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Oral Presentations

Quantitative Genetic Analysis of Metabolic Syndrome Traits Using Extended Families: *A direction towards exome sequencing*

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The global disease pattern has shifted, with a more dominant prevalence of chronic disease such as type 2 diabetes, metabolic syndrome, cancer and cardiovascular diseases. The inter-population differences in the prevalence of these diseases support the role of genetics and biological factors in the aetiology of these diseases. Most of the candidate gene and genome-wide association studies are conducted on large cohort of unrelated individuals. This has a major limitation due to the population subdivision and admixture that may lead to disease association even in the absence of linkage. Recent studies have focused on the use of extended family pedigrees in the study of heritability and genetic associations of complex traits like metabolic syndrome. Rapid developments in recent years with statistical methods have used family-based association designs to infer allelic association and linkage. In Oman, each individual is traditionally genealogically well-defined within their family tribe. In addition, Omani families have maintained homogeneity with extremely high levels of inbreeding due to the tradition of encouraging consanguineous marriages, mostly between first cousins. Therefore, Omani families in geographically-isolated regions like Nizwa provide a unique ideal population to provide the statistical power required to study complex diseases with confidence. The Oman Family Study consists of multigenerational pedigree subjects, descended from a small number of founders just a few generations ago, and with environmental homogeneity, restricted geographical distribution, detailed records, well-ascertained and validated pedigrees and a history of inbreeding. These families are used as a model to study the traits of metabolic syndrome: adiposity, hyperglycaemia, dyslipidaemia and hypertension. We have studied the heritability of these traits and the attributions of genetic *loci* for the adiponectin gene. Further analysis was done on genetic and familial clustering in non-alcoholic fatty liver disease as a complication of metabolic syndrome. With the emerging roles of exome sequencing and dark inheritance from rare variants, we identified clusters of inheritance units within one family, in which there were different segregations of type 2 diabetes. These units provide an excellent model to identify rare variants that contribute to the genetics of type 2 diabetes.

Clinical and Molecular Genetic Characteristics of Primary Open-Angle Glaucoma in Oman

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Glaucoma, an ocular neuropathy causing irreversible blindness, is both clinically and genetically diverse. Deoxyribonucleic acid (DNA) samples from nine families in Oman were collected for the identification of potential causative genetic factors driving the disease. Four of the families displayed primary congenital glaucoma (PCG) and three displayed juvenile open-angle glaucoma (JOAG). A combined phenotypic family displayed JOAG including PCG (JOAG-PCG) and one family displayed adult-onset primary open-angle glaucoma (AO-POAG). Single nucleotide polymorphism data were produced for a PCG family, yielding 14 chromosomal locations of interest, with four regions on chromosome 2 prioritised as a consequence of an influential *PCG* gene (cytochrome P450 subfamily I polypeptide 1 [CYP1B1]). However, sequencing of this gene did not reveal any mutations. Whole exome sequencing data were generated for the remaining families. A total of 26 individuals were sequenced with 5,659 variants in 3,979 genes. Sanger sequencing of 146 selected variants identified six co-segregating variants in four genes. *CYP1B1* variants (p.G61E and p.D374N) were found in the PCG families and the p.E229K variant was identified in a JOAG family. Novel variants in *nitric oxide synthase 3* (*NOS3*), p.G643S, and *class II major histocompatibility complex transactivator* (*CIITA*), p.L477I, were found separately in two PCG families co-segregating with *CYP1B1* variants. In the JOAG-PCG family, a new *chemotactic cytokine receptor 5* (*CCR5*) alteration, p.N48S, was identified. Two variants (*CYP1B1*, p.E229K, and *CCR5*, p.N48S) in two individuals who were asymptomatic at the time of enrollment predicted the presence of the disease in the JOAG and JOAG-PCG families. *CYP1B1* mutations are likely the primary cause of glaucoma in most families. However, the co-segregation of additional variants found in *NOS3* and *CIITA*, along with the identification of a variant in the *CCR5* gene, may indicate other genetic factors contributing to disease initiation and/or progression. As previously reported, the identity of the involved genes suggests autoimmune dysregulation, autoinflammatory events and oxidative stress in the disease pathophysiology.

This study also allowed for early diagnosis and identification of affected and at-risk individuals, enabling earlier medical intervention for the preservation of sight. The findings of this study warrant further investigation for improved clinical interventions with an aim to sight preservation.

Realising the Potential of the Role for Nurses in Genetics and Genomic Healthcare: *A review of the literature*

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A literature review exploring the role of genetics in the nursing profession was undertaken. As nursing is the backbone of the healthcare system, the aim was to define the valuable contributions they could make to shape the delivery of genetic healthcare. Advances in genetic science/technology have profound implications for healthcare and the growing importance and relevance of genetics in everyday nursing practice is increasingly being recognised. Nurses are expected to have the necessary knowledge to interpret genetic information and technology into client care, integrate genomic healthcare into healthcare systems and address associated ethical challenges. A search was conducted in January 2014 using the Cumulative Index to Nursing and Allied Health (CINAHL) and Google Scholar databases with the following keywords: nurses' role in genetics; genetics and nurses; genome, and genetics in nursing. Papers were included in the review if they had been published in English between 2005–2013 and included empirical data about the role of genetics in nursing. Findings indicated extensive agreement on the relevance of genetics in nursing practice. Empirical evidence highlighted widespread deficits in knowledge/skills and low confidence levels. However, significant progress has been made in identifying learning outcomes for nurses. Nurses expressed interest in educating and counselling patients. Studies conducted worldwide assessed nurses' perceived rather than actual genetic knowledge. Genetic nursing education was limited and inadequate across many countries and was hampered by a lack of strategic development. Research found that the delivery of genetics education was limited, although skill-based training, clinical scenarios and assessment have been identified as factors to promote learning. Nurses' knowledge of genetics was insufficient to provide comprehensive patient services; many studies identified gaps in professional competence/education. Nurses are expected to play a significant role in caring for patients with genetic predispositions/disorders. They must be able to identify hereditary/familial or environmental/lifestyle characteristics that increase disease risk; facilitate informed decision-making; promote surveillance behaviours; prescribe appropriate management strategies, and advocate optimal genetic healthcare. As counsellors, technicians, care managers and teachers, nurses will create new leadership roles in healthcare. The development of university-level programmes to improve counselling skills, as well as a basic curriculum in genetic nursing, are essential.

Poster Presentations

Griscelli Syndrome Type 2 in an Omani Child

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Griscelli syndrome type 2 (GS2) is a rare autosomal recessive disorder caused by a mutation in the *RAB27A* gene. It is characterised by partial albinism and cellular immune deficiency leading to an increased susceptibility to infections. Patients go on to develop life-threatening haemophagocytic lymphohistiocytosis (HLH) in the first few years of life. The prognosis is very poor unless allogenic haematopoietic stem cell transplantation is performed early. We report the case of a 2-year-old girl with a novel mutation in the *RAB27A* gene presenting with silvery-grey hair and recurrent episodes of HLH. This case is reported so as to increase awareness about this condition; GS2 is often underdiagnosed, especially in regions with high rates of consanguinity. Emphasising early diagnosis is crucial for successful treatment.

Mapping a New Recessively Inherited Blindness Disorder to Chromosome 16q23.3-24.1

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We previously described two families with unique phenotypes involving foveal hypoplasia. The first family (F1) presented with foveal hypoplasia and anterior segment dysgenesis and the second family (F2) presented with foveal hypoplasia and chiasmal misrouting without albinism. A genome-wide linkage search for F1 identified a 6.5 Mb *locus* for this disorder on chromosome 16q23.2-24.1. The aim of this study was to determine if both families had the same disorder and to see if the presentation in F2 was also linked to the 16q *locus*. Family members underwent routine clinical examinations. Linkage was determined by genotyping microsatellite markers and calculating logarithm of the odds scores. *Locus* refinement was undertaken with a single nucleotide polymorphism (SNP) microarray analysis. The identification of chiasmal misrouting in F1 and anterior segment abnormalities in F2 suggested that both families had the same clinical phenotype. This was confirmed when linkage analysis showed that F2 also mapped to the 16q *locus*. The SNP microarray analysis excluded a shared founder haplotype between the families and refined the *locus* to 3.1 Mb. We therefore report a new recessively inherited syndrome consisting of foveal hypoplasia, optic nerve decussation defects and anterior segment dysgenesis, known as FHONDA syndrome. The gene mutated in this disorder lies within a 3.1 Mb interval containing 33 genes on chromosome 16q23.3-24.1 (chr16:83639061-86716445, hg19).

The Identification of Novel Mutations in *GUCY2D* Causing Leber's Congenital Amaurosis in Two Unrelated Pakistani Families Using the TOPO TA Cloning Method

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Leber's congenital amaurosis (LCA) is the name given to cases of severe early-onset inherited retinal dystrophy; however, it is clear that this term actually encompasses a group of diseases with different underlying pathologies. It is a rare form of retinal dystrophy that presents in the first year of life. Studies of the molecular genetics of LCA have revealed 14 different LCA genes correlated to 70% of cases. Determining the molecular defect underlying the disease in patients is becoming increasingly important and recent gene therapy clinical trials have been performed with LCA patients. Genetic studies have identified many genes which cause the LCA phenotype but more have yet to be identified. This study aimed to map novel mutations in the *GUCY2D* gene in two unrelated families using the TOPO TA cloning method. Autozygosity mapping analysis was done on two Pakistani LCA families using the Genome-Wide Human Single Nucleotide Polymorphism Array 5.0 (Affymetrix, Inc., Santa Clara, California, USA). A shared region of homozygosity was identified among all of the affected individuals. A potential region of homozygosity at the *GUCY2D locus* (chr17:7,905,988-7,923,658, hg.19) was identified and confirmed. TOPO TA cloning was used to sequence the *GUCY2D* gene in the affected patients. Using unique methods, two novel homozygous missense mutations in the same gene were identified in both LCA families (c.582G>C, p.W194C, and c.530 G>C, p.R177P). The genetic investigation of LCA families may provide an ideal opportunity to identify other patients for phenotype-genotype analysis. This would identify new mutations to aid in the functional characterisation of LCA proteins. Genetic investigation of such families might also serve to molecularly characterise patients for future therapeutic clinical trials and identify families for future gene identification studies.

Inherited Causes of Chronic Kidney Disease in Omani Children: *A tertiary hospital experience in Oman between 2006–2012*

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This paper reports inherited and congenital causes of chronic kidney disease (CKD) in Omani children. The study is part of a larger project currently studying the descriptive epidemiology of CKD in children at Royal Hospital, a tertiary centre in Oman, where >80% of CKD patients in the nation are seen. This study is part of an initiative to establish local data on CKD to help plan possible preventative measures and strategies. A retrospective descriptive review of computerised medical records of all children aged <14 years diagnosed with CKD at the Royal Hospital, in Muscat, Oman, was undertaken from January 2006 to December 2012. There were 124 cases, of which 61% were male. The mean incidence of patients with advanced stages of CKD (glomerular filtration rate <60) was 18.2 per million of the age-related population. The mean age at diagnosis was three years. Date were collected via a questionnaire and parents of patients were contacted to complete any missing data. The questionnaire collected information regarding patient demographics; consanguinity; family history; clinical, biochemical and imaging data; details of identified causes; treatment modalities, and overall outcomes. The preliminary results could be used for future research on related topics. Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of CKD in children worldwide. In the current study, 48% of the patients had CAKUT. However, inherited causes were reported in 40% and consanguinity was observed in 40% of the patients. Autosomal recessive polycystic kidney disease and primary hyperoxalurea were the most frequent inherited causes. Mutations were also identified in consanguineous families. Although the complete coverage of all centres treating paediatric CKD in Oman was not achieved, the results of the current study may still reflect the actual condition nationwide. CAKUT and inherited renal diseases are the leading causes of CKD in children and the rate is even higher in countries with a high incidence of consanguinity.

Genetic Polymorphism in Mitochondrial Deoxyribonucleic Acid Hypervariable Regions I and II in a Sample Omani Population

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The analysis of the mitochondrial deoxyribonucleic acid (mtDNA) genome, in particular the control region of the genome, has been widely used in forensic analysis and population genetics to describe human variation, population substructure and migration patterns. This is due to the pattern of maternal inheritance, high mutation rate and lack of recombination. The mtDNA sequence polymorphism of the hypervariable regions I and II from 114 unrelated Omanis were analysed using polymerase chain reaction and Sanger sequencing. In order to identify polymorphic sites and their frequency and to determine the haplogroups' incidence compared to neighbouring populations, DNA sequences were aligned against the revised Cambridge reference sequence. The haplogroups were scored using online software tools. The frequency of the haplogroups was determined using standard statistical tools. The samples covered nine governorates with 59 different maternal tribes. Haplogroups J, H, U and R0 were highly prevalent. Haplogroups were observed to be more diverse in the coastal regions. In the interior regions, haplogroups were observed to be less diverse.

A New Case of Haemoglobin Fontainebleau/Haemoglobin Bleuland Compound Heterozygote in Oman

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Initially reported in an Italian family, haemoglobin (Hb) Fontainebleau (*HBA2*: c.64G>C) is a clinically silent Hb variant which exhibits a change from alanine to proline at codon 21 of the HBA2 gene chain. No change in the stability or oxygen-binding properties of the Hb molecule has been reported for this variant. Hb Bleuland is a clinically mild variant with an ACC-->AAC transversion and a threonine to asparagine change at codon 108 of the *HBA2* gene. Understanding the consequence of a new Hb variant has significant implications for

genetic counselling. The aim of this study was to predict the structural changes to the Hb molecule as a result of the Hb Fontainebleau/Hb Bleuland compound heterozygote variant. We analysed the *HBA2* deoxyribonucleic acid sequence from a 21-year-old female. Her fetal Hb was 0.4%, Hb A2 was 3.4%, mean cell volume was 43.7 fL (normal range: 76–96 fL) and mean cell Hb was 12.3 pg (normal range: 27–32 pg). The patient was a compound heterozygote for the Hb Fontainebleau/Hb Bleuland mutation. We conducted a protein structural bioinformatic analysis of the Hb variants for Hb Fontainebleau and Hb Bleuland using the HOPE online tool (Centre for Molecular and Biomolecular Informatics, Department of Bioinformatics, Radboud University, Nijmegen, Netherlands). Hb variant comparisons were also confirmed using the National Center for Biotechnology Information database and ExPASy tools (Swiss Institute of Bioinformatics, Lausanne, Switzerland). In Hb Bleuland, the mutant asparagine residue is bigger and more hydrophobic than the wild-type threonine. The domain where the Hb Bleuland mutation occurs is associated with iron-ion binding and haeme-binding. In Hb Fontainebleau, the proline that is introduced by the mutation is a very rigid residue and may abolish the required flexibility of the protein at this position. However, phylogenetic analysis revealed other conserved protein sequences with residues similar to the variant residue in Hb Fontainebleau. According to the results, the Hb Bleuland variant is possibly damaging, which is reflected in the mean corpuscular volume and mean corpuscular Hb data. The larger size of the asparagine molecule in the variant may also lead to steric hindrance. However, the Hb Fontainebleau variant was predicted to be acceptable and this is in concordance with experimental evidence reported in the literature.

Assessing the Need for Genetic Testing in Breast and Ovarian Cancer Patients in Oman

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Breast cancer (BC) is the most common cancer among Omani females. Ovarian cancer (OC) is also prevalent among Omani women. According to the 2011 National Cancer Registry, 178 cases of BC (33.7% of all female cancers) and 21 cases of OC (4% of all female cancers) were reported in Oman. Since 10–15% of BC and OC cases may occur due to genetic mutations in, for example, the *BRCA1* and *BRCA2* genes, the National Genetic Centre was approached by clinicians and patients to start genetic testing services for BC and OC. The aim of this study was to assess the need for initiating genetic testing in BC and OC patients in Oman. Data on BC cases were obtained for the period of 2009–2013 from the Medical Records Unit in Royal Hospital, Muscat, Oman. A list of OC patients from 2012–2013 was also obtained from the histology laboratory at the same hospital. We analysed the yearly incidence and age-specific trends for OC and BC. The data revealed that, in 2011 and 2012, the increase in BC cases was 17% and 12% compared to the previous year. In 2013, the number of BC cases rose dramatically by 148.7% (n = 475 cases) compared to 2012. Combined data from 2009–2013 indicated that the majority of BC cases diagnosed were among patients under 50 years old. With regards to OC patients, 20 were diagnosed in 2012 and 28 in 2013. In 2012, the majority of OC patients were 41–50 years old, whereas this cancer was commonest in the 21–40-year-old age group in 2013. In conclusion, the number of BC and OC patients seen at Royal Hospital in 2013 was 2.5 and 1.4 times more, respectively, than the incidence reported in the 2011 National Cancer Registry. The increasing numbers and rising trends of these early-onset cancers strongly indicate the need to initiate genetic testing in Oman as a major preventive strategy. Genetic testing will help to reveal the risk for a second cancer in BC and OC patients and clarify the risk for BC and OC in unaffected individuals with pertinent family historie, thus enabling earlier cancer detection and prevention.

Retinal Dysfunction in Inborn Errors of Metabolism: *Ophthalmic findings may be crucial for diagnosis*

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Inborn errors of metabolism (IEM) are a heterogenous group of disorders that occur due to inherited enzymatic defects. They often pose a diagnostic dilemma. Eye involvement is commonly encountered in IEM and its detection could aid in the diagnosis of these complex disorders. Early detection is extremely important in order to achieve appropriate therapeutic measures. The objective of this study was to highlight retinal findings that assisted in the diagnosis of IEM in order to demonstrate that retinal abnormalities can help in the targeted evaluation of this group of patients. The Sultan Qaboos University Hospital paediatric ophthalmology database was reviewed for children with retinal findings and confirmed/suspected IEM. Patient charts were retrospectively reviewed. Data pertaining to systemic and ophthalmic evaluation, photographs and results of ophthalmic procedures were reviewed and recorded. Institutional approval was sought. A total of 32 children were studied (19 male and 13 female). The age at presentation ranged from 2 months to 10 years old. All of the children had undergone a complete neurometabolic work-up but their diagnoses were still uncertain at the time of the ophthalmology consultations. All patients had undergone standard ophthalmic evaluations, including *fundus* photography. Optical coherence tomography, intravenous fluorescein angiography and electrophysiological tests were performed when indicated. Prompted by the findings of ophthalmic evaluation, appropriate biochemical, enzymatic or genetic investigations were undertaken, leading to a diagnosis. In some patients (n = 21), a diagnosis was confirmed, while 11 patients were evaluated for *fundus* findings, including maculopathy (n = 8), cherry-red spot (n = 6), bull's eye maculopathy (n = 2), atypical pigmentary retinopathy (n = 10), chorioretinal lesions (n = 2) and lipaemia *retinalis* (n = 1). IEM often present with non-specific signs and symptoms involving different systems. Visual symptoms may or may not be present. A careful and detailed ophthalmic examination might reveal characteristic features that could lead to a targeted diagnostic evaluation and early diagnosis. Certain retinal abnormalities strongly point towards a specific group of IEM disorders. A prospective study is being planned to establish criteria for ophthalmic referrals in patients suspected of having IEM.

Clinical and Molecular Characterisation of Mucolipidosis Type IV in Omani Patients

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Mucolipidosis type IV is a rare autosomal recessive lysosomal storage disorder with relatively high prevalence in the Ashkenazic Jewish population due to two founder mutations in the *MCOLN1* gene (19p13.3-p13.2). The aim of this study was to investigate the neuro-ophthalmic manifestations and molecular characteristics of mucolipidosis type IV in patients from Oman and emphasise the need for

ophthalmic examinations in children with unexplained developmental delay and/or spasticity. In the first family, a three-year-old child presented with psychomotor delay, spasticity and photophobia. A family history was significant for consanguinity and also revealed a similarly affected brother and two affected cousins. In the second family, an eight-year-old child presented with psychomotor delay and spasticity. A family history revealed a similarly affected younger sister. All of the patients (n = 6) were under the care of neurologists for their developmental delay and underwent a complete ophthalmic examination. Previously recorded neurological manifestations were reviewed. Conjunctival biopsies and molecular genetic assessments were performed. Informed consent was obtained from the parents and institutional approval was obtained. All of the children had been born at term. On examination, findings included minor dysmorphic features, developmental delay, spastic quadriparesis, photophobia, *strabismus*, nystagmus, poor vision, bilateral corneal haziness, cataracts and pigmentary retinopathy. High serum gastrin, low iron and ferritin, and microcytic hypochromic anaemia were detected. Magnetic resonance imaging of the brain showed structural anomalies. Molecular genetic testing showed a novel homozygous splice site variant in the *MCOLN1* gene (c.237 + 5G>A) in four of the six patients. Conjunctival biopsies revealed typical intracytoplasmic inclusions consistent with mucolipidosis type IV. A novel homozygous splice site variant in the *MCOLN1* gene was found. Mucolipidosis type IV is often underdiagnosed and mistaken either for cerebral palsy or a retinal dysfunction of unknown cause. Spastic paraparesis or quadriparesis in combination with iron deficiency anaemia and corneal haziness should prompt consideration of mucolipidosis type IV.

Genetic Diagnosis of Lysosomal Storage Disease in Iran

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Lysosomes are subcellular organelles responsible for the physiological turnover of cell constituents. They contain catabolic enzymes which require a low-pH environment in order to function optimally. Lysosomal storage diseases (LSDs) describe a heterogeneous group of dozens of rare inherited disorders characterised by the accumulation of undigested or partially digested macromolecules, which ultimately results in cellular dysfunction and clinical abnormalities. Organomegaly, connective-tissue and ocular pathology, and central nervous system dysfunction may result. Classically, LSDs encompassed only enzyme deficiencies of the lysosomal hydrolases. More recently, the group has been expanded to include deficiencies or defects in proteins necessary for the normal post-translational modification of lysosomal enzymes, activator proteins or proteins important for proper intracellular trafficking between the lysosome and other intracellular compartments. Over 50 LSDs have been described. The age of onset and clinical manifestations may vary widely among patients with a given LSD and significant phenotypic heterogeneity between family members carrying identical mutations has been reported. LSDs are generally classified by the accumulated substrate and include sphingolipidoses, oligosaccharidoses, mucolipidoses, mucopolysaccharidoses, lipoprotein storage disorders, lysosomal transport defects, neuronal ceroid lipofuscinoses and others. A genetic diagnosis of some of the LSDs diagnosed via genetic and prenatal diagnosis achieved through whole gene polymerase chain reaction sequencing methods is described.

Clinical and Molecular Study of Niemann-Pick Type C Disease in Iran

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Niemann-Pick disease type C (NPC) is a rare autosomal recessive neurovisceral disorder caused by mutations in the *NPC1* (95%) or *NPC2* (5%) genes. NPC disease has a variable phenotype, whereby an alteration in cholesterol and glycolipid homeostasis leads to a broad spectrum of symptoms that include hepatosplenomegaly, liver dysfunction and neurological abnormalities such as progressive *ataxia*, cataplexy, vertical supranuclear gaze palsy, seizures and impairment of the swallowing reflexes. NPC is rarely reported in Iran. Over a period of 18 months, 15 patients were diagnosed with NPC by Filipin staining in the Medical School of Tehran University. Reverse transcription polymerase chain reaction and sequencing methods were used for molecular investigation of the *NPC1* and *NPC2* genes in five patients, two of who were female. All of these patients had the juvenile form of NPC and had presented with *ataxia* gait. Additionally, all five patients were the result of consanguineous marriages. Case one was a 15-year-old boy who had hepatosplenomegaly and jaundice during his neonatal period. Liver biopsy findings were compatible with a lipid storage disease. He had developed supra vertical gaze palsy at the age of 11 years and progressive *ataxia*, dystonia and gelastic cataplexy at the age of 13 years. Magnetic resonance imaging (MRI) of the brain was normal. Case two was a 3.5-year-old boy; splenomegaly had been detected at the age of six months. He had psychomotor developmental delays, was unable to walk and had developed supra vertical gaze palsy one year previously. For the previous year he had also exhibited gelastic cataplexy even in a sitting position. A brain MRI was normal. Cases three and four were two sisters aged 13 and 17 years old, respectively. They were both products of a consanguineous marriage. Case three presented with a complaint of progressive *ataxia* and dysarthria since the age of nine years. At the age of 11 years, progressive dysphagia had begun but its progression had plateaued. The patient's cognitive state remained unchanged. She did not suffer from seizures or gelastic cataplexy, and lacked a history of neonatal jaundice or splenomegaly. Upon a neurological examination, the patient was found to have supra vertical gaze palsy. A brain MRI showed non-specific hypersignal changes in the white matter. The 17-year-old sister (case four) had been diagnosed with *epistaxia* when she was 6 years old. Splenomegaly was detected in her work-up. Progressive *ataxia* and dysphagia developed at seven years of age, leading to a wheelchair-bound state and nasogastric tube feeding at 14 years of age. A brain MRI showed cerebellar atrophy. Upon neurological examination she had supra vertical gaze palsy. She died a few months after the study. Case five was a 13-year-old boy who presented primarily with neurological symptoms. He had started to develop *ataxia* and dysarthria at the age of eight years. Dementia, dysphagia and seizures, in this sequence, followed within a couple of years. He was anarthric and bedridden four years after onset. Supranuclear vertical gaze palsy was found at the time of the examination. However, no hepatosplenomegaly or other physical abnormalities were noted. Whole transcribed exons of the *NPC1* genes were sequenced and four different unreported homozygous mutations were found: Case one: (c.1069C>T) p.S357L; Case two: (c.1180C>T) p.Y394H; Cases three and four: (c.1433A>C) p.N 478 T, and Case five: (c.1192C>T) p.H398Y. All of the mutations were analysed and found to be missense mutations.

Genetic Diagnosis of Primary Immunodeficiencies in Iran

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Primary immunodeficiencies (PIDs) are genetic disorders of the immune system comprising many different phenotypes. Although previously considered rare, recent advances in clinical, epidemiological and molecular definitions have revealed that much remains to be learnt about these disorders. Geographical and ethnic variations as well as the impact of certain practices influence their frequency and presentation, making it necessary to consider their study in terms of different regions. The genetic diagnosis of PID is very new in Iran. In the past three years, more than 12 tests have been developed using polymerase chain reaction (PCR) sequencing methods. New mutations were found by the investigation of the *IL2RG*, *ADA*, *RAG1*, *RAG2* and *IL7R* genes in 62 patients with severe combined immunodeficiencies. Investigations of the *CYBB*, *CYBA*, *NCF1* and *NCF2* genes in 58 patients with chronic granulomatous disease showed more autosomal recessive patterns than x-linked patterns in Iran. Patients with Wiskott-Aldrich syndrome (n = 28) were examined for the *WAS* gene and new mutations were found by sequencing methods. The hot spot exons, *RAB27A* and *MYO5A*, were investigated in 18 patients with Griselli syndrome. Additionally, 22 patients with Bruton agammaglobulinaemia and 20 patients with haemophagocytic lymphohistiocytosis were studied for the *SPX11* and *PRS I* genes. All results, including an investigation of neutropaenia, common variable immunodeficiencies and leukocyte adhesion deficiencies are presented in this seminar.

Molecular Investigation of Charcot-Marie-Tooth Disorder for the *PMP22*, *MPZ*, *EGR2*, *GJB1*, *MFN2* and *GDAP1* Genes in Some Iranian Patients

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Charcot-Marie-Tooth (CMT) disease is the commonest neurogenetic disorder with phenotypic and genotyping heterogeneity. Both the phenotypic features and disease severity can either be consistent or vary widely within families. The affected individual typically has distal muscle weakness and atrophy often associated with mild to moderate sensory loss, diminished or absent deep tendon reflexes, high-arched feet and skeletal deformities such as *pes cavus*. CMT hereditary neuropathies are categorised by mode inheritance and causative gene or chromosomal *locus*. Autosomal-dominant inherited CMT patients are usually classified according to demyelinating form, severely reduced nerve conduction velocities in type 1 (CMT1) and axonal form in type 2 (CMT2). An X-linked inheritance pattern is classified in the *CMTX* gene and an autosomal recessive inheritance pattern is classified in type 4. All patients (n = 142) were investigated for the *PMP22* gene according to their electroclinical results, neurological examination and pedigree. Polymerase chain reaction (PCR) restriction fragment length polymorphism and multiplex ligation-dependent probe amplification was undertaken for CMT1A patients. The *MPZ*, *EGR2*, *MFN2*, *GJB1* and *GDAP1* genes were determined by a PCR sequencing method for all the exons and exon-intron boundaries. In order to show that these found novel mutations were pathogenetic, 50 genetically normal controls with no such mutations were sequenced for all of these genes. According to this study, the frequency of duplication in the *PMP22* gene in comparison to other genes was very low. This is because of the high rate of consanguineous marriage in Iran. It is believed that other unknown genes are involved in the development of CMT disease in these patients. There are limitations associated with the genetic diagnosis of CMT, including the fact that many genes are involved in the same phenotype and many phenotypes are caused by same gene. Therefore, the cause of CMT should be clarified by an investigation of other genes associated with the disease.

Exploring the Need for Prenatal Diagnosis and Termination of Pregnancy in Oman: *The unspoken challenges*

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Genetic counselling and testing is an integral component in providing an effective clinical service for the management of families who are at-risk for or affected by a genetic disorder. Where a causative mutation is identified, options aimed at reducing the genetic burden in that specific family become available, such as prenatal genetic diagnosis. This form of genetic testing can lead to the detection of an affected fetus; parents are subsequently faced with the decision to continue or terminate the pregnancy. The termination of the pregnancy raises ethical debate in all societies; addressing this topic is particularly difficult in Islamic societies, where abortion is largely avoided. The increase in the number of requests for prenatal genetic diagnosis at the Genetic and Developmental Medicine Clinic of Sultan Qaboos University Hospital (SQUH) calls for an open ethical and legal discussion of this topic. In the current study, conducted in 2013, descriptive data were gathered and interviews undertaken with individuals requesting prenatal diagnosis for a genetically-confirmed disorder following extensive genetic counselling. A total of 10 cases were identified and included in the study. Patients most frequently requested testing for inherited metabolic disorders. Test results were discussed together with the patient-driven outcomes following either a positive or negative result disclosure. Interviews undertaken with each patient additionally provided data on the impact of the decision for the couple and their family. The effect of undertaking testing on future pregnancy-related decisions is also described in this study. These described experiences highlight the constellation of logistical, religious and psychosocial challenges faced by patients requesting the procedure in SQUH. Awareness of the situation faced by patients accessing prenatal diagnosis will be extremely valuable in developing services according to patient needs.

Molecular Analysis of Inborn Errors of Metabolism in Oman

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Inborn errors of metabolism (IEM) are a group of inherited recessive disorders associated with amino acid metabolism, fatty acid oxidation and pyruvate and carbohydrate metabolism. Many of the metabolic disorders carry serious clinical consequences to the affected neonates or young infants. These may include mild to severe irreversible mental retardation, physical handicaps or even fatality

if left untreated and results in a significant burden on the quality of life and socioeconomic status of affected individuals and their families. The investigation and recognition of IEM is fairly new in Oman, with the first cases being reported in 1998. In this study, patients from 56 families attending the Metabolic Clinic at Sultan Qaboos University Hospital were recruited from 2010–2012. Mutation analysis was carried out at the Molecular Genetic Diagnostic Laboratory using standard sequencing methods in the known genes associated with IEM disorders. Out of 56 families, 40 families displayed 24 homozygous mutations in 11 IEM disorders. Those include disturbances of amino acids, organic acids and carbohydrates as well as storage and fatty acid oxidation defects. From the identified mutations, 15 were novel mutations, including eight missense mutations, four premature stop codons and three frameshift mutations. Mutations identified in Omani patients will be further validated so that they can be integrated in the list of available Molecular Genetic Laboratory tests. The availability of molecular testing for IEM disorders in Oman has important implications for families and genetic counselling.

A Case of Jeune Syndrome in Oman: *Is this syndrome as rare as we think?*

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Asphyxiating thoracic dystrophy, also known as Jeune syndrome, is an autosomal recessive multisystemic disorder and infants born with the disorder have an average life expectancy of approximately two years. It has an annual incidence of 1–5 in 100,000–130,000. There have been 250 reported cases of Jeune syndrome in Oman but the true incidence in the Omani population has yet to be determined. In a country like Oman, where consanguinity is rampant, one may ask whether Jeune syndrome is as rare as it is commonly believed to be. A nine-year-old boy with disproportionate dwarfism was referred to hospital for evaluation of proteinuria. He had a history of repeated hospitalisations due to chest infections and had been diagnosed with nephrotic syndrome which had progressed to end-stage renal disease (with an estimated glomerular filtrartion rate of 5) which was resistant to steroids and tacrolimus. The child was suspected of having an undiagnosed skeletal dysplasia after he presented with one of its complications. Jeune syndrome was confirmed by clinical findings, including short stature, triangular face, high arched palate, bell-shaped thorax and radiological findings of thanatophoric dysplasia. This case highlights the fact that investigations for rare conditions such as Jeune syndrome should not be neglected. Reviewed literature suggests that, in children with Jeune syndrome who survive infancy, the thorax has the potential to grow. There is evidence of patients with this syndrome surviving beyond childhood. Early diagnosis, aggressive management in the initial years and regular follow-up with a multidisciplinary approach may yield better outcomes for these patients. Suspicion plays a major role in antenatal diagnosis and the need for awareness of this condition among medical practitioners is therefore essential. Interventions such as titanium rib surgery and renal transplantation could make a significant difference to patients' quality of life.

Mutational Screening of the PTPN22 Gene in an Omani Cohort Affected with Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune disease affecting 0.3–1.5% of the worldwide population. RA usually targets the synovial joints by initiating lymphocyte activation and immune complex deposition. Genetic factors involved in the aetiology of RA are reported to be complex, diversified and poorly understood. Among these, the *protein tyrosine phosphate non-receptor type 22* (*PTPN22*) gene, seems to play a major role at different levels. In this study, *PTPN22* mutations were screened in a cohort of Omani patients with RA by targeting hot spot areas of the gene and matching the obtained results with available clinical data. Deoxyribonucleic acid extracted from the blood samples of 30 patients (of whom 27 were female) and 14 controls was subjected to polymerase chain reaction amplification and sequencing of exons 13, 14, 15, and 18 of the *PTPN22* gene. While no mutation or single nucleotide polymorphism was found in exon 15, one novel mutation and one insertion was recorded in exon 13, in addition to the novel mutation and reported polymorphism detected in exon 14. Moreover, analysis of exon 18 revealed two reported mutations, three novel polymorphisms and 12 novel mutations. Pearson's Chi-squared test showed no significance ($P > 0.1$) between the number of mutations and different clinical parameters characterising RA. These findings suggest that a complex cocktail of events act independently in the formation of RA. Clinical parameters did not reflect aberrations at the genomic levels such as in the *PTPN22* mutations, deletions and polymorphisms involved in the pathogenesis of RA, at least in this Omani population.

Genetic Analysis of Patients with Neonatal Diabetes in Oman

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Neonatal diabetes mellitus (NDM) is rare, occurring in 1:300,000–400,000 births. NDM can be permanent (PNDM) or transient (TNDM). In PNDM, the diabetes affects the patient throughout their entire life, while in TNDM, the diabetes may disappear after the first few months of life but recur later in life. Distinguishing TNDM from PNDM has significant implications for patient management and prognosis and in monitoring the recurrence. Only genetic testing can make the distinction between PNDM and TDND. Testing for mutations in specific genes can also guide therapy and affect clinical outcomes. For example, PNDM patients with mutations in the *KCNJ11* or *ABCC8* genes can be transferred from insulin therapy to sulfonylureas. Hence, it is important to establish comprehensive genetic testing for NDM syndromes in Oman. The aim of this study was to identify the genotypes underlying NDM syndromes within the Omani population. Deoxyribonucleic acid from 23 patients with NDM who attended the Diabetic Clinic at the Royal Hospital from 2008–2013 were analysed for mutations in the *GCK*, *ABCC8*, *KCNJ11*, *INS*, *SLC2A2*, *EIF2AK3* and *FOXP3* genes using polymerase chain reaction and Sanger sequencing. The 6q24 region was also investigated to rule out 6q24-related TNDM. Of the 23 patients analysed, three patients were diagnosed with PNDM as they had homozygous mutations in the *GCK* gene which encodes for glucokinase, a key enzyme responsible for regulating insulin secretion in pancreatic beta cells. Two patients had mutations in the 6q24 *locus* and were determined to have TNDM. Another three patients were rediagnosed with Fanconi-Bickel syndrome due to mutations in the *SLC2A2* gene which encodes a protein that mediates bidirectional glucose transport. The other 15 patients did not exhibit any pathogenic mutations in the genes tested. Among these 15 patients, two were later classified as having autoimmnune diabetes. Of the 18 patients with actual NDM in this study, we were able to detect pathogenic mutations in only 28% ($n = 5$) of the patients. The lack of genetic test results in 72% of NDM patients supports the relevance of next-generation sequencing in genetic testing of monogenic diabetes syndromes. Hence, the testing of monogenic diabetes syndromes will be initiated at the National Genetic Centre in Oman.

Evaluating the Need for Initiating Colorectal Cancer Genetic Testing in Oman

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According to the 2011 National Cancer Registry, colorectal cancer (CRC) is the second most common solid cancer in Oman after breast cancer. CRC has a low five-year survival rate (55%). This is mainly due to late clinical presentation, when the disease is already in an advanced stage and has metastasised to other tissues. This highlights the importance of identifying individuals at risk of developing CRC. Of all CRC cases, 5–10% are due to genetic mutations in certain genes such as the *APC* gene. Early onset of disease and a family history of cancer are two strong indicators of a genetic predisposition towards CRC. Clinicians from the Royal Hospital observed a high incidence of CRC cases among young patients and hence approached the National Genetic Centre to initiate genetic testing for CRC in Oman. Providing this service may help us to understand the contribution of genetics to the prevalence of CRC in the Omani population and may reduce the healthcare burden of CRC cases by identifying high-risk individuals. It may also improve the management of CRC patients by informing their treatment decisions. The aim of this study was to assess the need for initiating genetic testing for CRC in Oman. A list of patients who had been diagnosed with CRC from 2009–2013 was obtained from medical records of the Royal Hospital and incidence data were analysed according to age and gender. The overall incidence of CRC cases increased by 80% between 2009–2013. In that same period, 444 patients were diagnosed and treated for CRC at the Royal Hospital clinics. Of those patients, 169 (38%) were ≤50 years old and 279 (62%) were ≤60 years old. Patients as young as 11 and 15 years old were diagnosed with CRC in 2012. Most CRC cases in Oman were found present at younger ages than those recorded in the Western world. For example, in 2011, only 15.77% of the total number of CRC cases in the UK occurred in those under the age of 60 years. During the same year, 60.9% of patients diagnosed with CRC in Oman were under the age of 60. Therefore, genetic testing is strongly indicated for CRC patients and their families in Oman.

Frequently Mutated/Deleted *HLA-DRB1* Gene in Omani Patients Affected with Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune disease affecting the synovial joints, surrounding tissues and many other organs of the body. RA is considered a multifactorial disease that stems from both genetic and environmental factors. Among the genes associated with RA, *HLA-DRB1* plays a major role in the immune system by presenting peptides derived from extracellular proteins on antigen-presenting cells (including B lymphocytes, dendritic cells and macrophages). In this study, we screened for *HLA-DRB1* mutations in Omani patients affected with RA, with the ultimate goal of targeting hot spot areas of the gene and matching the obtained data with the clinical presentation and laboratory investigations for RA. In parallel with 14 samples from healthy subjects used as controls, 30 blood samples from affected patients were examined. Patients' *HLA-DRB1* mutational statuses were examined using polymerase chain reaction and sequencing. Among the 30 Omani patients with RA and the 14 healthy controls, we found a total of 75 aberrations in the *HLA-DRB1* gene, 15 of which were polymorphisms (20%). The remaining cases (68%) were scored as mutations, 25.49% of which were silent mutations. Moreover, we identified six deletions and three insertions in 12% of the studied cases. The deletions occurred at amino acid position 101, introduced a stop codon at position 383 and were found in 10% of the affected population. Statistical analysis showed no significance between the genetics aberrations in the *HLA-DRB1* gene and the different clinical parameters used to assess RA ($P > 0.05$). The *HLA-DRB1* gene was found to be frequently targeted for mutation deletions in RA study cases and is, therefore, most likely involved in the pathogenesis of the disease. However, no significant correlation with clinical parameters was found. These findings suggest that *HLA-DRB1* and clinical parameters act independently in promoting the pathogenesis of this disease.

Inhibition of Breast Cancer Cell Proliferation by Novel Boswellic Acid Derivative Isolated from Omani Frankincense

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Despite the rapid progress in technology and the availability of various cancer treatment modalities, conventional medicine still faces several challenges, including drug resistance. In contrast, complementary alternative medicine is increasingly being practiced worldwide due to its safety and effectiveness. Boswellic acid (BA), the active ingredient in frankincense, is a well-known inhibitor of cancer cell growth. The aim of this study was to develop novel BA derivatives (*BCL21* and *BCL23*) from Omani frankincense and test their effect on the proliferation of the highly metastatic MDA-MB-231 breast cancer cell line, using normal human skin fibroblasts and MCF10A breast epithelial cells as control cells. Cell viability was examined using the alamarBlue® assay (Thermo Fisher Scientific Corp., Carlsbad, California, USA) and a dose-response curve was established. Our results revealed that the BA derivative *BCL21*, even at a very low dose, induced the death of a higher number of MDA-MB-231 breast cancer cells than either BA or *BCL23*, whereas the same concentrations of the compounds had no effect on the control cells. These results identified a novel BA derivative that not only can be produced in high quantities for commercial purposes but also appears to be a powerful agent for chemoprevention studies.

Genomics of Breast Cancer in Oman

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Breast cancer (BC), a heterogeneous disease, can invade locally or metastasise to the lymph nodes or other organs. Despite advances in technology and research in BC, the complexity of the molecular basis of BC development and progression is still nascent. In the multistep process of BC metastasis, invasion is the recurring defining event, and elucidation of its molecular mechanisms is critical for understanding BC progression. Previous studies have suggested that different breast tumour grades are associated with distinct gene expression signatures. This study aimed to test the following two hypotheses: (1) that a subset of specific genes is associated with the

transition from pre-invasive to invasive growth of breast tumours and (2) that the process of cell invasion involves specific anti-invasive and pro-invasive genes that interact to coordinate breast tumour cell migration/invasion. To test these hypotheses, ribonucleic acid was extracted from breast tumour tissues and a microarray analysis was performed. Our results showed that the analysis of the microarray data revealed a set of genes that could potentially interplay with signaling the pathways that regulate the switch from the premalignant to malignant phenotype. Further screening tests should be performed on these genes to identify and validate the candidate genes. Consequently, this will pave the way towards the design of targeted anti-metastasis therapeutic strategies.

Novel Leprechaunism Mutation in an Omani Child

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Donohue syndrome (DS), also known as leprechaunism, is an extremely rare autosomal recessive disorder that was first described in 1948. It often results in early infantile or childhood death. It is characterised by severe insulin resistance, intrauterine growth restriction and postnatal growth retardation. Common phenotypic features include a small elfin-like face with protuberant ears; thick lips; a broad *ala nase*; a distended abdomen; relatively large hands, feet and genitalia; abnormal skin with hypertrichosis; decreased subcutaneous fat levels, and acanthosis *nigricans*. Biochemical evidence for insulin resistance has been found, including markedly elevated plasma insulin levels and impaired glucose haemostasis. The insulin resistance in DS is the result of a gene deletion in the insulin receptor which interferes with proper insulin receptor function. There is a paucity of genetic data about this syndrome in the Arab population. There has been a report of a Yemeni family in the United Arab Emirates where five children out of eight were affected with the disease due to a homozygous mutation in codon 119 of exon 2 of the *insulin receptor* (*INSR*) gene. This paper focuses on the second reported case in the Arab population with a novel mutation (*INSR* homozygous variant c.671_685dup p.Lys224_Cys228dup) from Oman. The patient was a four-month-old male infant born to consanguineous parents (first cousins) with the novel leprechaunism mutation Cys807Arg. The aim of this case presentation is to increase health professionals' awareness of this extremely rare syndrome as it seems not to be as rare in the Arab region as was previously thought. This syndrome is often misdiagnosed or underdiagnosed.

The Molecular Genetics and Genomics Laboratory at Sultan Qaboos University Hospital

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The laboratory section of the Department of Genetics at Sultan Qaboos University Hospital (SQUH) involves the molecular-level study of disorders with a genetic basis. The investigations and studies are performed at the nucleic acid level. Currently, the service is at an early stage of development, with staff being trained in various techniques, equipment being modernised and the available physical space retrofitted to accommodate the nature of the work being performed. When completed, the laboratory will provide comprehensive and specialised molecular diagnostic services, including teaching and research, in line with SQUH's mission and vision. The laboratory has benefited from its proximity to research activities performed within the Department of Genetics as well as additional departments within the university. This has led to the translation of molecular-related findings into the development of routine diagnostic tests. It is anticipated that by the end of 2014, a basic menu of specific clinical tests will be available in support of the Genetic and Developmental Clinic and other specialty clinics within SQUH and in the region.

Y-Chromosome Polymorphisms in an Omani Population Using Microsatellite Markers

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The Y chromosome is one of the smaller human chromosomes, with an average size of 50 million base pairs. It contains different regions that can be detected to determine the variations among individuals and between different generations. In this project, short tandem repeat (STR) genetic markers were used. Due to their typing simplicity, high levels of diversity and tolerance of degraded deoxyribonucleic acid (DNA) samples, they are usually used to study population genomes, as well as in forensic medicine to identify victims, and to test paternity and identify males and male lineages. To amplify DNA from unrelated Omani males, 17 polymorphic DNA STR markers were obtained using an AmpFLSTR® Yfiler® kit (Thermo Fisher Scientific Corp., Carlsbad, California, USA). This kit uses polymerase chain reaction and fluorescently labeled primers to achieve identification. The genotypes and allele frequencies generated were analysed using the online Y Haplogroup Prediction from Y-STR Values program (www.hprg.com/hapest5/). In the studied Omani sample, 12 haplogroups were found. Males from the North Al Batinah region were found to belong to the J1, Rla, T, E1b1a and E1b1b haplogroups. In South Al Batinah, males were determined to belong to the J1, T and L haplogroups. Al Dhakhiliya shows the most variable number of haplogroups, with males representing haplogroups T, Q , J1, E1b1a and E1b1b; the group I2a (xI2a1) was also observed, which is a group found only in this region. Similarly, the G2a haplogroup is only found in the Al Dhahirah and Dhofar regions. Additionally, haplogroups T, J1, E1b1a and E1b1b are also found in Al Dhahirah and Dhofar. The group J2b was only found in Dhofar. Additionally, it was found that males from the Muscat region carry a unique haplogroup not found in any of the other regions—the I2b1 haplogroup. The other haplogroups found in males from Muscat were J1, T and E1b1b. Males from Ash Sharqiyah males belonged to the same haplogroups that were found in North Al Batinah, with the exception of the E1b1a haplogroup, which was not found in North Al Batinah. Finally, one male from the Al Buraimi region fell under the E1b1b haplogoup, which was also found in North Al Batinah. This may be attributable to the geographical proximity of the two regions.

Utilisation of Molecular Genetic Diagnosis by Omani Families with Monogenic Disorders: *Two years of experience*

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The utilisation of molecular genetic diagnostic information is one of the core services offered at the Genetic and Developmental Medicine Clinic at Sultan Qaboos University Hospital. The availability of molecular genetic testing is of particular importance to families with inherited genetic diseases as it offers the opportunity to reduce the risk of occurrence or recurrence. Oman is an Arab country where consanguineous marriage are culturally acceptable. This has been suggested as a contributing factor for the clustering of rare autosomal recessive disorders among families of the same descent in Oman. Molecular genetic testing can be utilised to provide these families with genetic information to facilitate family planning. Access to premarital counselling and testing for candidates at high risk of being carriers has the potential to reduce the genetic burden within families. Since the establishment of genetic services in August 2011, 1,104 samples have been sent for molecular genetic testing. Of these, 112 (10%) were from families with a confirmed diagnosis of a genetic disorder who were undergoing carrier status testing for family planning purposes. A total of 36 (32%) of those who underwent testing did so as part of premarital counselling and testing for autosomal recessive disorders and 58 (51.7%) were utilising the molecular genetic information for prenatal or preimplantation genetic diagnosis. The remaining 18 patients (16.3%) were tested for carrier status confirmation. During 2012, a total of 322 samples were sent for molecular genetic testing. This number has since more than doubled, with 782 samples sent in 2013. Considering that 56.4% of marriages in Oman are consanguineous, as well as the fact that the majority of genetic disorders are autosomal recessive in nature, premarital counselling and testing can be extremely valuable to Omani families. In this analysis, we present and discuss the utilisation of the molecular genetic diagnostic service with a focus on those families with a history of autosomal recessive disorders.