The 2008 ASHG meeting, which took place from November 11 to 15, brought almost 6,500 attendees to Philadelphia to learn about the latest advances in human genetics and genomics research. This conference is considered the world’s largest gathering of human genetics researchers, academicians, clinicians, genetic counselors, and nurses. This article reviews the 1,000 Genomes Project, Gaucher’s disease, warfarin dosing, and Huntington’s disease.

The 1,000 Genomes Project: Clinical Applications

- Francis Collins, MD, PhD, Former Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, Md.
- David Altshuler, MD, PhD, Associate Professor of Genetics and Medicine, and Director, Program in Medical and Population Genetics, Harvard Medical School, Cambridge, Mass.
- David Valle, MD, Henry J. Knott Professor, and Director, Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Md.

Originally announced in January 2008, the 1,000 Genomes Project is a collaboration between genomics institutes in England, China, and the U.S. The goal of this project is to sequence the genomes of more than 1,000 people, thereby creating the most comprehensive and detailed documentation of genetic variations in humans. From this research, it is expected that investigators will be able to create a catalogue of human polymorphisms that are present at a 1% or greater frequency in each of the sample populations.

The information garnered from this project “will increase the sensitivity of disease discovery efforts across the genome five-fold,” said Dr. Collins. He explained that a better understanding of human genetic variations will enlighten the medical community about possible mechanisms of disease and will point us toward possible new therapies, because many of these genetic variants “could very well be good drug targets.” It is hoped that the research will provide ways to predict future risks of illness in currently healthy people.

Previous large-scale genetic research relied on single-nucleotide polymorphism (SNP) chips to provide information about genetic variations among patients. The 1,000 Genomes Project should provide further insight into SNP variations and the larger differences in genome structure, called structural variants. These differences may play an important role in a person’s susceptibility to certain diseases.

Dr. Altshuler suggested that after the sequencing of genes in more than 1,000 individuals is completed, new data will be able to be projected into hundreds of thousands of previously collected SNP chip samples, thereby empowering researchers to learn about less common variants. This process of projecting new genetic data into previously gathered genetic information is referred to as imputation.

Since January 2008, three pilot studies, generating roughly 10% of the data for the project, have been completed. A large amount of data has been accrued, and 95% of the data is usable and of high quality for detecting unknown genetic variants. In light of these successes, the initial sequencing of nearly 1,200 unique individuals is expected to be completed by the end of 2009.

Although the raw data are available as they are collected, processing data for a project of this magnitude takes a considerable amount of time. Thus, the release of processed data is scheduled to begin in 2009 and to continue into 2010, with information on progress to be published quarterly. Although the 1,000 Genomes Project should expand our knowledge of the genetic basis of disease, Dr. Altshuler cautioned that “nobody expects that we will explain 100% of the heritable basis of disease, nor will there be drugs in the clinic based on the 1,000 Genomes Project.”

Dr. Valle indicated that clinicians are practicing “average medicine.” For example, after confirming the diagnosis of a patient’s illness, a practitioner uses a treatment plan based upon the average presentation of that disease. The 1,000 Genomes Project, as well as other genome-wide association studies (GWAS), may provide a better sense of how to characterize patients at the first clinical presentation to allow for a more predictive form of medicine more closely tailored to specific individuals.

Dr. Valle outlined what researchers will need to do in order to realize the long-term, patient-centered goals of GWAS: (1) develop new sequencing techniques to improve the efficiency of sequencing the genome, (2) conduct biological research to determine the consequences of the genetic variants identified by these studies, and (3) undertake clinical...
investigations to identify the impact of multiple genetic variants and environmental factors on disease risk. Methods of communicating this information to both patients and practitioners will need to improve as information is generated.

The 1,000 Genomes Project represents an exciting opportunity, but it does have limitations. The most important disadvantage may be that its anonymous nature prevents the ability to make specific associations between phenotype and genotype. Dr. Collins emphasized that the project is not meant to draw these conclusions; instead, he said:

[It] is a discovery project to basically build the catalogue of human genetic variation into a much more comprehensive view, reaching down into those variations that occur in the range of 1% to 5%, or even a little less. Then it will be the engine of many follow-on studies that will use that catalogue specifically to try and make connections of particular variants with particular phenotypes of their interest.

Alglucerase (Ceredase) and Imiglucerase (Cerezyme) in Gaucher’s Disease

• Hans Andersson, MD, Karen Gore Professor of Human Genetics, and Director, Hayward Genetics Center, Tulane University Medical School, New Orleans, La.

In children with type 1 Gaucher’s disease, continuous enzyme replacement therapy with Genzyme’s alglucerase (Ceredase) or imiglucerase (Cerezyme) can help normalize most clinical parameters, according to Dr. Andersson. His eight-year longitudinal study1 “is the first of its kind to document the long-term effectiveness of enzyme replacement therapy in children with type 1 Gaucher disease,” he commented.

This autosomal recessive lysosomal storage disease results from a deficiency of the lysosomal enzyme glucocerebrosidase. Patients lacking this enzyme accumulate glucocerebroside, a sugar–lipid complex, in the macrophages of the reticuloendothelial system. Characteristically, patients have signs of anemia, thrombocytopenia, organomegaly, bone disease, and delayed growth. Although three major forms of Gaucher’s disease have been identified, type 1 is recognized as the most common.

Analyzing the records of 884 children sampled from the International Collaborative Gaucher Group Gaucher Registry, a voluntary observational database of patients with Gaucher’s disease, the study authors targeted the therapeutic response of seven variables—Z score for height, normalized hemoglobin level, platelet count, liver volume, spleen volume, Z score for lumbar spine bone mineral density (BMD), and bone crises—to enzymatic replacement with alglucerase, imiglucerase, or both, over eight years.

A baseline assessment of the sample indicated a median height Z score of –1.4, a median normalized hemoglobin level of –0.3 g/dL, a median platelet count below 100,000/mcL, significantly enlarged liver and spleen volumes, a median BMD Z score of –0.35, and a history of bone crises in 17% of the sample population.

After eight years of continuous therapy, median height and BMD approximated the median values for the normal population, anemia resolved in all patients, platelet counts improved to levels above 100,000/mcL in 95% of patients, liver and spleen volumes decreased, and episodes of bone crises were reduced.

Because most type 1 Gaucher’s disease cases occur during childhood and adolescence, Dr. Andersson believes that the study should prove useful for pediatricians in tracking the progress of patients over many years of treatment.

REFERENCE


Genetic Determinants of Warfarin (Coumadin) Dosage

• Ralph E. McGinnis, PhD, Wellcome Trust Sanger Institute, Cambridge, U.K.

A number of researchers are using genome-wide association scans (GWAS) to screen for the presence of single nucleotide polymorphisms (SNPs) that can cause differences in phenotypes. Dr. McGinnis presented results from his recently completed study that used GWAS to investigate the pharmacogenetics of warfarin (Coumadin, Bristol-Myers Squibb) dosing.

Warfarin is the most widely prescribed therapy for reducing thromboembolic events. The dose needed to achieve a therapeutic International Normalized Ratio (INR) can vary from 10-fold to 20-fold among individuals, depending on various genetic and nongenetic factors. As a result, without predictive information for initial warfarin dosing, patients could have a subtherapeutic or supratherapeutic INR, putting them at a higher risk for complications, such as clotting and bleeding.

SNPs associated with warfarin dosing can be used to derive more accurate estimates of patients’ responses to this agent. In earlier studies, variants in the gene encoding for vitamin K epoxide reductase complex 1 (VKORC1), the warfarin drug target, accounted for 29% of the variance in required dose. Dr. McGinnis and his team, having recently evaluated 1,523 Swedish patients from the Warfarin Genetics (WARG) cohort, concluded that significant patient benefits resulted from predicting the required dose of warfarin.

The investigators noted that polymorphisms in VKORC1 were the strongest predictor of the required dose, followed by polymorphisms in the gene encoding for cytochrome P450 2C9, a warfarin-metabolizing enzyme. Combined, these two SNPs account for approximately 40% of variation in the required dose, whereas nongenetic factors (age, sex) account for approximately 15%.

Dr. McGinnis and his group then searched for additional genetic predictors of the required warfarin dose. After controlling for the influence of VKORC1 and CYP 2C9, the team performed additional analyses using a GWAS to test the effect of 370,000 SNPs genotyped in more than 1,000 patients from the Warfarin Genetics cohort who were receiving warfarin. Initial results identified CYP 4F2 as one additional genetic predictor of the required dose. Although the exact mechanism by which CYP 4F2 influences warfarin dosing is unknown, polymorphisms in this SNP account for 1.5% of variations in required dosing. This finding has been replicated in a study of 588 patients (combined P value, < 0.001).

In conclusion, the ability to predict warfarin dosages is
becoming a more realistic possibility, given that more than a 50% variation can be accounted for by demographics and SNPs in genes encoding VKORC1, CYP 2C9, and CYP 4F2.

**Inducing PGC-1α Expression in Huntington’s Disease May Slow Neuronal Dysfunction and Neurodegeneration**

- Albert R. La Spada, MD, PhD, Director, Center for Neurogenetics and Neurotherapeutics, and Associate Professor of Laboratory Medicine, Medical Genetics, Pathology, and Neurology, University of Washington, Seattle, Wash.

Huntington’s disease is an autosomal dominant neurological disorder, characterized by uncoordinated movements and cognitive decline that affect almost 40,000 individuals in the U.S. The pathogenesis of this disease results from the expansion of a CAG (glutamine) sequence in the huntingtin (htt) gene; the mutation produces a polyglutamine protein (polyQ) that misfolds and is not susceptible to degradation by proteasomes. There is no cure for HD, although some recent studies have highlighted the importance of mitochondrial function in maintaining neuronal function.

In their earlier work, Dr. La Spada and his associates had found that polyQ-expanded htt was localized to the nucleus and disrupted the transcription necessary for mitochondrial biogenesis and oxidative phosphorylation. The transcription co-activator PGC-1α, a key regulator of mitochondrial biogenesis, seems to be the main target for transcription interference.

More recently, Dr. La Spada’s team sought to determine whether inducing PGC-1α could improve neurodegeneration in Huntington’s disease in a mouse model. Based on motor tests, preliminary results indicated that restoring PGC-1α does ameliorate HD progression. In addition, the overexpression of PGC-1α led to a reduced buildup of misfolded htt proteins in the brains of transgenic mice. These findings indicate that htt protein indirectly interferes with PPAR-γ, a peroxisome proliferator-activator receptor that is positively modulated by PGC-1α.

Dr. La Spada said the results imply that potential new therapies are already available and are currently being used in humans. PPAR-γ is, in fact, a possible therapeutic target. Currently, PPAR-γ agonists are being developed and studied in human clinical trials. In addition, all-trans-retinoic acid, a systemic antineoplastic and topical dermatological agent, induces PPAR-γ to mediate pro-survival signaling. The researchers were excited about the results of their study, because “the findings could ultimately lead to the first potential treatment for this currently fatal disease.”