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International Conference on Consanguinity

Towards the discovery of genes predisposing to and protecting from disease

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The Importance of Genetics in Oman

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The Sultanate of Oman is located in the South East of the Arabian Peninsula with a coast line stretching from Yemen in the south to the Arabian Gulf in the north. This location served as a crossroads for the prehistoric worldwide spread of humans out of Africa. For centuries, the coast of Oman had been a sea gate to Asia and Africa through which Omanis traded and intermixed with other populations. Over the last forty-two prosperous years, the Omani population has grown approximately four-fold due to an increased birth rate and substantial decline in the death rate. The current population is mainly tribal Arab, but the numbers of Asian and African ethnic descendants are significant. The increased population growth as well as traditionally preferred consanguineous marriages has led to the emergence of a wide spectrum of genetic diseases. Recent public database searches reveal that only a fraction of those diseases have been studied at the molecular level. Interestingly, over 70% of the reported mutations and loci were novel. Commendable efforts by the Ministry of Health and Sultan Qaboos University Hospital to offer a comprehensive genetic service are progressing. The service's main challenges are to educate the public on the importance of genetic disease prevention as well as to identify disease-causing mutations or markers through transitional research. This surely calls for well-structured national and international collaboration.

The Return of the Human Genome Project to Clinical Genetics

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Traditionally, medical geneticists have relied on linkage, association, or candidate gene approaches to identify the genes responsible for Mendelian disorders. In aggregate, these methods have found about 2,700 disease genes or about 12% of our total complement of genes. Recent advances in genomics, plus the development of new sequencing technologies, provide the tools necessary to speed up dramatically the progress in disease gene identification. An essential requirement in this effort is the identification and careful characterisation of patients and families with Mendelian phenotypes that have not yet been explained at the molecular level. For example, Online Mendelian Inheritance in Man (OMIM) currently lists ~2500 Mendelian disorders for which the responsible gene is yet unidentified and in any active genetics clinic there are many patients and families with undiagnosed disorders that segregate as Mendelian traits. A high frequency of consanguineous unions increases the incidence of rare recessive disorders of this type. By combining these resources, we can expect that over the next few years there will be a substantial increase in the number of identified disease genes and, correspondingly, in the number of human phenotypes that we can connect to genes and biological networks. My presentation will focus on the lessons we can expect to learn by "solving" a large number of currently unexplained disorders. These lessons will include immediate benefits in diagnosis, counselling, and treatment, as well as long-term insights into the mechanisms of disease and its prevention.

Genetics and Society

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For much of human history, our common ancestors worldwide have practiced consanguinity, or "close cousin marriage". This has great

social benefits in keeping economic resources in the family and ensuring alliances with well-known and like-minded people; however, it also produces an extra risk of congenital birth defects. The Gulf region, with relatively high rates of consanguinity, natural fertility, and large families, presents an ideal training ground for internationally significant research and highly relevant clinical delivery that can make a big difference to local people's welfare. The information gained is important not only for the development of this region but also for information needed throughout the world. People living with genetic differences hold the key pieces to the jigsaw of the human genome. Without them we cannot make sense of the code we all share, and we cannot extract the messages of health and disease contained in the genetic framework. Highly motivated families play a hub role in research. They outline the family differences, find the experts, get their set of traits onto the funding agenda, and even help to write the scientific reports. The work involved in establishing genetic differences is rarely straightforward because a set of unusual features caused by a gene variant may play out in different degrees. Contrasting with these are traits that members of any family can share. However, when the gene variant is found, the different problems collapse onto the single underlying cause and this understanding makes it easier to coordinate services. Rare familial traits create a bond linking affected families when they can find one another. Organisations like the Genetic Alliance allow us to pool our efforts. With genetic testing comes the possibility of understanding genetic disorders and applying appropriate prevention measures such as family and premarital counselling. Positive examples of families and their supporters are very important in this effort, and journalists can help once they are given examples like the portraits of Rick Guidotti, founder of Positive Exposure, a non-profit organisation, that challenges stigma associated with difference by pioneering a new vision of the beauty and richness of genetic diversity.

Consanguineous Marriage: Facts versus fiction

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The most common misunderstanding with respect to consanguineous marriage is that somehow they causes genetic disease. While there is no doubt that the expression of rare recessive disorders is more probable in the progeny of a close kin marriage, the assumption of a causal relationship between consanguinity and inherited disease is erroneous and ignores factors such as founder effect, effective population size, drift and population stratification. In conjunction with failure to control for adverse demographic, social, and economic issues, exaggerated estimates of the harmful health outcomes of marriages between close family members have resulted. Globally, more than 1 billion people live in countries where 20–50+ % of marriages are contracted between couples related as second cousins or closer (F = 0.0625), and in these different societies intra-familial marriage has been preferential for many generations. Recent multi-national meta-analyses have indicated a mean excess of 0.5/1000 stillbirths, 12.5/1000 infant deaths, and 37/1000 pre-reproductive deaths in the offspring of first cousins. From a public health perspective, it is important to assess these statistics within a local context, and the lack of control for non-genetic variables in a majority of the studies strongly suggests that the mortality estimates are maximal. Significant variability was observed in complementary studies on morbidity, with reported excess birth defects at the first cousin level ranging from 0.3% to 10.0%, once again suggesting inadequate control for non-genetic variables, including maternal nutrition and medication, and trans-placental infection. Comprehensive multidisciplinary studies on consanguinity are urgently needed, with a thorough assessment of the perceived social and cultural benefits considered alongside epidemiological data, the patterns and extent of genomic homozygosity, and population genetic structure. To date, the primary focus on consanguinity has been on reproductive behaviour and health outcomes in the early years of life. Given the rapid ageing of most human societies, equivalent emphasis on the influence of consanguinity on adult health is overdue.

Community Needs for Genetics Services in Oman

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Over the past 30 years, Oman has witnessed remarkable social and economic growth, which is best reflected in its well-organised and efficient health care system. As a consequence, there has been an epidemiological shift in disease patterns, with a significant decrease in the incidence of communicable diseases, and in the mortality and morbidity rates of infants and children under 5 years. With the application of high quality standard medical care, natural selection forces are no longer in place, and children disadvantaged by birth defects and genetic conditions who would have died in past decades are now surviving. A recent population-based study confirmed genetic and congenital disorders are major contributors to childhood disabilities and handicaps. The figures of morbidity and mortality in newborns, infants, and children reflect the situation in a traditional Muslim community where communicable diseases were successfully controlled and primary prevention is in the preparation phase. Future planning of genetic services and effective prevention programmes will be discussed.

Genetic/Genomic Studies of Consanguinity in Inbred Populations

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Classical studies of consanguinity have taken advantage of the relationship between the gene frequency for a rare autosomal recessive disorder (q) and the proportion of offspring of consanguineous couples who are affected with the same disorder. We developed a new approach for estimating q using mutation analysis of affected offspring of consanguineous couples based on the possibility that the child born of consanguineous parents carries a double copy of the same mutation (true homozygosity), or alternatively carries

two different mutations in the same gene (compound heterozygosity) inherited through two different ancestors. The proportion of compound heterozygotes among children affected with a given autosomal recessive disorder, born of consanguineous parents, can be taken therefore as an indirect indicator of the frequency of the same disorder in the general population. Data from the offspring of consanguineous marriages affected with different autosomal recessive disorders collected by different molecular diagnostic laboratories in Mediterranean countries, and in particular in Arab countries where the frequency of consanguineous marriages is high, show the validity of this approach. Finally, recent experimental data show that the causative mutation for a rare autosomal recessive disorder can be identified by whole exom sequencing of only two affected children of first cousin parents. In conclusion, consanguinity becomes a powerful tool for the identification of disease genes and of the corresponding causative mutations in any inbred population when an effective collaboration is established between molecular geneticists, clinical geneticists and other clinical specialists. The present conference gives the opportunity to launch a common genome project based on the patient and population resources of each country of the Gulf region which are characterised by a typical social structure based on consanguinity. The aim would be to identify regions of homozygosity of the human genome harboring genes predisposing to or protecting from disease.

The Return of the Human Genome Project to Genetic Studies of Populations

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Population-based studies constitute an essential tool for harvesting the wealth of genomic information made available by the Human Genome Project. The initial aim of these studies was to provide a clinical dataset from a random sample of a population in addition to environmental information in order to evaluate epidemiological risk factors. The Kooperative Gesundheitsforschung in der Region Augsburg (KORA = cooperative health research project in Augsburg region) project is an example of such a population-based study. It led by the epidemiology departments of the Helmholtz Center in Munich. It started in 1984 with a succession of four surveys plus corresponding follow-up studies, and collected information and biomaterials from more than 16,000 individuals. Its continuing output is based to a great extent on genome-wide analyses of quantitative traits of medical relevance, and in contributing genotyped control samples to the study of dichotomous traits such as diabetes or myocardial infarction. Currently, this generation of transcriptomic and metabolomic data adds to the information content already available on the genomic and the phenotypic level. Cohorts such as KORA can only fulfill their potential in combination with studies in other populations, which provide increased power and the possibility of replication. Advancements in sequencing technology will allow the extension of genetic investigations to rare variants on a genome wide level. In this context, the study of genetically isolated populations with their specific spectra of allele frequencies becomes critical. While donors in population-based studies have clearly made personal contributions to the advancement of scientific projects, it remains to be demonstrated how these participants can directly profit from such studies. It can be argued that the latter is not essential for the field, as new insights into molecular mechanisms will foster pharmacological innovation in general. Nonetheless, the addition of rare genetic variation, the inclusion of transcriptomic and metabolomic datasets and, finally, the analysis of longitudinal datasets clearly have the potential to become relevant for individual study participants.

Genetic Basis of Common Diseases

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The recent advances in genomics and microarray technology at manageable cost, have enabled research groups, worldwide, to conduct successful genome wide association (GWA) studies. These studies have unravelled some aspects of the genetics of complex traits and common diseases, such as type 2 diabetes, obesity, myocardial infarction, stroke, asthma, schizophrenia, bipolar disorders, Alzheimer's disease, Crohn's disease, autoimmune diseases, and some cancers. The newly discovered genetic architecture of these diseases is helping in the understanding of pathophysiology and the development of novel approaches to prevention and therapeutic applications. However, most of the GWA studies have been designed to detect potential susceptibility in loci and genes attributable to common single nucleotide polymorphisms (SNPs), which are limited by the very design of microarrays. In almost all diseases tested to date, the variants discovered could only explain 10–15% of the inherited predisposition (heritability). The next major step will be to identify the probable source of this unknown heritability. An examination of copy number variants and rare variants that occur with low frequency await the design of novel microarrays and low-cost through sequencing.

Newborn Screening Program for Oman: The need of the hour

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Compared to Western countries, metabolic diseases are at least 3 to 5 times more common in Middle Eastern countries, and Oman is no exception. Delay in diagnosis is the major cause of the region's high morbidity and mortality. A large proportion of metabolic diseases are now amenable to simple and low cost, effective drug treatments, or simple modification of diet. Early intervention in the pre-symptomatic stage of disease is the only hope for a good outcome. Without a doubt, this is only possible by implementing an effective national newborn screening programme. Since the invention of the first screening test for phenylketonuria by Dr. Robert Guthrie in 1959, most Western countries have adopted the screening programme. Screening tests have now become even more efficient and, through tandem mass spectrometry, can detect multiple diseases from a single drop of blood. In the Middle East, Saudi Arabia, Qatar

and the United Arab Emirates (UAE) have already adopted a viable screening programme. Why should Oman lag behind? Without a shade of doubt, the investment in a screening programne today will certainly be rewarded many times over in terms of quality of life and the reduction of the burden of genetic diseases in the future.

The Role of Consanguinity in Reproductive Health and Disease Gene Identification in Arab Populations

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Consanguineous marriages have been practised since the times of the earliest humans. Until recent times, consanguinity was widely practised in several global communities at variable rates depending on religion, culture, and geography. Arab populations have a long tradition of consanguinity due to socio-cultural factors. Many Arab countries display some of the highest rates of consanguineous marriages in the world, and first cousin marriages specifically may constitute 25–30% of all marriages. While the frequency of consanguineous marriages in some Arab states (e.g. Bahrain, Jordan, Lebanon, Palestine) is decreasing, in other countries consanguinity rates are increasing in the current generation (e.g. Qatar, the UAE, and Yemen). Research among Arabs and worldwide has indicated that consanguinity could have an effect on some reproductive health parameters such as postnatal mortality and rates of congenital malformations. The main impact of consanguinity, however, is an increase in the rate of homozygotes for autosomal recessive genetic disorders. The Catalogue of Transmission Genetics in Arabs (CTGA) database indicates a relative abundance of recessive disorders (63%) compared to a smaller proportion of dominantly inherited traits (27%). Among 451 genetic disorders reported in the UAE, Bahrain, and Oman, 36.6% document the presence of patients resulting from consanguineous marriages, mostly among first cousins. On the other hand, the study of highly consanguineous populations in the region offers a unique advantage that could lead to the identification and characterisation of many genes responsible for human disease, and provide a new genotype-phenotype map of the human genome. The success of this approach can be seen in the large number of disease genes that have been identified by studying Arab families. Yet, of the 615 recessive diseases that have been reported in Arab families, the responsible loci are not known for 171 of them. Many other recessive diseases, especially those confined to single families, are not even reported.

Sickle Cell Disease (SCD): Genetic variations

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Sickle cell disease is a highly prevalent disease in Oman, with 5.7% of Omani people carrying the gene, and 0.2% of the population affected. Although SCD has been traditionally regarded as a disease of the red blood cells, it is in fact a complex disease which demonstrates a model for red cell interactions with white cells and endothelial cell lining. Recent work from our laboratory on acute chest syndrome, which is one of the major causes of death associated with SCD, and vaso-occlusive crisis (VOC), the most frequent presentation of SCD, has just demonstrated this complex interaction. An alteration in the level of nitric oxide as well as a shift in lymphocytes and monocytes activations plays a role in both conditions. Similarly, the altered red cells (sickled cells) leading to perturbed platelets and haemostatic functions plays an important role in stroke development, added to the hereditary component of thrombophilia in this SCD. These changes are promising an important opening for studies in the various therapeutic interventions that are available for SCD, such as hydroxyurea, and, more recently, low molecular weight heparin, nicosan, and other agents that are undergoing testing. More recently the work on interactions of SCD with other genetic markers has led to studies on its relationships with thalassaemia, particularly alpha thalassaemia and also co-inheritance with hereditary persistence of fetal haemoglobin (HPFH). All of these are definitely contributing to modulation of the disease's behaviour and allowing variations even among siblings within the same family. I am sure that other markers are also playing a role and, in particular, environmental factors need to be explored.

Studying Autosomal Recessive Disorders: Model for genechip technology in the Sultanate of Oman

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The use of genechip technology has revolutionised science advancements, and has directly impacted the medical field. Its application has become an integral part of the biological sciences across the board. In the Sultanate of Oman, this technology was purchased through His Majesty's Trust Fund, which supported a research project tilted "Family Genetic Understanding of Autosomal Recessive Disorders (FamGUARD)". This investigation utilised single nucleotide polymorphism (SNP) chips and was aimed at setting a model of identifying disease loci. Recently, a generous fund from the Omani Research Council (TRC) has been granted to continue the previous work. About 40 families with autosomal recessive disorders have been processed using Affymetrix 10K SNP GeneChip technology. The genotypes were analysed and regions of consecutive homozygous SNP calls were identified. The results showed new loci for some diseases and novel mutations for some known disorders. Population mutations that were previously reported in the literature for other populations were reported for the first time in Oman. The use of microarray technology has assisted greatly in defining regions and excluding others in an efficient way. The model has proved successful. However, the use of this technology does not remove the need for microsatellite utilisation; the methods in fact complement each other.

Pushing the Envelope with Mendelian Genetics

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Everybody was excited at the turn of the 21st century by the belief that Mendelian genetics in the post-human genome era would witness its golden era. However, the focus has now shifted to solving the genetics of common diseases. With few exceptions, the unprecedented investment that was made in the study of genetics of common diseases, mostly through the genome-wide association study (GWAS) approach, failed to deliver medically actionable results such as those routinely seen in Mendelian genetics. This juncture of time is best described as one of reflection upon where to go next with the study of the genetics of common diseases. I will argue in this presentation that there is much to be learned from Mendelian genetics in informing research into common diseases. In the Gulf region, we are in a unique position to take advantage of our population structure in order to make significant contribution to the field of common diseases by utilising Mendelian genetics to its full potential. The presentation will include both the utilisation of Mendelian genetics in common diseases (using such approaches as Mendelian phenocopies and the Carrier Phenome Project) as well as discussing how our unique population structure can inform research into the human genome, again using Mendelian genetics approaches.

Population Genomics of Hearing Loss in Palestine

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Recessively inherited phenotypes are frequent in the Palestinian population as a result of a long historical tradition of marriages within extended families. Traditionally, gene localisation in these families has been achieved with microsatellite linkage mapping. We demonstrate that genome-wide screening with high-density single nucleotide polymorphism (SNP) arrays is an effective method for pinpointing causative genes and novel loci in consanguineous Palestinian families. We generated deafness-associated homozygosity profiles from the SNP data in each family. Sequencing the relevant gene from each peak region identified 12 deleterious alleles, 10 of which were novel. Using advanced targeted DNA capture and massively parallel sequencing technologies in conjunction with homozygosity mapping, we identified five genomic regions likely to harbour novel genes for human hearing loss on chromosomes 1p13.3 (DFNB82), 9p23-p21.2/p13.3-q21.13 (DFNB83), 14q23.1-q31.1, and 17p12-q11.2 (DFNB85). Next generation sequencing of the captured exons in DFNB82 revealed a chr1:109,440,214 C>T resulting in a R128X mutation in the G protein stimulator regulator (GPSM2) protein. Functional biology is underway to reveal GPSM2's role in hearing loss. We just constructed a custom 1.6 MB design of complimentary ribonucleic acid (cRNA) oligonucleotides containing 250 genes, responsible for both human and mouse deafness. We prepared paired-end libraries, followed by cluster amplification on v4 Illumina flow cells with our bar-coded multiplexed samples. A 2x72bp paired end recipe was used, resulting in a median base coverage of 572x and, overall, 94.7% of our targeted bases were covered by more than 10 reads, which was our cut-off for variant detection. We generated SNP and indel calls for our samples and filtered the variants against those of dbSNP131 and the 1000 Genomes Project to identify private and rare variants. Novel mutations were identified. Discovery of additional deafness genes and mutations will allow for early clinical diagnosis, enabling prediction of phenotypes and enhanced rehabilitation. Characterisation of the proteins encoded by these genes will enable a comprehensive understanding of the biological mechanisms involved in the pathophysiology of hearing loss.

In Vitro Fertilisation/Pre-implantation Genetic Diagnosis in the Gulf Region

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In high-prevalence consanguineous societies, there is a need for well-established prenatal diagnostic services. These include preconception genetic screening, pre-implantation genetic diagnosis (PGD), and prenatal genetic and genomic testing. These tests may have implications related to the choice of a spouse, having children whether by spontaneous or assisted conception, and the continuity of a pregnancy depending on the cultural and religious values of the society. The advancement in technology, specifically assisted reproductive technology and PGD, will prove to be essential in couples with a known history of genetic diseases, especially if the termination of pregnancy is not an option. With PGD, disease-free embryos can be identified and transferred into the uterus reducing the risk of transmitting inherited disorders. Unfortunately, the availability of these services is limited in developing countries. The limitations may be due to a shortage of resources or training, or limited availability of experts in this field. Additionally, health care systems may not rank these services as a priority even though they can prove to be cost effective in term of health care resources in the long run.

Cultural Backgrounds and Legislations on Pre-Implantation Diagnosis (PGD) in Europe

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Although pre-implantation genetic diagnosis (PGD) is regularly practised in most European countries, this technique and its application are still debated, and national legislations differ significantly. In medicine and clinical genetics, PGD is considered a form of prenatal diagnosis, however, as PGD involves the manipulation and discarding of embryos, it raises a variety of legal and ethical issues connected

to the legal status of embryos and on the possible misuses of this technique for eugenic purposes. The ethical and legal aspects of PGD have been approached differently in different European countries due to cultural, religious, legal, and political factors. Although the restrictions applied to PGD vary significantly from country to country, in general national legislations prohibit PGD for non-medical purposes, in particular as far as sex selection is concerned. Of course, differing legislations affect access to treatment, forcing people residing in countries where this technique is not allowed to engage in "cross-border reproductive care". European institutions have expressed views on this issue, but in general the European Union has not yet adopted a clear, unified opinion on the practice of PGD. The situation is made even more difficult by the fact that PGD is still a very recent technique, whose areas of application and efficacy are constantly expanding, but also creating ambiguities in the use of this technology. This will certainly lead to further debates as far as regulation of these new developments is concerned. The European Society for Human Reproduction and Embryology (ESHRE) PGD Consortium was set up in 1997 aiming to: survey the availability of PGD; collect data on the accuracy, reliability, and effectiveness of PGD; initiate follow-up studies; produce guidelines and recommended PGD protocols; formulate a consensus on the use of PGD, and to educate in the science of genetics and reproduction. Since 1999, the consortium has published 10 data collections, analysing data related to 21,743 cycles. According to the consortium's data, between 1999 and 2008, about 5,135 babies were born worldwide following pre-implantation genetic diagnosis and screening (PGD/PGS) with no reports of increased fetal abnormalities. However, possible long-term consequences on the fetus are still unknown and will require further monitoring and follow-up studies.

Gene Database Banking in a Developing Country: Social, Cultural, Legal and Ethical Issues Related to Gene Databases in Oman

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The main objectives of this study were to investigate Omani public awareness of ethical, cultural, religious and legal aspects of gene studies (with consideration to regional variation) and to assess the public acceptance of initiating gene banking in Oman. The study will also help address society's concerns, thus building trust and cooperation with the people in carrying out meaningful work in the genomic sciences. The results will contribute to the country's policy-making in establishing gene databases for future research in the various genetic disorders in the country and the region. The study was undertaken through questions (on a self-designed Arabic questionnaire) chosen to explore the basic knowledge of the studied population sample in the field of genetics and the gene database. It was composed of a 5-point rating scale with close-and open-ended questions to give the sample the opportunity to report their own views on the subject. For illiterate subjects, structured interviews were conducted. A total of 1,644 (96.8%) questionnaires were successfully answered. The key findings showed that only 17% of those polled knew of or had heard about gene banking. In general, there was a statistically significant difference at a 99% confidence level in the level of education and regional variation in regard to the acceptance of gene banking, participation in research, and the requirement of protective laws and regulations framework. Further, public opinion on gene banking acceptance and participation in genetic research achieved good scores of 87% and 67% respectively in both those who were aware and non-aware. After explanation, 92% indicated that Islam encourages evolution and scientific research but that genomic sciences should adhere to ethical standards (80%). Organisations that supported the project included the World Health Organization (WHO) and the Committee on Scientific and Technological Cooperation (COMSTECH). The WHO office in Oman coordinated the study while the Omani Ministry of Health acted as the directorate of research and studies. Dr.Muna Al-Sadoon, Department of Child Health, Sultan Qaboos University, was the co-principal investigator.

Archeology and Structure of Ancient Omani Society: Prehistoric peopling of Arabia

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Recent investigations in southern Arabian prehistory have yielded a number of startling discoveries which have significantly augmented our understanding of modern human emergence and the peopling of Arabia. New findings in palaeolithic archaeology, palaeoenvironmental studies, and mitochondrial deoxyribonucleic acid (mtDNA) phylogenetic history indicate that the Arabian Peninsula was home to some of the first modern humans on earth, with the population expanding from Africa between 130,000 and 100,000 years ago. At that time, the Arabian Peninsula enjoyed much greater annual precipitation, providing ample grasslands for grazing animals and plentiful sources of freshwater across the landscape. Although a subsequent climatic downturn between 75,000 and 60,000 years ago may have culled many of these early populations in Arabia, traces of very ancient mtDNA lineages bearing haplogroup N1 and N2 were identified earlier this year among living peoples spread throughout the peninsula. Scholars now regard Arabia as the "staging post" for the rapid modern human colonisation of the earth that began some 50,000 years ago. Little is known of the period between 50,000 and 10,000 years ago; the previously widespread occupation of Arabia appears to have contracted into discrete environmental refugia in response to growing aridity, and early people's fate in this area is not yet known. The modern peopling of the peninsula only began some 10,000 years ago. Until recently, it was thought that these first immigrants were cattle pastoralists expanding southward from the Levant. New discoveries in Dhofar, however, have revealed a phase of late palaeolithic occupation reaching as far back as 13,000 years ago, complementing mtDNA studies of hapologroups R0a and R2 that also reveal deeply rooted populations in southern Arabia. The origins of these lineages remain a mystery.

Neural Tube Defects (Spina Bifida) in Prehistoric Fish-Eaters from the Necropolis of Rh5 (Qurum, Muscat Sultanate of Oman, 3.700-3.400 B.C.): A case of consanguinity in an isolated population.

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The extremely high frequency of neural tube defects (spina bifida) observed in the population of Ras al-Hamra 5 (RH5) seems to indicate that consanguinity rates were elevated in the past. This population of fish-eaters has been dated back to 3700–3400 BC. In the sample comprised of 79 individuals, the frequency of those affected by neural tube defects regarding all 5 sacral vertebrae is approximately 50% (48.1) but it increases to 65.4% when taking into account only the 26 individuals who died before reaching adulthood (with estimated ages at death below 20). When considering neural tube defects involving at least 3 of the 5 sacral vertebrae, these frequencies increase significantly, reaching 65.3% and 90.5%, respectively. The average age at death for the individuals with such defects was 25 years of age while it is 32 years in those not affected. Even though nutritional factors cannot be excluded, the most plausible cause remains that of consanguinity, a hypothesis that seems to be further supported by high frequencies in other morphological skeletal markers. Dental morphology seems, moreover, to indicate a great distance between this population and the other, both coeval and more recent, populations of the Arabian Peninsula and, more in general, of the Middle East. This distance, currently being confirmed through a DNA study, would support the hypothesis that the RH5 population was isolated from the surrounding populations. This would help explain the presence of these high consanguinity rates.

Consanguinity Link in Autism Research in Oman and GCC Countries

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Autistic spectrum disorder (ASD) is considered one of today's most urgent public health challenges. Based on World Health Organization estimates, ASDis a larger burden to society than type 1 diabetes, childhood leukemia, and cystic fibrosis. Since the 1970s, there has been a dramatic rise in the number of reports documenting increasing rates of ASD cases, especially in Western countries; however, there has not been a similar increase in research on autism or other child psychiatry topics in the Middle East. In fact, published research in child psychiatry is scarce in our region and ASD is not a frequent subject of research. The presentation will provide an overview of the current status of ASD-related research in Oman and other GCC countries. The strategic direction of research and services needed for autistic children will be highlighted. As consanguinity is the theme of the conference, results of preliminary observations and findings will be presented which might be useful in guiding towards developing more cost-effective strategies in the search for genetic markers. The presentation will also call for systematic, multi-disciplinary, and integrative research activities in the region.

Genetics of Autism

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The presentation will provide an overview over the latest findings on the genetics of autism. Autism is a complex neurodevelopmental disorder that interferes with the normal course of social, communicative, and cognitive development. Autism is considered the most strongly genetically influenced of all multifactorial child psychiatric disorders. Several genome-wide association and linkage studies have been completed. The evidence that common alleles affect the risk for autism is limited; however, researchers have identified multiple rare mutations and it is now assumed that a substantial proportion of genetic risk for autism resides in rare variants. Recent twin and sib studies also suggest that the heritability of autism may have been overestimated.

Management of Autism

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Autistic spectrum disorders (ASDs) are lifelong, developmental neurobiological disabilities which usually present in children before the age of three years. ASDs are characterised by impairments in both social and communication skills, in addition to the presence of stereotyped/repetitive behaviors and interests. ASDs consist of five disorders, but the clinical distinctions among them are not reliable even in the most experienced centres where standardised instruments are used. ASDs affect boys 3 to 4 times more than girls; however, when girls are affected they suffer from more cognitive impairments. The aetiology of ASDs is not yet known exactly, but it is attributed to the interaction between genetic factors in susceptible individuals and environmental factors. Comorbidity is high in ASDs, including mainly mental retardation, attention deficit hyperactivity disorder, epilepsy, and emotional disorders. As there are no biological markers for ASDs, detection is made by trained clinicians who evaluate the children's developmental progress to identify the presence of developmental disorders, and although symptoms appear early in life, the diagnosis is often delayed until after the age of 6 years. The prevalence of ASD increased dramatically during the last few years, to approach 1% in the USA. In Oman, a study showed that the prevalence of ASDs is 1.4 per 10,000, which is much less than the prevalence in other countries. Until now there has been no specific treatment for autism; however, early diagnosis and intervention will considerably improve the outcome of children with ASDs. Medical treatment is required in some cases of ASD, which can improve associated disorders (e.g. sleep problems, violent and self-

injurious behaviour, hyperactivity), or reduce the severity of the autistic behaviour (e.g. repetitive and stereotypical movements), thus improving the health and the quality of life of the patients and their families. The presentation will discuss the management of ASDs.

Cancer Genetics: The mean side

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The aetiology of cancer is multi-factorial, with genetic, environmental, medical, and lifestyle factors interacting to produce a known cancer. With the advent of molecular biology, our knowledge of cancer genetics is rapidly evolving and improving understanding, helping to identify at-risk individuals and families; furthering the ability to characterise various malignancies and evolution to molecular classification of cancers; establishing treatment tailored to the molecular blueprint of the disease, leading to the development of new therapeutic modalities, and studying and overcoming drug resistance in cancer therapy. This expanding knowledge base has consequent implications for all aspects of cancer management, including prevention, screening, and treatment. Cancer genetics is providing a platform for customised, individualised management of cancer patients; the theory of 'one size fits all' is no longer applicable to many cancers. The presentation will cover the application of genetics in the management of some common cancers seen in oncology clinics.

Functional Genomics of Breast Cancer

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The majority of common human diseases represent the culmination of lifelong interactions between the genome and the environment. Predicting the contribution of genes to complex disorders is a challenge, and determining the interactions between genes and the environment during any disease process is a daunting task. Identification of disease-associated genes requires functional studies to validate their biological relevance. Many human genetics diseases, including cancer, are caused by interactions of different genes, and between genes and the environment. Our work has long been focused on the identification of these genes, their interactions into signalling pathways, and the validation of their functional relevance in cancer. Specifically, we have been investigating the function, the downstream transcriptional gene targets, and interactions of two cell adhesion receptors, CD44 and CD146, in breast cancer. We have developed a novel validated enhanced green fluorescent protein gfp—an inducible system to study the function and understand the molecular mechanisms of the action of CD44 and CD146 using a microarray gene expression analysis as well as in vitro and in vivo experimental models. The results as well as future plans will be discussed during the presentation.

Breast Cancer in Oman

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Breast cancer represents the most common cancer in terms of incidence in females in Oman. Females with breast cancer in Oman tend to be younger than their Western counterparts and the majority of patients present with the disease already in advanced stages. Their tumours generally display aggressive features. The presentation will include a description of the clinico-pathological features of the disease in Oman, with analysis of prognostic factors and survival. A small proportion of patients have breast conserving surgery, and a relatively small number of patients received preoperative chemotherapy despite the advanced nature of the disease. The survival and disease-free survival rates as compared to other Asian and Arab countries are quite low. The presentation will explain in part the inferior survival figures as compared to Caucasian American and European females. The following are strongly recommended to improve morbidity and mortality: 1) increase breast cancer awareness; 2) introduce breast screening programs; 3) establish a multi-disciplinary approach to breast cancer management, and 4) support molecular biology and genetic research to further explore breast cancer in Oman.

Genetic Heterogeneity in Ovarian Cancer

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Epithelial ovarian cancer (EOC) is the second most frequently diagnosed cancer of the female genital tract, yet remains the leading cause of mortality amongst gynecological cancers. A vast majority of cases are diagnosed at a late stage, and despite the current standard-of-care, debulking surgery, and combination chemotherapy, only 10–15% patients have long-term, disease-free survival. Although the first line chemotherapy yields response rates approach 80%, the majority of patients relapse within 2 years, and the median survival of patients diagnosed at stages III and IV is 36 and 24 months, respectively. Unlike many other cancers where targeted therapies have offered new and realistic hope, there have been no significant breakthroughs in the management of EOC. Lots of questions remain unanswered or are only beginning to be answered. Is it possible to classify EOC into molecular sub-types, some of which may be candidates for targeted therapy? Is it possible to identify aggressive tumors from those of low malignant potential, and hence tailor the treatment, so as to include intra-peritoneal chemotherapy, and the use of anti-angiogenic compounds, which are known to enhance the response rates, but are also known to be fairly toxic, and hence not used in routine practice? Is it possible to identify patients who are

likely to develop EOC, and hence could be candidates for screening and early detection programs? Is it possible to identify prognostic groups? And finally, but most importantly, are there predictors of response to treatment, especially, when the disease relapses after first line paclitaxel-carboplatin combination chemotherapy? Genome-wide expression profiling has begun to provide data, which enhances our understanding of the genes which influence the development of EOC, histological sub-types, prognostic factors and response and prediction to chemotherapy. These data will be presented.

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