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**Genomics into Healthcare: the 5th Pan Arab Human Genetics Conference and
2013 Golden Helix Symposium**

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Abstract

The joint 5th Pan Arab Human Genetics conference and 2013 Golden Helix Symposium, “*Genomics into Healthcare*” was co-organized by the Center for Arab Genomic Studies (CAGS - <http://www.cags.org.ae>) in collaboration with the Golden Helix Foundation (<http://www.goldenhelix.org>) in Dubai, United Arab Emirates from 17-19 November, 2013. The meeting was attended by over 900 participants, doctors and biomedical students from over 50 countries and was organized into a series of nine themed sessions that covered cancer genomics and epigenetics, genomic and epigenetic studies, genomics of blood and metabolic disorders, cytogenetic diagnosis and molecular profiling, next generation sequencing, consanguinity and hereditary diseases, clinical genomics, clinical applications of pharmacogenomics and genomics in public health.

Key Words: meeting report, genomics, cancer, epigenetics, NGS, diagnostics

Introduction

The joint 5th Pan Arab Human Genetics conference and 2013 Golden Helix Symposium, “*Genomics into Healthcare*”, hosted by Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences and organized by the Center for Arab Genomic Studies (CAGS - <http://www.cags.org.ae>) in collaboration with the Golden Helix Foundation (<http://www.goldenhelix.org>) was held from 17-19 November, 2013 in Dubai, UAE. The 3-day conference was opened by His Excellency Prof. Najib Al Khaja, Secretary General of Sheikh Hamdan Bin-Rashid Al Maktoum Award for Medical Sciences (<http://www.hmaward.org.ae>) and President of CAGS.

The meeting was attended by over 900 participants, doctors and biomedical students from over 50 countries and featured 50 lectures and over 100 poster presentations. Sponsored by the Gulf Scientific Corporation, the meeting was organized into a series of nine themed sessions that covered: 1) cancer genomics and epigenetics; 2) genomic and epigenetic studies; 3) genomics of blood and metabolic disorders; 4) cytogenetic diagnosis and molecular profiling; 5) next generation sequencing; 6) consanguinity and hereditary diseases; 7) clinical genomics; 8) clinical applications of pharmacogenomics; and, 9) genomics in public health.

Opening Keynote

The opening Keynote lecture was given by Prof. David N. Cooper (Cardiff, UK) on the molecular basis of reduced (or incomplete) penetrance in inherited human disease. He discussed how reduced penetrance can be a function of factors such as specific mutation(s), allele dosage, differential allelic expression, copy number variation and the influence of additional genetic variants (in *cis* or in *trans*).

Studies of Arab populations

The Arab world comprises 22 countries and extends from Mauritania in the west to Oman in the east (Figure 1). Across this vast region also known as MENA (Middle-East and North Africa), genetic disorders are relatively common and account for a substantial proportion of physical and mental handicaps. Large family size, older parental age, high consanguinity rate (40-68%), first cousin marriages and the considerable presence of tribal groups contribute to the burden of genetic diseases in these societies. However, despite experiencing numerous cultural, legal and religious challenges, several Arab countries have active prevention programs for some common genetic disorders including hemoglobinopathies and Down syndrome.

Towards the goal of collecting omics data, several large-scale genetics initiatives relating to the Arab world were featured at the meeting. Dr. Abdul Rezzak Hamzeh (UAE) described the work of CAGS. Founded in 2003, it hosts the “Catalogue for Transmission Genetics in Arabs” (CTGA), an open-access database (http://cags.org.ae/ctga_search.html) that contains over 1,600 disease and gene records and is the major global resource for genetic information in Arabs. Other initiatives include the Genome Arabia Project that plans to sequence up to 500 individuals from seven countries in the region including Qatar, Bahrain, Kuwait, United Arab Emirates, Tunisia, Lebanon and Saudi Arabia using next-generation sequencing (NGS) technologies in order to identify disease-causing mutations (<http://www.bbc.co.uk/news/health-25216135>).

The Weill-Cornell Medical College in Qatar has conducted a number of next-generation medical genomics projects, including family and cohort studies of diabetes, obesity, inherited neuropathies and cancer. The data generated has been deposited in the Qatar Genome Browser (QGB), a web-based data portal, which provides an

interface to the public for study focused on NGS-omics data. QGB is the first of its kind in the MENA region.

Dr. Arif Anwar from Sengenics (Malaysia; <http://www.sengenics.com>), the first Asia-based genomics research and molecular diagnostics company, presented a novel pipeline for identification of clinically significant mutations using array-comparative genomic hybridization (a-CGH) combined with whole exome sequencing (WES). This large-scale study of pediatric disorders in the Arab population screened approximately 1,000 samples for variants in 20,000 genes. Identification of clinically significant mutations using combined aCGH/WES resulted in a significant increase in diagnostic yield.

Dr. Ilham Ratbi gave an outline of the Moroccan National/Ethnic Mutation Database (NEMDB; <http://www.sante.gov.ma/departements/inh/mohumuda/>) was initiated in 2007. It aims to provide researchers and clinicians with up-to-date information about genetic variants in various genes known to cause genetic disorders that have been detected in Moroccan patients. To date, the database contains 425 mutations and 208 polymorphisms found in 301 genes and 259 diseases. Autosomal recessive mode of inheritance accounts for 74.17% of the genetic disease burden in the Moroccan population. This database has recently been migrated to the new ETHNOS platform and upgraded with new data and novel data querying and visualization tools (Papadopoulos et al., 2014). The migration of the Moroccan NEMDB to the new ETHNOS platform is part of a broader project involving development of new and migration of existing NEMDBs to the upgraded ETHNOS platform that is encouraged by the Genome Informatics Working Group of the Genomic Medicine Alliance (www.genomicmedicinealliance.org).

Dr. Mohammed Naveed presented the results of his study in identifying the genetic modifiers of a rare and severe limb deformity in a large Emirati family. Dr. Erol Baysal from the Dubai Health Authority shed light on the use of chorionic villus sampling and the latest in DNA-based diagnostics and how the accurate detection and counseling of at-risk couples is helping to reduce the mortality and morbidity from beta-thalassemia.

Prof. Aida Al Aqeel explored the challenges as well as the progress and recent advances in the implementation of personalized transitional genomics in the clinical setting. She stressed that in Saudi Arabia, pre-implantation genetic diagnosis and neonatal screening for genetic metabolic disorders are, at present, the most important preventive programmes, and that the country is considering new therapeutic strategies, such as personalized therapeutic strategies at the genomics level.

Additional omics-based initiatives were presented during the conference including the European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (ECARUCA; www.ecaruca.net), which collects and provides cytogenetic and clinical information on rare chromosomal disorders, including microdeletions and microduplications. ECARUCA is a multi-lingual database that contains over 2,500 types of aberrations. In the same vein, the conference included a workshop about Rd-CONNECT (<http://rd-connect.eu>), which is a unique global infrastructure project that links up databases, registries, biobanks and clinical bioinformatics data used in research on rare diseases to act as a central resource for researchers worldwide. Together with other two multicenter projects, namely Neuromics (www.rd-neuromics.eu) and EURenOmics (www.rd-eurenomics.eu) coordinated by Prof. Olaf Riess and Franz Schaefer, respectively, RD-CONNECT allows scientists to share data from their genomics research projects leading to faster diagnosis, better treatments and quality of life improvement for patients with rare diseases.

Special medical issues in the Arab world

The conference highlighted some of the special medical issues in the Arab world such as increased homozygosity due to consanguinity, which is linked to a high overall risk of cancer. Dr. Lotfi Chouchane (Qatar) reported that breast cancer is the most common malignant disease in women from Arab populations comprising up to 42% of all tumors, and presenting 10 years earlier than in women from Western Europe (Chouchane et al, 2013). It was also shown that triple negative breast cancer (*i.e.*, any breast cancer that does not express the genes for estrogen receptor, progesterone receptor and *Her2/neu*) is more common in this part of the world. This data contrasts with the incidence of breast cancer in Europe and the USA, where the incidence has fallen in recent years.

Recessive disorders are highly prevalent in the UAE due to high rates of consanguinity among many of its subpopulations. However, the molecular causes underlying many of the rare recessive disorders are still unknown. Advances in NGS and bioinformatics have significantly expedited the discovery of the defective genes and mutations of many genetic conditions. Dr. Nadia Akawi (UAE) presented the UAE experience on the usage of WES for the identification of genes and mutations of several rare recessive disorders including those causing intellectual disability, macrocephaly, multiple dysplasia and distinctive facial appearance. Diagnoses were also obtained in heterogeneous cases of congenital muscular dystrophy with brain and eye anomalies, for camptodactyly-arthropathy-coxa vara-pericarditis syndrome (Akawi et al, 2012).

A poster by Amal Al hashem and colleagues presented a study of 19,165 births in a Saudi population that showed that consanguinity is an independent risk factor for the high rate of birth defects in a population with a high rate of consanguineous marriages (Saadallah and Rashed, 2007). Consanguinity has a statistically significant contribution

in cases of genetic syndromes, and isolated renal defect. However, consanguinity has no statistically significant contribution in cases of chromosomal aberrations, isolated congenital heart disease and multiple malformations.

The role of inbreeding and the risk of developing type 2 diabetes (T2D) was presented through a poster by Dr. Ibrahim Gosadi (Saudi Arabia) suggesting that consanguinity might increase risk of T2D by earlier development of the disease, and by strengthening possible genetic effects on fasting blood glucose.

A poster by Dr. Tim Yu and colleagues showed the contribution of consanguinity in autism spectrum disorders (ASDs) in a study of over 200 families. Multiple approaches, including linkage analysis, homozygosity mapping and WES, show that consanguineous families with autistic children have a significantly different genetic architecture than non-consanguineous families, with fewer *de novo* events and an enrichment of recessive point mutations and deletions. Recessive cases also demonstrate that ASD can be an unexpected manifestation of partial loss-of-function mutations in genes with more classical syndromic associations, and illustrate how further study of consanguineous ASD families will be important in dissecting this complex and heterogeneous disorder.

Prof. Hanan Hamamy provided a highly instructive talk on the feasibility of applying new technologies to help consanguineous couples at risk of having affected children. These techniques could help in the detection of shared known autosomal recessive pathogenic variants giving the opportunity for these couples to decide on their reproductive options.

Furthermore, a significant number of the presentations and posters addressed specific problems in Arab countries including: birth defects and genetic conditions in Oman (Prof. Anna Rajab); breast cancer and hearing loss in Palestine (Dr. Moien Nihad

Kanaan); pharmacogenetics of warfarin metabolism, oral-facial-digital type 1 syndrome and geleophysic dysplasia in UAE (Dr. Hayat Aljebeji); intellectual and developmental disabilities in Lebanon (Prof. Andre Megarbane); autosomal recessive disorders, myeloproliferative neoplasms, and copy number variants in Qatar (Dr. Tawfeg Ben-Omran and Dr. Khalid Fakhro); nasopharyngeal carcinoma, psoriasis and breast cancer risk in Tunisians (Dr. Wijden Mahfoudh); mutated ANKRD26 gene and familial thrombocytopenia. in Saudi Arabia (Dr. Walid Dridi); hypertriglyceridemia and risk of coronary artery disease (CAD) in arterial hypertensive Moroccan patients (Dr. Sanaa Ouatou); genetic polymorphisms and cardiovascular risk factors of Alzheimer disease in Algerian population (Dr. Ouldjaoui Ahmed); and novel mutations in the NLRP7 gene in two Egyptian families (Dr. Ebtesam Abdalla).

Pharmacogenomics

Pharmacogenomics holds promise to rationalize drug use by increasing drug efficacy and minimizing drug toxicity. In developing countries, pharmacogenomics can also contribute towards reducing healthcare expenditure at a national level. Prof. George Patrinos (Greece) presented preliminary data indicating that there are significant differences among various European populations regarding pharmacogenomic biomarkers allele frequencies that can be readily applicable to rationalize drug use in these countries (Mette et al., 2012). Also, he presented data from whole genome sequence analysis of 482 unrelated individuals of various ethnic backgrounds to obtain their personalized pharmacogenomic profiles, indicating that a significant number of novel pharmacogenomically relevant variants can be identified using this approach (Mizzi et al, submitted). Also, these findings were replicated in a 7-member family of Greek origin in an effort to explain the variable response rate to acenocoumarol

treatment in two family members. Overall, these data demonstrate that whole genome sequencing is necessary to accurately determine an individual's pharmacogenomics profile.

Additional clinical applications of pharmacogenomics were illustrated by Prof. Ron van Schaik, who described the work at his laboratory. They have offered PGx testing in close collaboration with the hospital pharmacy since 2005 and have tested over 2,000 patients. The fifteen different markers, most commonly ordered involve the *TPMT* and *CYP2D6* genes, including the HLA-A*3101 with a growth rate of 40-50% tests requests per year (Elens et al, 2013). In this context, an important PGx resource is Pharmacogenomics Knowledge Base (PharmGKB, www.pharmgkb.org), a publicly available Internet research tool developed by Stanford University that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations, and genotype-phenotype relationships. PharmGKB collects curates and disseminates knowledge about the impact of human genetic variation on drug responses.

Large-scale sequencing projects

Another theme running through the conference was how to implement large-scale sequencing projects on very large groups. The largest of these initiatives is "The Million Human Genomes Project" launched in November 2011 by Beijing Genomics Institute (BGI; <http://www.genomics.cn>) to decode the genome of over 1 million people. Features of this project, illustrated by Prof. Jun Wang (BGI, Beijing, China), comprise five essential parts: 1) Ancient genomes; 2) Population genomes; 3) Medical genomes; 4) Cell genomes; and, 5) Personal genomes. The aim of this project is to establish a research baseline and reference standard for specific populations, as well as to connect

the phenotypes of diseases and traits with the genetic variations in order to understand the disease mechanism. The integrative genome message and scientific discoveries obtaining from the project will lay the foundation for guiding innovative clinical diagnosis and treatment, and ultimately advancing personalized healthcare and improving human health (http://www.genomics.cn/en/navigation/show_navigation?nid=5658). The technology employed for this endeavor was shown by Dr. Radoje Drmanac, who illustrated the benefit and advantages of nanoarrays for sequencing at several tera-bases per day per instrument (Drmanac et al, 2010).

Genomics into Healthcare

The conference highlighted a number of issues at the interface of genomics and healthcare and the importance of NGS. Prof. Hilger Ropers (Germany) discussed intellectual disability (ID) and presented a novel diagnostic tool that utilizes WES and a proprietary algorithm to detect mutations in most of the presently known ID genes. This work is based on a previously described test for ~600 severe recessive childhood disorders (Bell et al, 2010) and on a comprehensive list of genes implicated in ID. Furthermore, he anticipated that the technology will shed light on the molecular causes of ID and related conditions such as autism, schizophrenia and epilepsy, which are still largely unknown.

Prof. Maurizio Ferrari (Italy) showed his work with 91 patients that resulted in the identification of novel variants which could be critical for improving risk stratification and clinical management of asymptomatic patients with Brugada syndrome. The predisposition for these patients to develop fatal arrhythmias cannot be easily predicted and no anti-arrhythmic drug is effective in preventing these life-threatening arrhythmias.

Prof. Ahmad Al Marzouqi's lecture introduced three new chromatin remodelers that have been identified by his team: Fun30, Irc5 and Irc20. All three complexes share some common features, including the presence of a distinct ATPase domain.

How the transcriptional and epigenetic programs interact on the chromatin encompassing the human alpha globin cluster and its regulatory elements on chromosome 16 was shown by Prof. Douglas Higgs. The interaction was uncovered, using a variety of approaches to show how genes within their natural chromosomal environment are switched on and off during hematopoiesis. These findings add to our general understanding of the relationship between genome structure and function.

The aldehyde dehydrogenase (ALDH) superfamily (19 genes in the human genome) is of increasing interest. Prof. Vasilis Vasilou (USA) presented work on the recent discovery of ALDHs as markers of cancer stem cells and their involvement in cancer cell resistance to chemotherapy and radiotherapy. As a result, it is anticipated that ALDH may be a therapeutic target in cancer in the near future.

Prof. Achilleas Gravanis (Greece) described his work on the neuroprotective actions of microneurotrophins in various animal models of neurodegenerative diseases as well as in fetal and adult neural stem cells. Microneurotrophins may serve as lead molecules to develop neurotrophin-like small molecules that can cross the blood-brain barrier with potential applications in the treatment of neurodegenerative diseases.

Closing Keynote

The meeting closed with a keynote speech by Prof. Angela Brand (The Netherlands) on "*Genomics in Public Health*". She stressed the need to change our perspective from diseases to diseasomes, risk factor to risk pattern, clinical utility to

personal utility, and from complex disorders to multiple rare diseases (Brand, 2012). This is in line with P4 Medicine (predictive, personalized, preemptive and participatory) and the anticipated era of precision medicine (Hood and Flores, 2012). Dr. Brand described public health genomics (PHG), the area of public health ensuring that scientific advances in genomics are effectively and responsibly translated into health policies and practices for the benefit of population health, and the connected activities needed for its implementation (Brand, 2012). Her Institute aims to fulfill this task for European Member States via the European Centre for Public Health Genomics (ECPHG).

Conclusions

The joint 5th Pan Arab Human Genetics conference and 2013 Golden Helix Symposium offered a highly valuable opportunity for Arab scientists to join forces with international geneticists in order to accelerate the advancement of human genetics worldwide. The importance of this event stemmed from bringing together multidisciplinary expertise with the goal of improving medical care. In fact the worldwide divide between “blue sky” research and clinical practice is a huge barrier to applying recent advances in genomics into the practice of medicine. This divide was directly targeted by this conference, which met its objectives of attracting top-level research and making scientists and medical professionals think of their work in a new way so as to serve the ultimate goal: a healthier society through cutting-edge scientific discoveries.

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Figure Legends

Figure 1.

Map of the Arab World (Algeria, Bahrain, Comoros, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, Yemen (Western Sahara is a disputed territory). Comoros is not shown)

http://en.wikipedia.org/wiki/File:Arab_World_Green.png#filelinks

