This Month in *The Journal*

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

Gene Ontology Analysis of Bipolar Disorder

Holmans et al., page 13

As the first wave of association studies has come through and the size of these association studies has grown, it has become clear that searching for single common SNPs that are associated with complex disease is going to identify only a small proportion of disease-causing genetic effects. Many researchers have suggested that a variety of rare variants in certain genes will be found to be responsible for increased disease susceptibility. In addition, it has been proposed that a number of alleles within genes in the same biological pathway or group will contribute collectively to disease risk. The effects of these individual variants may be difficult to observe by standard single-SNP association approaches because their independent effect sizes can be too small to register as significant signals. To overcome this hurdle, methods have been developed to combine biological or functional relationships between genes with association data. Holmans et al. present their method, ALIGATOR (Association List Go AnnoTatOR), which allows them to search through a list of SNPs that reach a threshold of significance in a genome-wide association study and assess whether or not a gene-ontology category of genes is overrepresented within that list. The authors first apply their method to Crohn disease data to demonstrate that they are able to identify the pathways that are known to be affected in the inflammatory bowel disease. They then follow this up with an analysis of data from a bipolar disorder (BD) study and implicate gene groups that are proposed to be altered in BD.

Mutations in *HGF* Cause DFNB39

Schultz et al., page 24

Hearing loss can present in combination with other features in a syndromic form, or it may present in isolation in a nonsyndromic form. Hundreds of loci have been mapped for nonsyndromic hearing loss, but the genes mutated in many of them have yet to be identified. One type of recessive nonsyndromic deafness, DFNB39, was previously linked to a large region on the q-arm of chromosome 7 in a consanguineous Pakistani family. Now, Schultz and colleagues report their identification of an additional 40 families, from India and Pakistan, in which deafness seems to map to the same locus. Refinement of the region allows the authors to focus on 13 candidate genes, and each gene is sequenced in the deaf patients of the families. Although no coding mutations in any of the candidates are identified, three mutations that are predicted to affect the regulation of *HGF* are found; the hearing loss in each of the 41 families segregates with the homozygous state of one of the mutations. Additional evidence for the role of *HGF* mutations in DFNB39 is provided via two different mouse models. The authors first show that mice conditionally deficient for *Hgf* in the inner ear present with significant hearing loss across all frequencies tested. Pathological examination of the cochlea in these mice reveals alteration of many inner ear structures. In addition, mice that overexpress *Hgf* are also deaf, and degeneration of their outer hair cells is evident.

Evolution of Human β-Adrenoreceptors

Cagliani et al., page 63

Adrenergic receptors interact with several different catecholamine ligands, including adrelane and noradrenaline. These G protein-coupled receptors have seven-transmembrane domains that transmit signals outside a cell to pathways inside a cell, mediating cellular responses. Adrenergic receptors come in two known varieties, α (ADRA) and β (ADRB). Some ligands, such as epinephrine, can utilize either receptor type, and the response to binding typically activates the fight-or-flight, sympathetic, response. Other ligands are specific to either ADRA or ADRB and elicit more specific responses. Humans possess three ADRB genes, *ADRB1*, *ADRB2*, and *ADRB3*, that again have specialized functions. ADRBs are thought to play a role in obesity, asthma, and cardiovascular disorders, as indicated by the fact that variants in these genes have been associated with disease. In addition, they are the targets of several pharmacological agents. Here, Cagliani and colleagues examine the evolutionary history of the three ADRB genes. Analysis of genomic DNA from different human populations and chimpanzee reveals that the three genes have diverse evolutionary histories. *ARDB1* is found to be undergoing neutral evolution, *ARDB2* is likely under balancing selection, and *ARDB3* is found to undergo a selective sweep specifically in African populations. Their data indicate the Trp64 variant of *ADRB3* is the likely target of the selective sweep and support the "thrifty gene" hypothesis; variants responsible for increased incidence of obesity were once positively selected.

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FTO Defect Causes Malformative Syndrome

Boissel et al., page 105
Single-nucleotide polymorphisms (SNPs) in and around the fat-mass and obesity-associated gene, *FTO*, have been associated with higher body-mass index and obesity risk in Europeans. Although this finding has potential in identifying pathways influencing type 2 diabetes and other metabolic disorders, there is little known about how these *FTO* variants mediate this risk. Some clues can be learned from *Fto* knockout mice, which present with growth retardation and reduced adipose tissue. The phenotype of these mice suggests that inactivation of *FTO* may be protective against obesity and possibly type 2 diabetes. However, inactivation of this gene in mice has other less desirable consequences, including frequent postnatal death. Here, Biossel and colleagues study a family presenting with symptoms similar to those of the *Fto* knockout mice. By using linkage analysis, the authors identify a common haplotype on 16q12 encompassing 28 genes. Sequence analysis is subsequently used to identify a causative homozygous mutation in an evolutionarily conserved region of *FTO*. Not only do these findings associate mutations in *FTO* with a previously unidentified malformative syndrome, but they shed further light on the potential role of FTO in normal development.

Gene Conversion between Sex Chromosomes

Rosser et al., page 129
Genetic exchange between the X and Y chromosomes has important implications in sex-chromosome evolution. Gene conversion between the pseudoautosomal regions of X and Y is well recognized, but recombination outside of these areas has not been observed. To search for evidence of exchange at additional loci, Rosser et al. look for sequence switching at a translocation hotspot. This hotspot, HSA, lies upstream of *PRKX* on the X chromosome and upstream of *PRKY* on the Y chromosome. Translocations between these two genes are well studied and are known to be involved in translocations resulting from nonallelic homologous recombination. Because such translocations are considered recombination intermediates, resolution of the translocations might result in heritable sequence exchange at the site. To investigate, the authors study segments of sex-specific sequence within the HSA in a group of Y chromosomes from a diverse panel of males. They identify samples in which X chromosome segments are found among the Y chromosome segments. In the reverse analysis, the authors also identify X chromosome samples that contain Y chromosome HSA sequence. This evidence, coupled with additional data from great apes, supports the authors' conclusion that heritable genetic exchange occurs between the sex chromosomes outside of the pseudoautosomal regions.