Highlights of This Issue

Recurrence Risk in Bardet-Biedl Syndrome

Bardet Biedl syndrome (BBS) is a highly pleiotropic, multiple anomaly syndrome which shows considerable locus heterogeneity. Mutations have been identified in at least 14 genes that lead to BBS and such heterogeneity complicates the estimation of recurrence risk in families. In a study in this month's issue, Sapp et al., (page 623) derive locus-specific recurrence risk estimates in BBS. The authors analyzed 187 probands with BBS and assayed the relative proportion of families with mutations in each of 10 loci, estimating the locus specific carrier rates using Hardy-Weinberg principles and an incidence estimate of 1/100,000 for the general phenotype. The locus specific carrier frequencies ranged over an order of magnitude from 1/250 to 1/22,000 and recurrence risks also ranged widely from 1 in 1,500 to 1 in 13,000. Such locus specific recurrence risk calculations will be increasingly important as genetic heterogeneity is increasingly the rule. Ultimately however, robust whole genome analysis may allow us to dispense with recurrence risk estimations and directly determine carrier status for families with a wide variety of disorders.

Genomics and the Electronic Medical Record

A facile and rich electronic medical record (EMR) is critical if we are ever to deal with the sheer magnitude of information that will confront us as genomic analysis becomes more common place in medicine.

In a report this month by Dumitrescu et al., (page 648) the Vanderbilt DNA databank (BioVue) was queried to determine whether administratively assigned race/ethnicity contained in the EMR could be used as a proxy for genetic ancestry. BioVue contains over 80,000 DNA samples linked to EMRs. In this work, 360 SNPs were genotyped in almost 2,000 BioVue samples and self-reported, as well as assigned, ethnicity/ancestry were compared with the results of genetic analysis. The investigators found high correlation between the genomically defined race/ethnicity and self-reported, as well as observer-reported, ethnicity. This study illustrates how a well constructed biorepository can be tied to medical records and queried in a productive manner. In a commentary in this month's journal related to this same topic, Ellen Wright Clayton et al., (page 616) explore a number of the challenges that will confront us as we obtain and store large amounts of information in the EMR including ethical, legal, social and policy issues.

News Briefs

Highlights of the *AJHG*
A Novel Gene Therapy Strategy

In spite of many setbacks the dream of gene therapy remains an active area of investigation. Towards that end a recent report in the *AJHG* by Hartmann et al. describe a strategy in which aberrant but potentially corrective splicing in a Fanconi anemia gene is encouraged in cell culture. Individuals with mutations involving the canonical splice donor GT dinucleotide in *FANCD2* appear to have milder than usual clinical manifestations. In this report, the authors demonstrate that low efficiency mRNA processing occurs at the mutant TT dinucleotide and that minute levels of normal posttranslationally processed FANCD2 protein could be identified in patient fibroblasts; perhaps at least partially explaining their milder clinical presentation. The investigators were able to "encourage" use of the alternative splicing by introduction of lentiviral vectors which express TT-adapted U1 snRNAs in primary Fanconi anemia C (FANCC) patient fibroblasts. They demonstrated correction of the DNA damage-induced G2 cell cycle arrest in these cells. Although such a strategy would obviously only be amenable to mutations which affect splicing, it could offer advantages, especially when (due, for example to size constraints) the native gene cannot simply be "replaced".

Identification of a major Kabuki actor

Kabuki syndrome has long defied efforts to identify the causative gene or genes underlying this distinctive developmental syndrome. Now, a group from the University of Washington in Seattle (Ng et al *Nat Genetic* 2010;42:790) has applied whole exome sequencing to pinpoint one gene that underlies Kabuki syndrome. This effort was especially challenging since Kabuki syndrome is genetically heterogeneous, a fact that presented difficulties for the researchers during their investigations. Initially, the investigators completely sequenced the exomes of 10 unrelated individuals thought to have Kabuki syndrome by clinical criteria. They found exome variants which were shared among 3 genes in 9 of the patients, 6 genes in at least 8 of the patients and 16 shared genetic lesions in 7 of the exomes. They then ranked the phenotypes of the patients according to how they classically they "fit" with the Kabuki phenotype. The combined analysis suggested a gene, *MLL2* as the culprit. The researchers then went on to Sanger sequencing in 43 additional Kabuki syndrome cases; in 26 of the 43 cases *MLL2* deleterious variants were found. This work will immediately benefit diagnostic efforts in patients thought to have Kabuki syndrome although it is clear that additional genes are out there, which when mutated, result in this disorder. Finally, this work highlights the importance of collaboration between those that sequence and the clinicians who assess phenotypes. As we proceed in this new era of next generation genomics, clinicians and laboratory scientists will need to work ever more closely.