sequence ever increasing numbers of human genomes for personalized diagnostics and medicines will generate even more data. Current database and software technologies are becoming progressively ineffective for managing, processing and analyzing these new levels of information. Synamatix addresses this need by leveraging SynaBASE™, which is an innovative database solution based upon indexing patterns in data. Rapid cross referencing of clinical patient sequence data back to the human genome is a critical step in SNP discovery and identifying potential disease states. Performance improvements of between 100 and 10,000 fold for comparative and differential genomics and for mapping-based genome assembly from 2nd generation sequencers will be reviewed.

P34

Etiological and Clinical Profile of Neonatal Seizures in a Highly Consanguineous Population

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A prospective longitudinal study was conducted on all neonates admitted with a diagnosis of neonatal seizures in the neonatal intensive care unit of Jordan University Hospital Amman from April 2003 to March 2005 to examine the cause and clinical profile of seizures in a community, which culturally favors consanguineous marriages. Of 35 neonates studied, inborn errors of metabolism accounted for 28.6%, hypoxic ischemic encephalopathy for 17.1% and cerebral malformations for 14.3%. The consanguinity rate among parents of affected neonates was 54%, and 22.9% of these probands had a similarly affected sibling. Compared with 78 matched controls, consanguinity proved to be a risk factor for neonatal seizures (P =0.007, odds ratios=3.02; 95% confidence intervals 1.22 to 7.51). The hospital-based incidence of seizures was 5.6 per 1000 live births. Poor outcome in the form of mortality or morbidity was present in 67.8% of the cases. Early-onset seizures and status epilepticus accounted in 40% and 22.9% of cases respectively, with subtle seizures being the commonest type. Based on our results, inborn errors of metabolism and cerebral malformations make a significant contribution to the etiology of clinical neonatal seizures. This is accounted for by the consanguineous population being at risk for a number of neurogenetic disorders leading to convulsions on one hand and by improved methods of diagnosis of neonatal seizures on the other. In future, genetic counseling may help to minimize the contribution of underlying genetic factors to neonatal seizures in our community.

P35

Apolipoprotein Gene Polymorphisms and Coronary Artery Disease in the Tunisian Population

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Coronary artery disease (CAD) is a multifactorial disease caused by genetic and environmental factors. In some world populations gene polymorphisms involved in lipoprotein synthesis and metabolism are analyzed for studying the susceptibility to CAD. The aim of this study is to accomplish these analyses in the Tunisian population. Four apolipoprotein gene polymorphisms (APO (a) PNR, APO E, APO CI and APO CII) were determined in healthy blood donors and in patients with CAD complicated by myocardial infarction (MI). Plasma levels of total homocysteine, total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HLD-C) and apolipoproteins (apo A-I, Apo B, Apo E) were measured. Results show a high level of homocysteine associated with CAD and with its severity. For all apolipoprotein gene polymorphisms there are no statistically significant differences in allele and genotype frequencies between patients and controls. However, the APO E4 allele associated with high levels of atherogenic parameters (TC, LDL-C, apo A) and low level of apo E (anti-atherogenic element) appears to be a risk factor to CAD in Tunisian population. In addition, this allele shows significant increased frequencies when the number of diseased vessels increases suggesting its involvement in the determination of the CAD severity. On the other hand, the APO E2 allele, which increases the level of apo E and decreases the level of atherogenic parameters, seems to protect against CAD.

P36

The First Successful Twin Pregnancy after in vitro Fertilization (IVF) and Pre-Implantation Genetic Diagnosis (PGD) for Cystic Fibrosis (CF) in the Gulf Area

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In vitro Fertilization (IVF) with Pre-implantation Genetic Diagnosis (PGD) allows the selection of the unaffected embryos only to be returned to the uterus after screening the embryo for the affected mutations. With the advancement of IVF techniques and its applicability in many centers in Saudi Arabia, PGD and IVF was useful for families with cystic fibrosis (CF) to prevent another pregnancy with a CF child and to give hope to these parents to have a normal child. A total of 132 families with known cystic fibrosis transmembrane regulator gene mutations (CFTR) were observed since the establishment of the center in 1998. IVF/PGD for Cf started in 2002. A total 4 mothers for confirmed CF children with known CFTR under went IVF/ PGD procedure. One mother (of an affected CF sibling with homozygous 3120G>A Intron 16), had one transfer with a twin pregnancy and delivered normal twins. The remaining 3 mothers: 1 patient had 2 transfers but no pregnancy, the other 2 mothers, each had 1 transfer but no pregnancies. In conclusion, IVF/ PGD should be applied for CF families to give them a chance to have normal children

P37

Similarities and Differences of Cystic Fibrosis Transmembrane Regulator Gene Mutations (CFTR) between Saudi Arabia and Other Gulf Countries

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(CFTR) of the Arabian Gulf countries have been described before. In this report: A retrospective review of similarities and differences of all reported CFTR in the Gulf countries were reviewed and compared with the recent data of CFTR from Saudi Arabia (KSA). Of the mutations that are shared between gulf Countries are: DF-508 in 15% of KSA alleles, 30% of Baluchi descent of United Arab Emirates (UAE), 1.5% in Qatar, 7.7% in Bahrain, 13% in Oman. 3120+ 1G→A in 11.5% in KSA, and 3.8 in Bahrain, but doesn't exist in UAE, Qatar or Oman. N1303K in 3.5% in KSA, 1.5% in Qatar 7.7% in Bahrain. S549R in 3.5% in KSA, 70% in UAE of Bedouin origin, 73% in Oman. (I1234V) in 11.5% in KSA, 97% in Qatar and doesn't exist in UAE, Bahrain, or Oman. K1177X in 3.5% in KSA of Palestinian origin and 3.8% in Bahrain. H139L in 8.5% in KSA, and 19% in Bahrain. In conclusion, Gulf countries share common mutation according to its proximity to each other, but have new mutations that are specific to each Gulf country ranges from 30-50% of total CFTR alleles according to the nature of the population and the extent of immigration form other Arabian and Asian countries.

P38

Hexasomy of the Prader-Willi/Angelman Syndrome Critical Region in a Patient with Severe Phenotype and Ito Hypomelanosis.

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Supernumerary marker chromosome 15 also referred to as inv dup(15), is the most common SMC accounting for up to 50% of all SMCs. Two cytogenetic types of inv dup(15) marker chromosome have been identified. One of them is small, not containing the Prader-Willi/Angelman syndrome critical region (PWACR). Most of the patients with this aberration have a normal phenotype. The second type is a large SMC containing two additional copies of the PWACR and is associated with abnormal phenotype. Almost reported SMC(15)s cases occurred de novo and were of maternal origin. Less than 20% were reported to be mosaic. We report a case of a 13-years old male patient presenting with mental retardation, epilepsy, behavioral problems, dysmorphism (long face, prominent upper lip, and short philtrum), scoliosis, hypospadias and hypomelanosis of Ito. Standard karyotype from peripheral blood lymphocytes identified a unique supernumerary marker chromosome in 83% of the cells. FISH using D15Z1 and SNRPN probes showed the SMC to be dicentric and having four copies of SNRPN. Thus the karyotype was interpreted as 47,XY,+ mar.ish der(15) (D15Z1x2; SNRPNx4;D15S10x4)[41]/46,XY[9]. The proband presents with SMC(15) carrying four copies of the PWACR and Ito hypomelanosis. Ito hypomelanosis is sporadic; it is not a syndrome but rather a non-specific expression of chromosomal mosaicism. Our patient is as far as we are aware the third patient described to be hexasomic for the proximal 15q11q13 region. The patient reported by Akahoshi et al is also associated with a pigmentary dysplasia . Clinical features are very similar in both patients even. The abnormal phenotype in patients carrying a large SMC(15)s is highly variable, however, the phenotype associated with tetrasomy of the PWACR is more severe than in patients with duplication. Parental origin and delimitation of quadriduplicated region extend are being studied in our case.

P39

Autosomal Recessive Acro-Fronto-Facio-Nasal Dysostosis Associated with Genitourinary Anomalies: A Third Case Report

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We report a Tunisian 22-days-old boy born of consanguineous (first-cousin) parents (F=1/16) and a non followed pregnancy. The patient presents wide forehead with frontal encephalocele, wide anterior fontanel, marked hypertelorism, coloboma of the upper lids, proptosis, congenital glaucoma, broad nose, syndactyly between fingers 3 and 4, hypoplastic 3rd, 4th and 5th toes with ungueal dysplasia, hypospadias with cleft glans, bifid scrotum. Brain MRI showed right frontal encephalocele with anomalies of the cortical gyration without any corpus callosum anomaly. Normal chromosomes and parents' consanguinity are suggestive of autosomal recessive inheritance. Facial midline anomalies associated with limb and genitourinary anomalies is very uncommon. Richieri-Costa described in 1989 a new type of an autosomal recessive Acro-Fronto-Facio-Nasal dysostosis associated with genitourinary anomalies. Naguib also described one year earlier from Kuwait a presumably autosomal recessive new hypertelorism-hypospadias-polysyndactyly syndrome in 3 male and female siblings. Compared to the reported patients, our patient has similar major signs, marked hypertelorism, syndactyly, hypospadias and the inheritance pattern. However, he presents some differences such as the encephalocele and congenital glaucoma. We assumed that these three conditions correspond to a single clinical entity with a broad spectrum of severity.

P40

Aberrant Methylation of p16 and MGMT Genes in Lebanese Smokers

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Recent studies have demonstrated that aberrant methylation of p16 (fumor suppressor gene) and / or MGMT gene (DNA repair enzyme) is detected in DNA samples from sputum in 100% of patients with squamous cell carcinoma as early as 3 years before clinical diagnosis. Moreover, the prevalence of these markers in sputum from cancer-free, high-risk subjects approximates life - time risk for lung cancer. Knowing that the casual relationship between smoking and lung cancer is well established and that 90 percent of all lung cancer deaths can be attributed to smoking, the goal of my research was to assess the methylation status of p16 and MGMT genes in a population of smokers versus a control population of non smokers. So, sputum samples were collected randomly from 200 people; 100 smokers (50 above 40 years old and 50 below 26 years old) and 100 non smokers (50 above 40 years old and 50 below 26 years old) in sterile specimen cups and were subjected to molecular genetic analysis. Aberrant promoter methylation of p16 was seen in 64% of smokers above 40 years old, and in 15 % of smokers below 26 years old, where as methylation of MGMT was not detected at all. As for non smokers, methylation of p16 gene was detected in 4 % of controls above 40 years old and non below 26 years old where as methylation of MGMT was also not detected at all. The strong association seen between p16 methylation and smokers seems to offer a potentially strong approach to population – based screening for the early detection of lung cancer, and possibly other forms of cancer.

P41

von Hippel-Lindau Syndrome – Molecular Genetic Diagnostics of a Severe Tumor-Predisposing Disease found in the Arab Population: Genotype-Phenotype Correlation

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The von Hippel-Lindau (VHL) syndrome is an autosomal dominant inherited tumor susceptibility syndrome predisposing to a complex pattern of benign and malignant tumors including renal cell carcinomas (RCCs), and brain tumors as the most severe complication. The phenotypic expression is highly variable. So far, in one family from Kuwait a VHL mutation was reported. We present our international study on 23 families, including 3 Arabic families with unequivocal clinical VHL features. Conventional sequencing did not reveal VHL alterations in 8 of them. However, by applying a new technique: Multiplex Ligation-dependent Probe Amplification (MLPA), we were able to detect large intragenic deletions in all these 8 cases. Combining both methods, sequencing and MLPA, resulted in a detection rate of over 90 %. Large deletions turned out to have a specific phenotypic consequence improving the predictability of RCCs significantly. As MLPA improves the detection rate also in other diseases, this new technology will improve the management certainly not only for VHL. To our knowledge, this is the first report detecting VHL mutations in a series of Arab families, applying a genotype-phenotype correlation.

P42

Oro-Dental Anomalies and Gingival Biopsy as a Possible Diagnostic Tool in Some Autosomal Recessive Neurodegenerative Disorders

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Fifteen patients suffering from autosomal recessive neurodegenerative disorders underwent extensive clinical and neurophysiological investigations. Ophthalmologic examination, brain CT and/or MRI were carried out for all the patients. Complete oral and paraoral examination was performed. Gingival samples were taken and studied using transmission electron microscope. Patients were diagnosed as: six patients with Neuroaxonal dystrophy (NAD), one with Hallervorden-Spatz syndrome (HSS), five with Neuronal ceroid lipofuscinosis (NCL) and three with Wilson's disease (WD). The most common oral abnormalities in NAD and HSS were long philtrum, thick and everted lips and high arched palate. The most common oral abnormalities in NCL were thick and everted lips and high arched palate, whereas the oral abnormalities in WD were cleft lip, thick and everted lips and high arched palate. The gingival biopsies in NAD, HSS revealed Spheroid bodies, intra-and intercellular vacuoles, and widening of intercellular spaces, and WD revealed Spheroid inclusions, intracellular vacuoles containing finely granular material, while gingival biopsies of NCL revealed granular osmiophilic deposits, curvilinear bodies and widening of intercellular spaces. Conclusion: Study of the orofacial manifestation proved to be useful adjuvant to the diagnosis of some neurodegenerative disorders. Gingival biopsy could reveal histological changes similar to other body tissues less accessible for biopsy and more traumatic.

P43

A Common Mutation in the CBS Gene Explains a High Incidence of Homocystinuria in the Qatari Population

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We report the results of a study carried out to delineate genetic and epidemiological aspects of homocystinuria in the Qatari population. 64 patients with homocystinuria (37 males, 27 females, age 1 to 29 years) from 31 nuclear families were ascertained over a period of more than four years. The incidence of homocystinuria in Qatar was calculated to be ≥ 1:3000, the highest in the world known so far. All patients in whom data were available were vitamin B6-nonresponsive. Molecular studies were performed in all patients. All 53 patients from tribe M and all three patients from tribe K were homozygous for the mutation c.1006C>T (p.R336C) in exon 9 of the CBS gene, with additional 7 patients resulting from mixed marriages between tribe M and tribe K. A single patient from tribe S was homozygous for mutation c.700G>A (p.D234N) in exon 6 of the CBS gene. Both mutations have been previously reported but involve hypermutable CpG dinculeotides and may be recurrent mutations in the Qatari population. The results of this study illustrate a strong founder effect causing a high prevalence of an autosomal recessive disease in a highly consanguineous Arabian population. Molecular neonatal screening may be suitable for early detection of homocystinuria in this population.

P44

Highly Multiplexed Genotyping with Molecular Inversion Probes (MIP): a Solution for Screening of All Known Mutations in the Arab Population?

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The screening for Mendelian mutations is often complicated by the lack of knowledge of what specific variants to screen for. Even if the specific locus to be screened for is known, setting up a great number of different tests can be operationally challenging. An alternative would be to set up one test that can assess all known mutations of Mendelian disease in the Arab population. This test can be then used to screen all the high risk population (e.g. consanguine couples) to identify couples that are at-risk to have a child with a Mendelian disease. This requires a technology that can detect mutant alleles in a highly multiplexed assay. In addition it is imperative that the data be of high quality: high conversion and accuracy. We have developed a technology, the Molecular Inversion Probes (MIP), which fit these requirements. MIP probes are circularizable oligonucleotides, where the two ends carry two sequences that are complementary to two sequences on the genome separated by one nucleotide (exactly where the variant to be genotyped is). After hybridization to the genomic DNA, the reaction is split into 4 tubes where a single nucleotide is added to each tube. Upon the addition of the nucleotide (only in the tube with the nucleotide that is complementary to the allele on the genome) the MIP probe is then ligated turning the probe into a circle. This structure can be selected for by the use of exonucleases allowing for minimal “cross talk” between probes and the ability to obtain high quality data from highly multiplexed assays (>50,000 plex). Ultimately these products are amplified and hybridized onto an Affymetrix microarray to identify the present products. An automatic algorithm makes the genotype calls.

P45

Genetics Study in Sudanese Deaf Family

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In recent years, enormous progress has been made in defining the underlying genes and their disease-causing variants. In Caucasian populations, nonsyndromic recessive deafness was mostly found to be of the DFNB1 type, which results from a great number of distinct mutations of the GJB2 gene encoding connexin 26 (Cx26) (www.crg.es/deafness/). We, therefore, performed a linkage analysis in a small affected and GJB2-wildtype consanguineous pedigree. The twelve members of the pedigree comprising six congenitally affected and six normal hearing individuals were considered informative for linkage. We tested for linkage to recessive deafness loci recognized to be responsible for nonsyndromic deafness with 81 microsatellite markers covering DFNB1 -DFNB30 on chromosomes 1-4, 7, 9-11, 13-15, 17-19, and 21-22. Genotyping of microsatellite markers was done on an ABI 377 DNA Sequencer and the Genehunter software was applied for linkage analysis. PCR assays were established to amplify the TMC1 structural exons 3-22. Linkage analysis yielded a peak on chromosome 9q13-q21 with the maximum LOD score to 3.08, with θ of 0.05, at marker position D9S1876. D9S1876 is located within the first intron of the transmembrane channel-like gene 1. DNA sequencing of the TMC1 structural exons 3-22 of the twelve individuals revealed a heterozygous C>T substitution at nucleotide position 1165 of exon 13 (c.1165C>T; GenBank AY546106), resulting in the stop codon p.Arg389X, in four affected and in two normal hearing individuals. In addition, a G>A transition at the c.19+5 splice donor site (c.19+5G>A; GenBank AY546105) occurred homozygously in two deaf individuals of the pedigree without the stop codon p.Arg389X, in compound heterozygosity with TMC1 Arg389X in four deaf and, heterozygously with the normal sequence, in four hearing individuals. This results from the fact that in the pedigree under study, two different mutations were associated with the phenotype. A priori, only a single mutation would be more likely to cause the phenotype in this pedigree. Genetic counseling will help affected parents to understand the reasons of deafness and to estimate the risk of having deaf children. Early diagnosis leads to improved education with the acquirement of a more extended vocabulary, and, thus, improvement of communication skills. Generally, the Sudanese population should be educated about genetic disorders and about the potential hazards of consanguinity

P46

Bioethics and Biotechnology: "Ethical Implications of Preimplantation Genetic Diagnosis"

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Major technological advances are typically followed closely by policy and laws that seek to regulate those technologies in a way that benefits the population. It has long been speculated that there will soon be a day when parents will be able to create their own "perfect baby" using the developing technology of genetic engineering. Currently there is technology created that enables couples to chose the sex of their baby. Soon who knows they could be able to choose eye color, height, weight, hair color, or even intelligence. Being able to have this much control will creates ethical questions about whether we should be able to "play god". The ability to control sex selection is also starting to raise these ethical questions, as well as the possibility of sex discrimination and upsetting the male: female ratio. Controlling Reproduction is no longer just a matter of science fiction.

P47

Physical Mapping and Study of Candidate Gene Variations and their Interaction to Understand the Sporadic Breast Tumor Heterogeneity

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The NCAHG is involved in integrating: i) the information generated by low resolution physical mapping and ii) the study of genomic variation in biologically relevant candidate genes, for an association with complex diseases such as Leprosy, Tuberculosis, Diabetes and Cancer. The variations, especially the SNPs/SSRs, studied in the regulatory region are analyzed by functional assays to draw a genotype-phenotype correlation and understand the extent of SNP-SNP interaction between studied genes. One of the diseases worked upon by our group, sporadic breast cancer, which represents 90% of all breast cancer cases, is not only heterogeneous clinico-pathologically but also enigmatic in showing very minimal association with the known genes, BRCA1 and BRCA2, involved in familial breast cancer. With this background, we have adopted three different approaches to look into these tumors. One, that of physical mapping of selected regions of chromosomes 16 and 17, implicated cytogenetically in these tumors. Here, coupled with in-silico analysis and the ab-initio gene prediction methods, we have already established a sequence of interest and a 3'UTR SNP with functional implication in strong association with a set of sporadic breast tumors. Second approach of studying the germline and somatic status of genes such as, p53, is correlated with structural or functional status of genes involved in DNA damage response (DDR) pathway. We show that transcriptional alterations of the DSB repair pathway facilitated by nonfunctional p53 and negative ER/PR status are involved in tumor development. However, a set of sporadic tumors with ER and PR positivity show copy number alteration in H2AFX gene, significantly associated with early age-onset (<50 Yrs). Also, the germline genotype status of a functional SNP in the 5'UTR of BRCA2 gene along with codon 72 status of p53 decides the risk or protection against sporadic breast cancer. The third approach adopted is to understand the genotype and functional status of the promoter regions of some of the cytokine genes to understand the reasons for poor immune surveillance and also for possible intervention to contain the tumor growth. These approaches together have made it possible to classify the sporadic breast tumors in different groups, paving the way to look for differential survival potential and therapeutic responses in future. [This is an on-going study supported by: UGC (New Scheme Grant, since 2002) and the DBT (Infrastructure-grant, since 2007); # all Ph.D. students have contributed equally to this work].

P48

Premarital Genetic Counseling among Jordanians

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Premarital genetic counseling is considered an important pillar amongst the strategies for the prevention and control of genetic and congenital disorders in Arab countries where selective abortion of an affected fetus is culturally, religiously and legally unacceptable. This strategy is unique for countries where arranged marriages are still practiced. Marriage in Jordan is regarded as a family decision and not just the couple's decision. Although, the frequency of "arranged marriages" may be declining in recent years due to the increasing number of females reaching university level education which gives them a broader choice of marriage partner, there still are many marriages that are arranged. Premarital genetic counseling constituted on average 10% of all counseling sessions at a main genetic counseling clinic in Amman over the last 5 years, with increasing frequency in recent years due to the public awareness after launching the national premarital thalassemia screening program in Jordan. Counselees presented to the clinic asking for information regarding the possibility of having affected children if they contemplate the marriage, whether consanguineous or non-consanguineous. A discussion on the reasons for families to seek premarital genetic counseling, which members of the family present, their expectations from the sessions and their reactions to the information given will be presented.

P49

Sickle Cell Disease and Thalassemia Studies in Oman

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Hemoglobinopathies continue to be one of the most prevalent genetic disorders throughout the world. In Oman, more than 10% of the population is estimated to be carriers of thalassemia traits. Hence, it is imperative to provide services which facilitate early detection and characterization of the many variant Hemoglobin disorders so that appropriate counseling can be provided to couples and families who are at risk of being affected by conditions such as Sickle Cell Disease and the Thalassemias. The recent initiation of a molecular genetics laboratory under the Ministry of Health, Oman, has strengthened the provision of routine diagnostics for Sickle-cell Disease and the thalassemias. This has helped to establish the presence of mutations associated with Beta-thalassemia that were heretofore not chronicled in the Omani population

P50

Thyroid Dysfunction in Down Syndrome

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The objective of this study is to assess thyroid functions among Jordanian individuals with Down syndrome as part of a Down syndrome project where patients were assessed according to a special evaluation protocol that aims at offering guided health management for the affected and counseling parents. Thyroid function tests: (thyroid stimulating hormone, free thyroxin, triidothyronine, anti-thyroperxidase antibodies, thyroglulin antibodies) were performed for 54 infants, children and adolescents having Down syndrome at the National Center for Diabetes, Endocrinology and Genetics (NCDEG) in Amman over the period January to December 2006. Male to female ratio of the tested individuals was 1:1. Among the 54 tested individuals, 27 (50%) showed a disorder in thyroid functions, where 7.4% manifested primary hypothyroidism, 40.7% manifested subclinical hypothyroidism and one patient (1.8%) had subclinical hyperthyroidism. Thyroid dysfunction is a common disorder among a population of Jordanian Down syndrome. It is recommended that thyroid functions testing should be performed yearly for Jordanian Down syndrome individuals with timely and proper management to avoid any deterioration in body and brain functions.

P51

Comprehensive Cystic Fibrosis Mutation Detection from Immigrant Arab / Middle Eastern Patients in the United States

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Classic Cystic Fibrosis (CF) is characterized by an elevated sweat chloride test, chronic obstructive pulmonary disease, pancreatic exocrine deficiency with malabsorption and malnutrition, and congenital bilateral absence of the vas deferens (CBAVD) leading to male infertility. Atypical CF presents with a subset of these symptoms. Mutation panels have been designed to detected common mutations, predominantly in Caucasians, and the spectrum of the mutations in such panels, albeit expanding, does not cover different ethnic populations. Therefore, comprehensive mutation detection by DNA sequencing and detection of exon deletions duplications are essential in confirming diagnosis of CF patients where mutation panels fail. Our laboratory received several samples from patients self-identified as Arab or originating from Arab/ Middle Eastern countries. These patients were analyzed usually after mutation testing using the American College of Medical Genetics (ACMG)-recommended CF panel failed to identify one or two mutations. In these patients, comprehensive mutation analyses revealed heterogeneity of mutations that are not part of the ACMG-CF panel. Examples of mutations identified include R75X, 1716 G>A, D579G, S1426F, L732X, L183I, E92D, -680T>G, Y89C, and D1152H. These results supports the notion of the need for comprehensive mutation analyses in patients from different ethnic groups, and especially from Arab populations, where until recently, CF was not well studied.

P52

Single Tube Assay for the Concurrent Detection of Deletions, Duplications, Conversions, and Total Dosage of Alpha Globin Genes from Alpha Thalassemia Patients, Including Newborn Blood Spots

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The determination of the total dosage of intact alpha globin genes is important to establish alpha-thalassemia (AT) diagnosis, as deletions in the alpha globin gene cluster are the predominant cause of AT. The objective of this study was to develop an automated reliable method for detection of total alpha globin gene dosage that can substitute Southern Blot analysis or Gap PCR. A semi-quantitative fluorescent PCR (SQF PCR) assay was developed for alpha-globin dosage assay (αGDA). Primers that amplify specific fragments from the alpha-globin gene cluster were included in a single PCR reaction together with primers that amplify fragments from 3 different normalization genes. DNA from whole blood and blood spots was analyzed. We validated the αGDA assay on samples that were analyzed by gap PCR assay of seven common deletions. We obtained concordance between the αGDA and the gap PCR assay in most samples, and where discrepant results were noted, further analyses showed the αGDA was correct in identifying the correct dosage. The αGDA was superior to Southern blot in detection of gene conversions, and in simplicity of operation. We further obtained α-globin dosage from newborn blood spot samples, a feat that Southern blot can not accomplish due to limitation of amount of DNA available from blood spots. Using αGDA we detected duplications and gene conversions events as well. We designed a simple single-tube αGDA assay can that detect deletions and duplications in the alpha globin gene cluster, providing information to total alpha-like globin dosage and rearrangements. The αGDA assay is far better than gap PCR assays which are limited to detecting known mutations with no reliable information about total dosage of intact alpha globin genes. The method can be used as a primary screen for total alpha globin dosage, especially in newborns. Combining the αGDA with our in-house developed DNA sequencing assay of α2, α1 and α3.7 provides comprehensive analysis for mutations in the alpha-globin gene cluster.

P53

Successful Application of A-CGH in Multi-Center Group: Preimplantation Genetic Diagnosis Collaboration on Patients with Recurrent IVF Failure

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The success rate of pregnancy achieved as a result of Assisted Reproductive Technology (ART) does not exceed 50%. This is particularly true in patients where all parameters that could potentially affect such a result, including; female age, male sperm quality and optimal ART setting are excluded. It is well known that the chromosomal contribution to the failure of pregnancy is major. The last decade witnessed an important focus on the role of chromosomal abnormalities in ART success. After studying a number of randomized trials, two main conclusions were deduced; firstly to recognize that chromosomal abnormality in embryos largely contributes to a low pregnancy rate. Secondly, to appreciate the importance of chromosomal screening in producing better pregnancy results. Along with these conclusions, we focused our effort on the analysis of the entire chromosome sets of single blastomere in Pre-implantation Genetic Diagnosis (PGD). We optimized the Array-Comparative Genome Amplification A-CGH on single blastomere by detecting most of the cell chromosomes using this technique. The second step consisted of structuring collaboration with different groups where all patients with 3 or more recurrent IVF failures were recruited for PGD using A-CGH. Sixty embryos belonging to 10 patients have been so far analyzed with many ongoing pregnancies. The details of the results and the collaboration will be presented and discussed. Such collaboration permits the consolidation of the results and efforts on one hand, while, and on the other it shows the first application worldwide on A-CGH in clinical ART cycles by PGD.

P54

Screening for Mutations in BRCA1 Gene (Exon 11) among Jordanian Patients with Breast Cancer

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To date, BRCA1 mutations in breast and/or ovarian patients have not been investigated in the Jordanian population. We investigated the presence of BRCA1 mutations in 43 individuals with and without a family history of breast and/or ovarian cancer. We have identified 5 mutations using combined techniques involving Single-strand conformation polymorphism analysis and direct DNA sequencing. The five mutations were, Proline to leucine at residue number 871 (P871L), glutamic acid to glycine at amino acid position 1038 (E1038G), lysine to arginine at position 1183 (K1183R), aspartic acid to asparagine at position 693 (D693N) and a new mutation which was asparagine to histidine at position 550 (N550H) in addition to one polymorphism which was leucine to leucine at residue number 771 (L771L). Notably, K1183R mutation was found in 7 patients, six of them were heterozygous. Additionally, two other mutations; N550H and D693N were rare and found in one patient each. The relevance of these missense mutations we found is remains unclear and hard to assess their risk in breast and ovarian cancer without their allele frequencies in the general population and without carrying functional assays on them. Identification of BRCA1 mutations in a proportion of our patients indicates that this gene play a role in the incidence of breast cancer in the Jordanian population.

P55

Challenges in Large-Scale Genetics Studies to Identify Markers for Complex Disease and Drug Response

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The analysis of genome wide variation is potentially a powerful tool for identifying markers for complex disease and drug response. For such studies to deliver on their promise it is imperative to ensure optimum study design and robust analysis. The presentation will discuss the challenges in the design, analysis, interpretation and clinical utility of large-scale genetics studies aimed at identifying genes involved in the etiology of complex disease and drug response.

P56

Genomic Analysis of Inherited Hearing Loss in the Palestinian Population

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Recessively inherited phenotypes are frequent in the Palestinian population as the result of a long historical tradition of marriages within extended kindred, particularly in isolated villages. In order to characterize the genetics of inherited hearing loss in this population, we worked with West Bank schools for the deaf to identify children with prelingual, bilateral, severe to profound hearing loss not attributable to infection, trauma, or other known environmental exposure. Of 156 families enrolled, hearing loss in 17 families (11%) was due to mutations in GJB2 (connexin 26), a smaller fraction of GLB2-associated deafness than in other populations. In no families was hearing loss due to previously reported Palestinian mutations in other deafness-related genes. In order to estimate how many different genes might responsible for hearing loss in this population, we evaluated ten families for linkage to all 40 known human autosomal deafness-related genes, utilizing Microsatellite and 250Kb SNP chip analysis, and fully sequencing hearing-related genes at any linked sites in informative relatives. Thus far, we have identified and characterized POU4F3 as DFNA15, MYO3A as DFNB30, and TRIOBP as DFNB28. We have also discovered novel deafness-associated alleles of TMPRSS3, CDH23, MYO15A, Pendrin, Otoancorin, and Pejvakin. We conclude that inherited hearing loss is highly heterogeneous in the population, with most extended families functioning in this context as genetic isolates, harboring private alleles of either known or novel genes.

P57

Phenotypic and Molecular Exploration of Genetic Diseases in Central Tunisia

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Our investigations are focused on human genetic diseases in the Centre of Tunisia. Samples are collected in various services in the hospitals of Sousse, Mahdia, Monastir and Kairouan. We focused our works on hemoglobinopathies which constitute a real public health problem in Tunisia. Phenotypic explorations are made by blood counts, hemoglobin electrophoresis and isoelectrophoresis. Molecular analyses on DNA are done by PCR, enzymatic digest, DGGE and/or SSCP and sequencing. The combination of these methods allowed us the identification on the beta globin gene of 20 mutations causing beta thalassemias in the Centre of Tunisia. All the methods cited are used to set a prenatal diagnosis protocol. More than ten families have benefited on this test in our laboratory. In addition, sequencing polymorphisms are analyzed on the 5' region of the beta globin gene and used to trace back the origin of the most frequent thalassemia mutations in the Tunisian population (IVSI nt 110 and stop codon 39). In another hand, focusing on the IVSI nt 2 T-G mutation, we found that mutation at the 5' splice site of β-globin intron 1 accommodates multiple cryptic splicing pathways. In vivo and ex vivo analyses of mRNA showed that these cryptic splicing sites are differentially utilized. We also conducted molecular analyses to explore other genetic diseases on samples carrying the Brugada Syndrome (BS) and chronic obstructive pulmonary (COP) disease. Our works aimed to search for eventual correlation between genetic markers and the development of these diseases. We explored the SCN5A gene and its polymorphisms described in the BS pathology. We also analyzed the C3*S and C3*F polymorphisms of the third component of the Complement (C3) gene and the PiS and PiZ alleles on the alpa1 antitrypsine gene previously described in relation with COP. Therefore, no correlation seems to exist between the markers analyzed and the risk of developing the BS or the COP diseases.

P58

Apolipoprotein E Polymorphism in General Population and in Patients with Myocardial Infarction in Constantine City

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Mean level of lipid and Apolipoprotein, as well as genetic of Apolipoprotein E (apoE) were determined in control and in myocardial infarctus (MI) subjects in Constantine a selected population of east of Algeria. The investigation has taken nine months; the study population consisted of 218 patients with diagnosis of myocardial infarction, and 457 randomly selected healthy controls. The apoE allele frequencies of patients and controls were 5% vs. 5.15% for ϵ2, 78.2% vs. 83.8% for ϵ3, and 16.8% vs. 11.05% for ϵ4. The patients with MI compared with control subjects had statistically significantly higher mean triglycerides (155 ± 75 mg/dl vs 117 ± 7 mg/dl, p< 0.001) and ApoB (122 ± 49mg/dl), vs (91 ± 31 mg/dl), p< 0.01 and lower apoA1 and HDL cholesterol with mean values of (105 ± 67mg/dl, vs 135± 45 mg/dl, p< 0.01.), (41±25mg/dl), vs (45±15 mg/dl),p< 0.05 respectively .The carriers of allele ϵ4 and ϵ3/ϵ4 subjects compared with ϵ3/ϵ3 are associated with an increased incidence of myocardial infarctus (MI) with odds ratio 1.77 [95% CI, 1.17 to 2.69] p<0.01 and 1.95[95% CI, 1.27 to 3.01] p<0.01 respectively. In summary, our findings demonstrated that epsilon 4 is particularly susceptible to myocardial infarctus in Algerian population.

P59

Associations between HLA Class I Alleles and the Prevalence of Nasopharyngeal Carcinoma (NPC) among Tunisians

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The high prevalence of nasopharyngeal cancer (NPC) in Southern Asia and Mediterranean Northern Africa suggests genetic predisposition among other factors. While Human Leukocyte Antigen (HLA) haplotypes have been conclusively associated with NPC predisposition in Asians, Northern African Maghrebians have been less intensely studied. However, low resolution serological methods identified weak positive associations with HLA-B5, B13 and B18 and a negative with HLA-B14. Using sequence based typing (SBT), we performed a direct comparison of HLA class I frequencies in a cohort of 136 Tunisian patients with NPC matched for gender, age and geographical residence to 148 normal Tunisians. The bimodal age distribution of NPC in Maghrebians was also taken into account. HLA frequencies in normal Tunisians were also compared with those of Northern Moroccan Berbers (ME) to evaluate whether the Tunisian population in this study could be considered representative of other Maghrebian populations. HLA-B14 and -Cw08 were negatively associated with NPC (odd ratio = 0.09 and 0.18 respectively, Fisher p2-value = 0.0001 and = 0.003). Moreover, positive associations were observed for HLA-B-18, -B51 (split of -B5) and -B57 (p2-value < 0.025 in all) confirming previous findings in Maghreb. The HLA-B14/Cw*08 haplotype frequency (HF) was 0.007 in NPC patients compared to 0.057 in both Tunisian (OR = 0.12; p2-value = 0.001) and Moroccan controls. This study confirms several previous associations noted by serologic typing between HLA class I alleles and the prevalence of NPC in Maghrebians populations. In addition, we identified a putative haplotype rare in Tunisian patients with NPC that may serve as a genetic marker for further susceptibility studies.

P60

Pedigree-Free Identity-By-Descent Mapping for Localizing Disease Genes

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Genetic risk factors for disease result in a Founder Effect, where affected people in the present population share a DNA fragment tracing back, Identical-by-Descent (IBD), to a common ancestor. Traditionally, such fragments are detected by genotyping members of a pedigree extending back to the founder. In contrast, we present a new method we have developed that uses high density SNP genotyping to directly infer that fragments of DNA are inherited IBD between affected individuals, without any pedigree information. This approach requires only a few samples to successfully map genes, and thus greatly reduces the study costs and also enables mapping genes for rare disorders where few samples are available. We present applications of our Pedigree-Free IBD Mapping technique, to demonstrate the extreme power and potential of this approach. These include mapping genes for rare genetic disorders in families of Arab origin, using only a few affected individuals. We also suggest that founder effects in the Arab population make this an efficient way to systematically map the genes involved in many regional genetic disorders, such as those cataloged in the Centre for Arab Genomic Studies (CAGS) database.

P61

Genomic Copy Number Analysis Using High Density Genotyping Arrays

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Genomic deletions and duplications can cause genetic disease, and thus identifying such copy number variations helps localize disease genes, and aids in diagnosing genetic disorders. Traditional detection methods based on karyotping or FISH have resolution limited to several megabases or larger, while advances in DNA microarray technology are providing rapid improvements in array-based copy number detection. Here we summarize the resolution limits, genomic coverage, and discovery rates from using high density SNP genotyping array data to copy number detection. Specifically, we apply Affymetrix 500K SNP chips to detecting micro-deletions and duplications, using data from more than 20,000 genomic samples. We estimate that deletions exceeding 100kb can be detected with > 90% probability, and we establish a comprehensive database of several thousand such variants that occur in the normal population. The majority of these samples are of European origin, but by focusing on a small set of samples of Arab origin, we demonstrate that there are Arab-specific copy number variants, and thus that the Arab populations would benefit from a comprehensive survey of copy number variants, in both normal and disease sample sets.

P62

Genetic and Phenotypic Variability of Microcephaly vera in the Arab Population

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Microcephaly vera is a relatively common autosomal recessive genetic disorder in the Arab population, and is characterized by severe congenital microcephaly, normal motor development, and a lack of spasticity and seizures. Six loci and four causative genes have been identified to date. Despite its common occurrence, no studies of microcephaly vera in the Arab population have been reported. We studied Arab patients with microcephaly vera, and identified five mutations in ASPM (MCPH5), and one in microcephalin (MCPH1). Only two families shared a same ASPM mutation, suggesting an absence of a strong founder effect. ASPM is the most common cause of microcephaly vera in Northern Pakistan, and this appears to be the case in the Arab population as well. However, several atypical clinical features were noted in the patients we studied. Two patients in a family from Saudi Arabia with an ASPM mutation had epilepsy. Another patient from Oman with an ASPM mutation had spasticity and facial features reminiscent of Seckel syndrome. It appears that short stature, gross motor delay and spasticity, all of which are thought to be absent in microcephaly vera, may not be infrequent. Furthermore, there are three additional families in which we have not found mutations, and they may represent novel microcephaly vera loci.

P63

Prostate Cancer – What can be learnt from Global Populations?

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The global incidence of prostate cancer displays a high degree of racial variability, being highest in African men and lowest in East Asian men. In Arab countries the Prostate Cancer (PCa) incidence is low and correlates with low prostate volume and testosterone. PCa mortality risk is associated with an increased sensitivity to testosterone via transactivation of the androgen receptor (AR) through truncation of CAG repeats. In Arab men a recent study indicated that 78% of patients present with incurable advanced disease despite significantly lower testosterone levels, indicating increased sensitivity to this steroid. This paper presents an investigation of the AR-CAG repeat in Sudanese and Caucasian PCa patients. Sudanese men have a complex genetic background with contributions from both high (African) and low (Arab) PCa risk populations. A significant correlation between CAG repeat number and disease stage (P=0.04) was detected. Additionally, there was a significant correlation (P=0.05) between stage of disease and repeat number in the Caucasian samples that was not observed in the Sudanese samples. This may indicate that CAG truncation predisposes the individual to more aggressive PCa and could be utilized as a prognostic marker. The lack of correlation between stage and repeat number in the Sudanese samples may indicate a predisposition to aggressive PCa. Further investigation of African and Arab populations is required to verify the prognostic potential of this genetic marker.

P64

Analysis of CCG Repeats in Huntingtin Gene among Huntington's Disease Patients and Normal Japanese Populations

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Huntington's disease (HD) is a hereditary autosomal dominant neurodegenerative disease characterized by motor, cognitive, and psychiatric symptoms. The molecular basis of the disease is the expansion of the trinucleotide CAG in the first exon of a gene on chromosome four (4p 16.3). There is another triplet sequence, a CCG repeat, immediately 3′ adjacent to the CAG repeat in Huntingtin. This triplet sequence is also polymorphic, alleles of 7 or 10 repeats are predominant in populations, and strong linkage disequilibrium between the CCG (7) allele and HD has been shown in western HD chromosomes, whereas Japanese HD chromosomes strongly associate with an allele of (CCG)10. Distribution of CAG and the CCG repeats in Huntingtin in 15 patients with HD living in southern Japan were selected to evaluate the regional difference in the CCG repeat number in Japan. Among our 15 HD patients, only 4 patients had the (CCG)7 allele, and the (CCG)10 alleles were found in the remaining 11 patients. In this study, a linkage disequilibrium was found between Japanese HD chromosomes and (CCG)10, whereas western HD chromosomes are strongly associated with (CCG)7. These data suggest that (CCG)10 allele is dominant in southern Japan.

P65

Functional and Computational Assessment of Missense Variants in the ATM Gene; Mutations with Increased Cancer Risk

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The functional consequences of missense variants are often difficult to predict. This becomes especially relevant when DNA sequence changes are used for diagnosis of patients with mild symptoms. To analyze the consequences of thirteen missense variants in patients with mild forms of ataxia-telangiectasia (A-T), we employed site-directed mutagenesis of ATM cDNA followed by stable transfection of a single A-T cell line to isolate the effects of each allele on the cellular phenotype. After induction of the transfected cells with CdCl2, we assessed: 1) intracellular ATM protein levels, 2) ionizing radiation (IR)-induced kinase activity, and 3) cellular radio-sensitivity. We also calculated SIFT and PolyPhen scores for the missense changes. Nine variants produced little or no correction of the A-T cellular phenotype and were interpreted to be ATM mutations; SIFT/PolyPhen scores supported this. Four variants corrected the cellular phenotype, suggesting that they represented benign polymorphisms. Three deleterious variants were associated with an increased risk of cancer (6679C>T, 7271T>G and 8494C>T). In situ mutagenesis represents an effective experimental design for distinguishing deleterious missense mutations from benign missense variants because the consequences of single alleles can be assessed on an identical genetic background.

P66

Genetic -Epidemiologic Study of Mental illness in a Hospital Population

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Mental illnesses are common, serious, brain disorders that seriously hamper an individual's ability to think feel and act. Various studies have shown that the risk of developing an illness is increased if another family member is similarly affected, suggesting strong hereditary component (N.I.M.H. Report, 1997). The study sample consists of 721 mentally ill patients. The patients were diagnosed in the out-patients department of Psychiatry, Pakistan Institute of Medical Sciences, Islamabad. The Department of Psychiatry was visited from June 1998 to September 1999. This study comprises 721 mentally ill patients. Bipolar (manic-depressive) patients are 62.97% (n=454); Personality disorders 26.21% (n=189) and schizophrenics are 10.89% (n=78). The ratio of females to males is 100 Š Š: 100.27‰. Married males are 26.77% (n=193) and unmarried male are 23.30% (n=168). Among female patients married are 31.06% (n=224) and married are 18.86% (n=136). Mean age at diagnosis of mental illness in sample is 25.86 } 0.40 years. The study shows total number of inbred marriages to be 400(55.47%) while outbred marriages are 321 (44.52%). The coefficient of inbreeding (F) for mental illness patients is 4F= 0.0348 and that of control sample is F=0.0273. There were 220 (30.51%) patients with positive family history. Consanguinity is more in positive (23.35%) and negative group (3.30%) while in sporadic cases outbred cases are more in number (39.43%). Stressful life events were reported preceding the illness in 453 (62.82%) probands while in 268 (37.17%) probands, no precipitating factor was found. The majority of mental illness patients attained education until school level (n=318; 44.10%). Origin of patients was mainly of urban areas (n=523; 72.53%) while 198 cases (27.46%) reported from rural areas. This study shows a role of consanguinity in occurrence of mental illnesses evidenced from a big coefficient of inbreeding

P67

ApoE Polymorphism and Alzheimer Disease in the Algerian Population

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The Alzheimer disease (MA) is a progressive neurodegenerative affection which leads to a dementia. It is very heterogeneous as well on the clinical level as genetic; its clinical expression is a complex function of multiple genetic and environmental factors. Our study proposes to describe apolipproteinE alleles frequencies among Algerian patients with Alzheimer's disease and to compare these frequencies with observed in normal controls study. This investigation to lasted 6 months and carried on 82 subjects of the general population and 60 Alzheimer subjects. In a first time, this investigation found a prevalence of E3/E4 genotype 31.7% vs. control 17.2%. The E4/E4 genotype is more important in Alzheimer disease 9.8% than control 1.2%. Odds ratio for AD cases versus controls were 3.2. The other results show a more important prevalence of the DNID and HTA among patients. The vascular factors seem to play an important part not only in the development of the vascular insanities but also in that of Alzheimer disease. This study is a preliminary study which must be supplemented (sampling) and for the search for other factors of risk. Our data reinforce the idea that apoE epsilon4 allele increases the risk for AD in Algerian population.

P68

Study of CYP2D6 Polymorphism in Parkinson's and Control Subjects from India

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Parkinson's disease (PD) is the second most common neurodegenerative disorder next to Alzheimer's disease. It accounts for about 0.2 to 1% of the age of 65 – 69 and raises to 1 – 2% of the age of 80 and above. It is mainly characterised by the involvement of the four classical symptoms - tremor, bradykinesia, postural instability and the rigidity. It may be due to the cause of the environmental toxins and also due to the genetic factors. There is high relationship for the PD with the environmental toxins. The enzyme CYP2D6 is one which acts on the chemical 1-methyl-4-phenyl-l,2,3,6- tetrahydropyridine (MPTP), 1,2,3,4-tetrahydroisoquinoline (TIQ) and many other neurotoxins that cause the PD. An exciting possibility is that chemical transformation to produce PD toxin in the course of the detoxification mediated by CYP2D (cytochrome P450). The CYP2D comprises many isoenzymes which are involved in the metabolism of exogenous and endogenous toxins. The CYP2D subfamily comprise of genes which are highly specific for the debrisoquine- 4 hydroxylase activity. In this, the CYP2D6 is widely studied polymorphism. In the present study, we analyzed this CYP2D6*4 polymorphism in both the PD cases and controls using polymerase chain reaction (PCR) and Restriction Fragment Length polymorphism (RFLP). Bearers of the CYP2D6 gene variants may be classified as the extensive metabolizers (EM) and poor metabolizers (PM). PM allele carriers have lower gene activity and they are more prone to the environmental toxins. In this study we determined the CYP2D6*4 allele in both PD and control to evaluate the relation of this allele with the PD.

P69

Correlation of UGT1A1 Gene Haplotypes and A(TA)nTAA Promoter Configurations in Sickle Cell Disease Patients from Sultanate of Oman

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Sickle cell disease (SCD) is a congenital hemolytic anemia with increased red cell destruction and variations in the UDP-glucuronosyltranferase1A1 (UGT1A1) enzyme activity can lead to hyperbilirubinemia and its complications. Several polymorphisms in the UGT1A1 gene have been reported to be associated with decreased enzyme activity. The aim of this study was to define the underlying molecular genetic basis of reduced expression in UGT1A1, leading to increased serum total bilirubin concentration in Omani sickle cell anemia patients. The study enrolled a total of 248 SCD patients (192 SS homozygotes; 7 SD heterozygotes; 2 SC heterozygote; 56 S + Thal double heterozygotes), with a median age of 22 years (22.1 + 9.1; Mean + SD). 129(52%) were males. Serum samples for biochemical investigations including total serum bilirubin were obtained after an overnight fasting. UGT1A1 gene was studied for the promoter region A(TA)nTAA configurations and several described polymorphisms namely -3440C>A; -3401T>C; -3729T>G; -3154G>A & +211G>A. Amongst 248 patients analyzed, 100(40%) were homozygous for (AT)6 UGT1A1 allelle;114(46%) were heterozygous for (AT)6 and (AT)7 alleles and 23(9%) were homozygous for the (AT)7 allele. Mean serum bilirubin was significantly higher in the homozygous (AT)7 group as compared to the (AT)6 group(47.7 v/s 23.4; p <0.001). Furthermore, the mean serum bilirubin concentrations were also higher in -3440AA homozygotes, -3279GG homozygotes, and -3154AA homozygotes respectively when compared to the relative wild alleles. In conclusion, apart for the UGT1A1 (AT)7 homozygosity, -3729GG homozygosity, -3154AA homozygosity were significantly associated with raised total bilirubin levels. This study did not find any statistically significant association between -3440 C>A, -3401T>C and +211G>A polymorphisms and the bilirubin levels in Omani SCD patients.

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Family Organizations and their Role in the Delivery of Genetic Services

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Families involved in chronic and life threatening diseases are confronted with severe emotional, psychosocial, physical and economic implications. In contrast to healthcare professionals, they have never chosen nor volunteered for this involvement, they are not educated nor paid for managing these consequences, and they have limited time, knowledge, energy or resources to fulfill the daily required tasks. The burden of disease is manifest on the social, personal, and medical levels. Thanks to great technological and bio molecular advances, medical progress and the unraveling of the genetic background of genetic diseases, there are new options and perspectives for early detection, accurate diagnosis, effective therapy and considerable improvement of quality of life and also for prevention. A substantial reduction of the burden of genetic disease is a current realistic opportunity. These developments require social awareness, reliable, up to date and well-balanced information, education, competent networks of genetic services, integration of these services in the healthcare system, adequate communication between all stakeholders, supportive legislation in relation to quality, safety and transparency and also thoughtful reflection on ethical values and a well informed society. Family organizations, realizing the opportunities, have united on the local, national, continental and global levels, both disease-bound and subject-bound. This development has recently been extended by collaborations with science and industry. The International Genetic Alliance (IGA) counts over 2.600 patient organizations via regional alliances in the Americas, Europe, Australasia, Middle East, India, and South Africa and there are increasing contacts with groups in Japan, China and Malaysia. All these groups represent a wealth of expertise from practical experience valuable for policy makers in healthcare. Together with academia and industry they can significantly contribute to the research effort into the cause, prevention and treatment of their diseases. Parent and patient organizations deserve extensive support from government for their contributions in empowering their members, reducing the burden of disease and voicing the interests of their members. IGA participates in the World Alliance of Organizations for Prevention and Treatment of Genetic and Congenital Conditions (WAO), an alliance of scientific organisations, institutions and societies dedicated to the prevention, cure and amelioration of genetic and congenital conditions, and to decreasing the gap between new scientific discoveries and their practical applications in healthcare and prevention. Recently IGA established a collaboration with the World Life Sciences Forum BioVision. IGA, WA and BioVision have an interest fostering the development of community and parent/patient groups in developing countries. A global awareness campaign is envisaged. These networks can effectively contribute to adequacy and efficiency in healthcare systems providing early detection, management, and prevention of disease and moreover contribute to achieving an alert and involved society.

P71

A Bilateral Approach to Outreach and Advocacy Concerning Genetics

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Empowering individuals and communities in matters concerning genetics and personal health through access to education and information provides the public with the tools they need to understand the health of their families. Such access leads to positive behavioral changes, such as improved lifestyle modification, preventative care, and seeking timely treatment of conditions. Public outreach efforts concerning genetics- and health- related matters are of vital importance for this reason. Such efforts can provide a personal, attainable method of providing information and education to patients, families, and the general public. Creating a system of outreach and advocacy that focuses on issues such as newborn screening in North Africa and the Middle East should be developed through a bilateral approach that emphasizes public education and empowerment. The first part of this system is to establish a series of non-governmental organizations throughout North Africa and the Middle East that would serve as organizing bodies for family support and patient advocacy. These collaborative organizations would be affiliated with the International Genetic Alliance (IGA). The IGA was formed to unite other similar organizations from different areas of the world with similar missions objectives of promoting medical genetic services, research, technologies, and access to information, in order to alleviate the burden of genetic conditions for individuals, families, and communities. Establishing such organizations would provide a credible unifying source of information that could be tailored to different areas of North Africa and the Middle East concerning genetics- and health-related matters. Moreover, just as other similar organizations affiliated with IGA have developed collaborative relationships with governments of their respective regions of the world, the collective of these organizations could work with the governments within this region working to establish formal programs such as newborn screening. The second part of this system is to develop a grassroots system of health promoters throughout North Africa and the Middle East. These health promoters could be organized through the aforementioned nongovernmental organizations or by interested governments. Health promoters have a proven history of success in different cultures and countries throughout the world as early as the seventeenth century. Health promoters come from the community in which they work and are well trained to promote different messages/programs concerning specific health matters among groups that lack adequate health care/information. As a grassroots system, health promoters would provide an “on-the-ground” public outreach effort that is more difficult to attain solely through a formalized organization or government program.

P72

Coinheritence of Alpha and Beta Thalassemia in Maldives

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Thalassemia prevention programs can face challenges in countries like Maldives where prevalence of hemoglobinopathies, and simultaneous presence of hemoglobin variants are high. Maldives has the highest prevalence of β thalassemia in the world (18%) and the extent of α thalassemia is estimated to be over 15%. Coinheritence in this small population has emerged as a problem in recent years. Evaluation of extent of this problem is empirical in terms of premarital counseling and reproductive choices. Comprehensive molecular analysis of α and β globin genes was performed on 120 unrelated, healthy individuals identified as β thalassemia carriers through routine hematological screening. Hematological and hemoglobin typing results were compared among the groups heterozygous for β thalassemia only and double heterozygotes for α / β genotypes. Five β mutations were identified successfully. Out of the 120 cases analyzed more than 24% have coinherited α thalassemia mutations. These cases had milder hematological phenotypes. Though coinheritence may be suspected in the cases that have elevated hematological indices with borderline A2 values it remains very complex to apply these parameters for reliable carrier detection. Coinheritence is widespread in the Maldivian population. Knowledge gained from this study will enable to strengthen the prevention program in the country. The crucial step in the success of any prevention program would be the precise identification of carrier status. Molecular analysis is the most accurate tool to identify carrier status in populations susceptible for coinheritence.

P73

Cloning of Deafness Causing Genes in Both Isolated Populations and ENU Mutant Mice

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Geographically isolated populations have been successfully used to localize genes for recessive inherited diseases, including non-syndromic sensorineural recessive hearing loss (NSRHL). To date, 67 loci for NSRHL have been localized on human chromosomes (DFNB loci), and 22 of the corresponding genes have been identified; eight of those loci were first mapped in Palestinian families. We mapped recessive, severe to profound, prelingual NSHL in a four-generation consanguineous Palestinian Family K. The maximum LOD score was 4.19 at the 6.1MB interval on chromosome 22q13 bounded by recombinants in D22S1045 and D22S282. The DFNB28 region is distal to MYH9 and to the region deleted in Velo-cardio-facial Syndrome. Other Palestinian families were found to be linked to the same region, suing homozygosity mapping across all linked families, the causative gene was finally cloned. Deaf mouse mutants in conjunction with linkage analysis of families with deafness have been instrumental in the identification of human genes. Nevertheless, a great number of human deafness loci do not have a corresponding “mouse model”; and on the other hand there are a large number of deaf mouse mutants with no human homologue. Part of the deficit we hope to complete using mouse models generated form the ENU mutagenesis program. In our lab, we have cloned a number of those ENU mutants including Doarad, Beethoven, headturner, and recently Headchuk which is the second ENU mutant mouse in our lab that has a mutation in Jagged1. More work is now being done on other ENU mutants in the lab, to determine their causative genes and to characterize their ear phenotypes.

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Mutation Screening of the Ligand Binding Domain in the Low Density Lipoprotein Receptor of Four Arab Gulf Individuals with Familial Hypercholesterolemia

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Familial hypercholesterolemia (FHC), a major risk factor for coronary heart disease and stroke, is an autosomal dominant disorder caused by defects in the low density lipoprotein receptor (LDL-R). Five different classes of mutations have been described, each of which includes several different gene defects. The LDL-R gene comprises 18 exons and 17 introns and spans 45kb; its mRNA is 5.2Kb that encodes 839 amino acids in mature form. Our study was undertaken to identify mutations among four Arab Gulf individuals with clinically diagnosed FHC. The majority of the worldwide reported mutations are in the ligand binding domain of LDL-R. Thus, we screened for mutations in the promoter and the first six exons of the LDL-R gene using PCR amplifications, Restriction Fragment Length Polymorphism (RFLP) and ultimately DNA sequencing. DNA sequence analysis showed a single nucleotide polymorphism in exon 2 (T174C) in all four individuals and a normal control. Additionally, several single nucleotide substitutions were found in exon 4 of one individual. Importantly, a substitution was found in codon (G554T), changing glutamine to histidine in that position. The lack of a database for LDL-R mutations among Arabs and the presence of a large number of mutant alleles (more than 900) in the LDL-R gene worldwide necessitate more studies to be done to establish such a database.

P75

Leptin and Leptin Receptor Polymorphisms are Associated with Increased Risk and Poor Prognosis of Breast Carcinoma

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Leptin (LEP) has been consistently associated with angiogenesis and tumor growth. Leptin exerts its physiological action through its specific receptor (LEPR). We have investigated whether genetic variations in LEP and LEPR have implications for susceptibility to and prognosis in breast carcinoma. We used the polymerase chain reaction and restriction enzyme digestion to characterize the variation of the LEP and LEPR genes in 308 unrelated Tunisian patients with breast carcinoma and 222 healthy control subjects. Associations of the clinicopathologic parameters and these genetic markers with the rates of the breast carcinoma-specific overall survival (OVS) and the disease free survival (DFS) were assessed using univariate and multivariate analyses. A significantly increased risk of breast carcinoma was associated with heterozygous LEP (-2548) GA (OR = 1.45; P = 0.04) and homozygous LEP (-2548) AA (OR = 3.17; P = 0.001) variants. A highly significant association was found between the heterozygous LEPR 223QR genotype (OR = 1.68; P = 0.007) or homozygous LEPR 223RR genotype (OR = 2.26; P = 0.001) and breast carcinoma. Moreover, the presence of the LEP (-2548) A allele showed a significant association with decreased disease-free survival in breast carcinoma patients, and the presence of the LEPR 223R allele showed a significant association with decreased overall survival. Our results indicated that the polymorphisms in LEP and LEPR genes are associated with increased breast cancer risk as well as disease progress, supporting our hypothesis for leptin involvement in cancer pathogenesis.

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KID Syndrome: Two Observations

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KID is a rare ectodermic dysplasia with erythrokeratoderma, deafness and keratitis to which can be added other diverse abnormalities. We report here, the two little girls of non consanguineous parents and without any similar family historical background. The clinical examination of the 2 patients revealed: A cutaneous affection with erythrokeratodermia spots of the face, hypotrichosis, on palms, pachydermatoglyphia, an ophthalmic affection with photophobia and a slight short sightedness, and hearing affection with hypoacousy. A Malformation of the posterior cerebral fossa – a dandy walker syndrome – was revealed at computed tomography (for a case). On the therapy side, the oral retinoid was moderately effective. We believe that we should recognize the KID syndrome as possible cause to pachydermatoglypha.

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Three Observations of Continual Skin Peeling Syndrome

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The continual skin peeling is a rare icthyosis. However several cases have been reported in the south bank of the Mediterranean Sea (Strong endogamia hot climate). We report 3 male patients born to case at the age of five and later in the two others at the age of ten. All the 3 patients have the same predisposing factors (summer, heat, sweat, friction). In one case, the efficiency of acitretine at a 60 mg dose per day resulted in improvement.

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Naxos Disease in an Arab Family is not caused by the Pk2157del2 Mutation; Evidence for Exclusion of the Plakoglobin Gene

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Naxos disease is a rare hereditary disorder characterized by plamoplantar keratoderma, woolly hair and cardiomyopathy. This study aims to determine whether Naxos disease in a Saudi Arab family is caused by the Pk2157del2 mutation that was identified in Greek families from Naxos Island, where the disease had originally been described. The disease has recently been encountered in a 2-years old girl and her 30-years old aunt of a Saudi Arab family. DNA samples of this family were analyzed by PCR amplification of the respective region of the plakoglobin gene, and direct nucleotide sequencing of the PCR-products. Segregation analysis was performed employing the newly detected IVS11+22G/A polymorphism. Results will be discussed during presentation.

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Towards the Establishment of a Registry for Type 2 Diabetes Patients in the United Arab Emirates

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Type 2 Diabetes (T2D) is a major public health problem in the United Arab Emirates (UAE). The latest study revealed that 26% of UAE nationals suffer from diabetes, and that 40% of those aged 60 years and above suffer from the disease. It is evident that both lifestyle and inherited risk factors lead to the development of T2D. A number of evidence-based interventions have been developed and implemented with success in European communities but have not yet been examined in the Arabic speaking communities. Genome wide scans to map T2D susceptibility loci have been conducted with success in many different populations. The aim of this project is to develop a registry for type 2 diabetic patients from all major hospitals and Diabetes centers in UAE. The registry will include patient demographic and lifestyle data, disease complications, quality of life, and family history, as well as biochemical results like fasting blood glucose, impaired glucose tolerance, and hemoglobin A1C. Patients' consent and confidentiality of data will be maintained according to international ethical guidelines using anonymous coding. Data from the registry will help in defining risk factors in the UAE Arab population, developing new trends in management, and preventing complications. Large extended families will be identified from the registry and recruited to map diabetes type 2 susceptibility loci by linkage analysis.

P80

Consanguinity and Trisomy 21 in a Highly Inbred Population

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The objective of the current study is to asses the role of consanguinity as a risk factor in the occurrence of trisomy 21 in Jordan where one fourth of all marriages are first cousin marriages. Consanguinity data on 78 families with Down syndrome (DS) was obtained through direct questionnaire to parents of affected from January to December 2006. The parents were contacted through the database of the cytogenetics laboratory at the National Center for Diabetes, Endocrinology and Genetics (NCDEG), and through the special education schools of affected offspring. Consanguinity rate and first cousin marriage rates among parents of Down syndrome were 19% and 14% respectively, among maternal grandparents were 29% and 15%, respectively, and among paternal grandparents were 29% and 24%, respectively. These rates showed no significant differences when compared to the consanguinity and first cousin marriage rates among the general population from the same area and with similar marriage dates. Consanguinity did not have a role in the occurrence of trisomy 21 in Jordan. It is important to provide an evidence based message to health care providers that consanguinity does not increase the risk for having a DS child.

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An Angelman Syndrome Natural History Study

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Angelman syndrome (AS) may be caused by either a loss of function or a mutation in the maternal copy of UBE3A. The natural history of AS due to the different molecular defects remains unclear. Therefore, we are conducting a study to obtain a better understanding of the natural history of AS, including the behavioral phenotype, neurodevelopment and morbidity in children and adults with AS. A 5-year multi-center longitudinal study on the natural history of AS is being conducted, involving newborns to adults aged 60 years with AS. We have enrolled 84 AS patients –70% have a deletion in the AS critical region, 12% have UBE3A mutations, 7% have imprinting defects, 4% have paternal uniparental disomy, and 7% have methylation abnormalities due to a molecular defect that remains to be determined. Among the more common characteristic behavioral features are: "mouthing" behavior, short attention span, sleep difficulties, and fascinate on with water. In contrast, inappropriate laughter, which has traditionally been associated with AS, was seen in only about 60-65% of our patients. We hope that our findings will help health care providers recognize AS, leading to earlier diagnosis and intervention for these children.

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Diagnostic Utility of Array-Based Comparative Genomic Hybridization in a Clinical Setting

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Chromosomal disorders are often suspected in patients who present with mental retardation, dysmorphic features and multiple congenital anomalies, but standard chromosomal analysis is unable to detect many of these chromosomal abnormalities. Array-based comparative genomic hybridization (aCGH) is a new technique for detecting submicroscopic deletions and duplications across the entire human genome. In this study, we investigated the efficacy of a clinically available aCGH for cytogenetic diagnosis in a clinical setting. A total of 444 patients were tested with aCGH over 1 year. We analyzed the findings in 374 patients with normal karyotype, and analyzed the proportion of patients with mental retardation (MR)/global developmental delay (GDD) (n=225), facial dysmorphic features (n=113) and multiple congenital anomalies (MCA) (n=57) who have abnormal aCGH results. Abnormal aCGH results were found in 36 patients, 22 of whom (5.9%) had pathogenic cytogenetic abnormalities and 14 (3.7%) patients had copy number variations. When the data were further analyzed, 14/225 (6.2%) of patients with MR/GDD, 10/113 (8.8%) of patients with facial dysmorphism, and 5/57 (8.8%) of patients with MCA had abnormal aCGH results. Targeted aCGH is a clinically available diagnostic aid that can help broaden the phenotype of known microdeletion and microduplication syndromes. However, currently it does not replace routine chromosomal analysis.

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Wilson Disease in an Omani Family

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Wilson Disease (WD, Hepatolenticular Degeneration) is an inherited autosomal recessive disorder of copper transport, due to mutations of the ATP7B gene. It is characterized by impaired biliary excretion and deficient incorporation of copper into ceruloplasmin. Toxic accumulation of copper causes tissue damage primarily in the liver, brain and kidney. WD occurs in populations of every geographic and ethnic origin. Two Omani families with index Wilson Disease individuals were investigated. One was of Dhofari; the other of Balushi origin. A total of 16 SNPs were identified in ATP7B gene in the two families. The SNPs sets were different in the two families. Haplotyping analysis estimated one haplotype block with three haplotype tagging SNPs (htSNPs). A possible disease-causing mutation (IVS13-2A>G) was detected in the Balushi family, but not in the Dhofari family. It is a novel substitution mutation located in the splicing site of exon 13 which encodes the phosphatase domain of the ATPase functional region of the gene. It segregates in a recessive manner with the disease in the Balushi family. It has not been reported previously in the NCBI/SNP database, the Wilson Disease database or any other publication. Therefore, this novel mutation may explain WD in the Balushi family. Yet the definitive proof awaits functional studies. Absence of this mutation in the Dhofari family supports the genetic heterogeneity of WD in Oman.

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