Translating genes into health

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A major challenge for genomics is to provide clinical benefits to the genetically diverse human population. Genome science has achieved a catalog of mutations and informative SNPs. Next-generation sequencing is rapidly delivering thousands of complete human genomes, but understanding and applying genomic knowledge remains a daunting undertaking. These challenges and opportunities for genomic medicine were central themes of the Golden Helix Symposium held in Turin, Italy, 18–21 April 2012.

Genomics has become a mainstay of biomedical research, and it offers opportunities for understanding the genetic and epigenetic contributors to disease and elucidating the cellular pathways and biological processes involved in disease. However, according to Najib Al-Khaja (Centre for Arab Genomic Studies), there are still several barriers to overcome, and improvements in the effectiveness of health care cannot realistically be expected in the coming decade. Larger and more numerous clinical studies will be required to translate genomic discoveries into diagnostic or therapeutic tools and to demonstrate their efficacy in medical practice.

Genetic diversity across the entire human genome must also be considered in identifying the specific genetic factors that may be associated with disparate disease risk, incidence and severity, both within and between populations. As John Burn (Newcastle University) explained, there are new opportunities to address these issues and grounds for optimism about the potential contributions of genomics to improving the diagnosis, treatment and prevention of human disease. Some such advances have already changed medical practice, and a future direction is to introduce clinical care that is based on genomic information. A theme that pervaded the meeting was the idea that understanding the full significance of genome variation in disease will certainly be made easier by collaboration and data sharing via readily accessible databases (see URLs).

Innovation in nucleic acid technology has progressed at a rapid pace and has had a crucial role in the remarkable achievements of increased throughput and reduced cost for DNA sequencing. We have very quickly moved into the era of next-generation sequencing. Micro- and nanoarrays on silicon substrates underlie many next-generation sequencing technologies. For example, Radoje Drmanac (Complete Genomics) presented an innovative whole-genome sequencing technology based on a grid pattern of 'sticky spots' on a silicon chip to which DNA nanoballs of 200 nm in diameter adhere. The generation of more sequencing data also requires innovation in analysis. Elliott Margulies (Illumina) described a new data analysis system with four bioinformatic variant calling filters to improve the reliability and accuracy of variant identification (with a call rate of 99.9%) and condense data from four genomes into just 16 Gb.

Over the past decade, the specific genes involved in ~3,000 monogenic diseases have been identified, and, for some diseases, this knowledge has led to the development of practical treatments. For example, cystic fibrosis is linked to sequence variations in the *CFTR* gene, and more than 1,900 mutations of this gene have been identified. So far, using new technologies, it has been possible to improve genetic testing for cystic fibrosis so that it is useful both for the diagnosis of borderline clinical cases and for newborn screening and prenatal testing. Garry Cutting (Johns Hopkins University) described ongoing efforts to incentivize the collection of all these genetic results into a database that is accessible to both clinicians and patients. However, only some of the variants associated with cystic fibrosis have been characterized from a functional point of view with a clear genotype-phenotype correlation.

Another major genomic challenge relates to diseases with a more complex mode of inheritance. Hilger Ropers (Max Planck Institute) emphasized that the genome-wide association study (GWAS) does not live up to his expectations of a strategy for the discovery of disease-related genes because, in his opinion, it is mostly wrong to assume that common genetic risk factors underlie all common disorders. Many complex disorders are not multifactorial but instead are genetically heterogeneous. Genome research is rediscovering the systematic elucidation of monogenic disorders, which is informative in terms of identifying the function of human genes and of the genome as a whole. This genetic architecture applies to severe intellectual disability, an almost purely genetic, early-onset condition that is largely caused by defects in individual genes (the number of genes associated with intellectual disability runs into the thousands). Similarly, there are also strong monogenic components in epilepsy, autism and schizophrenia, and such components are probably also involved in many other complex disorders.

GWAS approaches have led to important discoveries of new biological pathways involved in the etiology of cancer, as Ian Tomlinson (University of Oxford) showed for the bone morphogenetic protein (BMP) pathway in colorectal carcinoma predisposition. Inherited BMP variation can modulate cancer risk, and the recent discoveries of seven SNPs that influence the BMP pathway and associate with colorectal carcinoma (CRC) risk were

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highlighted. The identification of these disease-associated SNPs may be useful in evaluating CRC predisposition in asymptomatic patients at an earlier age, and it should lead to new diagnostic and therapeutic strategies.

Another important application of next-generation sequencing technologies presented at the meeting is in diagnostics for the detection of free DNA in plasma. Allen Chang (Chinese University of Hong Kong) described a recent study of aneuploidy detection during pregnancy based on a highly accurate analysis of fetal DNA in maternal plasma (with 98.6% sensitivity and a false positive rate of 0.2%). Even if the main limitation of the method is the relatively high cost, it does provide a new highly accurate approach that is potentially applicable for noninvasive prenatal diagnosis of fetal chromosomal aneuploidies.

Yet another major challenge of the genomics era is the development of improved therapeutic approaches that have genotype-specific effects. The development of new pharmaceuticals using genomic knowledge of specific targets and their roles in disease has already been markedly successful and is becoming increasingly widespread. Depending on the drug and disease, genetics is estimated to account for 20–95% of the variability in therapeutic response and toxicity. Federico Innocenti (University of North Carolina) and Chung-Fang Xu (GlaxoSmithKline) showed the fundamental role of pharmacogenomics and the importance of GWAS in cancer drug discovery and in the identification of SNP associations with the toxicity phenotype. Correlation of genomic signatures with therapeutic response will enable the treatment of appropriate patients at appropriate stages of illness in clinical trials, resulting in more effective drugs, as well as better dosing and monitoring. Chung-Fang Xu also presented another example of a direct clinical application of genetic medicine: the successful use of human leukocyte antigen (HLA) testing to reduce the risk of a serious hypersensitivity reaction to abacavir, which is used to treat AIDS. Pharmacogenomics can improve dosing precision and outcomes for all drugs for which metabolism is affected by genetic variation. Ron van Schaik (Erasmus University) provided an example in patients with *CYP2D6*-related intermediate metabolizer status (predicted from the genotype at *CYP2D6*). Doubling the dose of tamoxifen (from 20 to 40 mg per day) in this phenotype group increases the concentration of the active metabolite endoxifen to levels comparable with those seen in extensive metabolizers with two wild-type *CYP2D6* alleles. Thus, adjusting drug dosage on the basis of genotype overcomes the decreased enzyme activity caused by inactive alleles of *CYP2D6*.

Genomic research can have a fundamental role in the understanding of population differences in disease prevalence, treatment response and the influence of gene-environment interactions and epigenomics on disease. It is important to identify the specific genetic factors that may be associated with disparate disease risk in different population groups. For example, a few genetic variants can be correlated with population-specific differences associated with increased risk for several diseases, and one example was provided by Eileen Hoal (StelIenbosch Universtiy). The degree of susceptibility and the progression of some infectious diseases (for example, tuberculosis, malaria and AIDS) are influenced by the host genetic component. Thus, finding susceptibility genes and identifying new pathways involved in pathogenesis should aid in combating these pathogens and in developing appropriate therapies while improving the efficacy of existing therapies. Linkage studies and GWAS have produced a large number of candidate gene loci for tuberculosis, but their relevance in African populations is unclear because the SNP chips used were designed for use in European populations with greater linkage disequilibrium. Tools specific for African populations (which are characterized by the greatest human genetic variation) must be developed to take into account the lower degree of linkage disequilibrium and the possibility that African risk-associated alleles may be different from those identified in populations outside of Africa. Approaches based on next-generation sequencing are currently being explored with the hope of extending the benefits of human genome projects to the people of Africa.

The symposium concluded with an expert panel (Larry Kricka, John Burn, Paolo Vineis (Imperial College London), Ron van Schaik, Najib Al-Khaja) that considered various facets of the shift in genomics from discovery to precision medicine. On one hand, there was optimism for rapid testing and confidence in the development of suitable technology, whereas, on the other hand, there was concern over ensuring and maintaining the quality of clinical diagnosis and healthcare delivery. Ensuring quality was an issue that resonated with several of the panel members and with symposium delegates. Nucleic acid testing is one of the most complex types of testing undertaken in the clinical laboratory, and there clearly requires adequate controls and an error-free test and testing device. The notion of undertaking preemptive universal sequencing so that a patient's sequence would be directly available to a clinician in the Cloud did not gain much traction. Investment in integrated bioinformatics and medical informatics to catch them up with sequencing technology seems an important priority.

URLs. Golden Helix Symposia, http://www.goldenhelixsymposia.org/thesymposia/upcomingsymposia/2012_golden_helix_symposium_april_1821_2012.html; EpiPGX, http://www.epipgx.eu/; Epi4K, http://www.epgp.org/epi4k; Human Variome Project, http://www.humanvariomeproject.org/; Clinical and Functional Translation of CFTR, http://www.cftr2.org/; Leiden Open Variation Database (LOVD), http://www.lovd.nl/; International SAE Consortium, http://www.saeconsortium.org/; database of Genotypes and Phenotypes (dbGAP), http://www.ncbi.nlm.nih.gov/gap/.

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COMPETING FINANCIAL INTERESTS

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