This Month in *The Journal*

Kathryn D. Bungartz[1] and Robin E. Williamson[2]

C2ORF71 Mutations and Retinits Pigmentosa

Nishimura et al., page 686; Collin et al., page 783
Although the number of genes in which retinitis pigmentosa (RP)-causing mutations have been identified is growing, the etiology of a large proportion of cases remains unknown. Homozygosity mapping can be a useful tool in identifying loci for autosomal-recessive diseases in consanguineous families and isolated populations. In this issue, Nishimura and colleagues and Collin and colleagues use homozygosity mapping to search for the genes disrupted in their RP families. The region identified is quite large, so Nishimura et al. narrow the list of candidate genes by comparing gene expression in wild-type mice to that of mice lacking photoreceptors. The idea is that genes that are specifically expressed in the photoreceptors are more likely to be critical in the development of the retina; therefore, disruption of such genes might cause RP. This approach allows both groups to focus on and then identify mutations in *C2ORF71* that segregate with RP in their families. The Nishimura team then goes on to characterize the gene product of *C2ORF71* in cellular assays, in localization studies, and through analysis of a zebrafish model.

16p13.11 Deletions in Epilepsy Syndromes

Heinzen et al., page 707
Copy-number variants (CNVs), caused by genomic rearrangements, have recently been associated with a myriad of common disorders. Among these are several neurological conditions, including schizophrenia, mental retardation, and idiopathic generalized epilepsy. Interestingly, several CNV risk loci are shared among these conditions, pointing to a common origin. Despite these associations, there is a general lack of understanding concerning how CNVs actually lead to most associated disorders. In this issue, Heinzen and colleagues investigate the propensity of CNVs in a spectrum of epilepsy disorders. Because CNVs on 15q13.3, 15q11.2, and 16p13.11 have previously been associated with idiopathic generalized epilepsy, these authors evaluate the same risk loci in a cohort of nearly 4000 patients with diverse types of epilepsy. Although CNVs in neither of the 15q regions are found to play a significant role in epilepsy cases other than idiopathic generalized epilepsy, a significant number of cases are found to carry deletions greater than 100 kb at 16p13.11. Additionally, deletions greater than 2 Mb are found at this same locus in some epilepsy patients, whereas no such deletions are detected in controls. Functional analyses indicate that haploinsufficiency may play a role in the pathogenesis of these CNVs.

Genetics of ER Stress Response

Dombroski et al., page 719
The endoplasmic reticulum (ER) is a site of protein and lipid processing in cells. When cell conditions are not ideal, ER functions can be affected and unfolded proteins can accumulate and aggregate in the ER. This altered state, termed ER stress, is harmful and has been implicated in human disease. Cells work to reverse the negative effects through the unfolded protein response (UPR). The UPR involves inhibition of general protein synthesis, degrading of misfolded proteins, and increased ER capabilities. If the pathways initiated via the UPR are not effective in reducing the ER stress, cells will undergo apoptosis. In this issue, Dombroski and colleagues perform expression analyses to identify which genes are activated after pharmacological induction of ER stress and to see how much individual variation is present in expression levels. The authors then examine these genes in twin pairs to establish which elements of the UPR are most likely to be under genetic control. It is hoped that a comprehensive analysis of UPR genes not only will further elucidate the cellular response to ER stress but will also contribute to understanding the pathways that are dysfunctional in certain diseases.

Causal Variants in GWAS

Wang et al., page 730
Unlike the traditionally held hypothesis that a marker significantly associated with a disease either is causal itself or is in high linkage disequilibrium (LD) with a causal marker, it is possible that a common disease-associated SNP does not proxy for a single causal variant but in fact tags several rare causal alleles. If multiple variants that contribute to disease risk each happen to arise on the same haplotype background containing a common SNP, then the common SNP will appear to be significantly associated with the disease. The situation can be even more complicated, because some of the rare variants may be in

[1]Science Editor, *AJHG*; [2]Deputy Editor, *AJHG*
DOI 10.1016/j.ajhg.2010.04.009.

LD with the "risk" allele of a common SNP whereas other rare causal alleles are on the same haplotype as the "protective" common-SNP allele. Here, Wang and colleagues examine this situation further to see how the phenomenon can affect the results of association studies. The authors demonstrate that the presence of multiple rare causal variants can produce underestimates of effect size and also lead to lower measures of heritability. Importantly, they also examine how current fine-mapping procedures are ill-equipped to identify multiple rare variants and propose that careful selection of cases for resequencing will be crucial for effective identification of these causal alleles. Ideal cases for this procedure are those who contain long-range haplotypes at the associated locus. These haplotoypes are likely to be enriched with newly acquired rare alleles, and sequencing of such individuals will hopefully improve the chance that the rare causal alleles will be identified in fine-mapping efforts.

Chromosomal Array: An Economical First-Tier Test

Miller et al., page 749; Regier et al., page 765

Array-based methods designed to detect the presence of unbalanced copy-number changes within a genome are becoming more routine in the clinical setting. These molecular-genetics techniques, commonly referred to as array genomic hybridization (AGH) or chromosomal microarray (CMA), are commonly used to identify chromosomal changes in patients with intellectual disability (ID). AGH/CMA is much more sensitive than traditional G-banded karyotyping; detecting chromosomal imbalances around 100 times smaller than those identified by standard karyotyping. However, to date, there is relatively little that has been published concerning the efficiency or the cost-effectiveness of such methods. In this issue, two groups tackle these separate questions individually. Reiger and colleagues conduct an in-depth analysis of the economics of AGH. These authors compare simulations of two scenarios of treatment for patients suspected of having a trisomy; in each scenario, either AGH is used as a first-tier test or karyotyping is the front-line method. Realistic follow-up procedures are calculated into each scenario. Although AGH costs more than traditional cytogenetic methods, these authors conclude that in the case of ID detection, AGH is cost effective. In a related, but distinct, study, the International Standard Cytogenomic Array (ISCA) Consortium, reported here by Miller and colleagues, analyze published studies and compare the efficacy of CMA and G-banded karyotyping. They recommend that CMA be used as a first-tier approach in cases of ID, autism spectrum disorders, and multiple congenital anomalies. Recommendations are also made regarding the use of karyotyping. Together, these two studies highlight the utility and cost of AGH/CMA and provide suggestions regarding the implementation of such methods.