

David Altshuler, MD, PhD, MGH continued the July tutorial series with a discussion of Genomics and the Human Genome Project. Genomics involves the study of biology on a global scale, with all genes considered simultaneously. Currently 90% of the human genome has been disclosed by the public sequencing consortium and over 70 % of that published sequence is complete in the sense that it has been verified a number of times. The genome has also been mapped and described by a group at the private company, Celera. The function of about 3% of human genes, or about 1000 out of the 30,000-50,000 human genes, is well known and extensively studied. Some key challenges for genomics were enunciated:

- Understanding all human genes and how they interact
- Reclassifying diseases based on the underlying molecular signatures
- Finding genetic variations underlying inherited diseases.

New functions for genes are being discovered. For example, in the nemotode there are short sequences that do not encode proteins but rather attach to the end of other genes and turn them off. The Rosetta stone of biology (for understanding the functions of genes), is likely to be in the comparative study of genome sequences across species. The goal of genome studies is finding all functional parts of the genome. This will involve assigning function to all uncharacterized genes, correlation studies linking disease with genes and studies of the expression and sequences of genes or proteins. Such studies of gene function will involve experimentation on a large scale and include examination of the effect of mutations and of exogenously-induced changes. Correlation studies of gene expression will use microarrays based on a variety of technologies. Such studies have already been applied to the study of cancer. For example, different types of leukemias can be distinguished and the survival of patients with heterogeneous tumors, such as medulloblastomas can be predicted. These large-scale studies should lead to a new taxonomy of human disease based on underlying patterns of genetic variation.

Genetics was defined as the inherited contribution to phenotype variation. Type 2 diabetes was cited as an example of a disease that has a strong inherited component. While a few diseases such as Huntington's are due primarily to a mutation of a single gene, most diseases appear to be caused by multiple genes as well as by the environment. Association studies have the greatest power for finding genetic variants with a modest impact on disease, but careful study design is needed to avoid obtaining deceptive P-values.

Lewis B. Holmes, MD, MGH spoke on "Genetic Testing". Clinicians use genetic testing for both routine genetic screening and for testing related to signs and symptoms of a specific disease. Genetic screening is applied to newborns using tandem mass spec for some 29 diseases including cystic fibrosis. Pregnant women in ethnic groups known to have a high incidence of specific diseases, such as Tay-Sachs, sickle cell and cystic fibrosis, are screened for being carriers of those recessive diseases. Disease-related screening includes routine testing offered pregnant women 35 or older. This includes not

only the well-known procedure of amniocentesis, but also the use of specialized ultrasound to determine nuchal translucency of the back of the neck of the fetus. The types of genetic tests used involve: chromosome analysis, Fluorescence In-Situ Hybridization (FISH), mutational analysis for single-gene abnormalities and gene linkage studies. Numerous focused studies for specific problems are now available.

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