This Month in *The Journal*

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LOXHD1 and Deafness

Grillet et al., page 328

Nonsyndromic sensorineural hearing loss (NSHL) is a common form of deafness. It is typically caused by impaired sensory hair cell function within the cochlea, the hearing organ of the ear. Although aging is thought to be responsible for a progressive form of hearing loss, other forms have underlying genetic causes, as is the case for autosomal-recessive NSHL (ARNSHL). Numerous genetic loci have been linked to ARNSHL and are referred to as DFNB1 through DFNB76. Though mutations in numerous genes have been associated with the DFNB loci, only three genes have previously been associated with the progressive form of ARNSHL; all of which encode proteins that localize to the cochlear hair cells. Here, Grillet and colleagues use SNP mapping and genetic sequencing to identify a mutation in *Loxhd1* as causative for the ARNSHL observed in a genetically modified mouse line called samba. They find this protein to consist exclusively of PLAT domains and to be expressed in cochlear hair cells. They then take their research into humans and identify a previously uncharacterized ARNSHL locus, DFNB77, mapping to 18q12-q21 and containing *LOXHD1*. The authors further identify mutations in *LOXHD1* as being causative for a DFNB77 family presenting with progressive hearing loss. Together, these results help elucidate a role for PLAT domains and shed insight into progressive ARNSHL.

Cerebral Folate Transport Deficiency

Steinfeld et al., page 354

Folate deficiency affects a variety of cellular functions and can be caused by nutritional inadequacies or by disruption of folate transport and metabolism. Many of the proteins and pathways involved in folate uptake and processing have been well studied, and disruption of these processes has been reported to cause generalized folate deficiency. In contrast, Robert Steinfeld and his colleagues are studying three patients with developmental regression, movement disturbances, epilepsy, and leukodystrophy due to a brain-specific folate deficiency. An analysis of the cerebral spinal fluid in the patients reveals very low folate metabolite concentrations, but normal levels are observed in plasma and erythrocytes. After screening the patients for mutations in the genes involved in folate transport, the authors identify mutations in *FOLR1*, the gene that encodes folate receptor alpha. Functional studies with patient cells demonstrate that the mutations significantly decrease folate binding and that this function can be rescued by the introduction of wild-type *FOLR1*. Importantly, each of the patients is treated with folinic acid therapy and shows significant clinical improvements.

Generalized Disequilibrium Test

Chen et al., page 364

As the wealth of genotype information collected from disease data sets has grown, there is an ongoing need for methods that will allow efficient and proper analysis of these data. In the world of association analysis, studies are usually designed to use either population-based data, in which affected cases are compared to unaffected controls, or family-based data, in which between-family and within-family differences are exploited for the identification of genetic associations. Well-established advantages of family-based designs are that they allow for the use of families that have already been collected for linkage studies and they are also robust to population stratification. Here, Chen and colleagues add to the arsenal of family-based data-analysis tools with the development of their generalized disequilibrium test (GDT). Some highlights of the important capabilities of the GDT are that the method is able to use all of the data from a variety of different relative pairs, it can incorporate covariates, and its calculations are reliable even when handling information from a small number of families of unequal size. In comparisons to five other established methods on data simulating a variety of affectation status and missing data situations, the authors evaluate the power advantages and universality of the GDT. Chen et al. then use the methods to look for variants associated with type 1 diabetes in a large family data set consisting of affected sibling pairs, discordant sibling pairs, other discordant relative pairs, and missing parental data. The GDT efficiently confirms previously reported associations at a greater significance level than the other methods and also identifies potentially interesting sex-related effects.

Allele-Specific Epigenetics of Asthma

Verlaan et al., page 377

Allelic expression refers to the potential of a variation on one allele to alter the expression of one or more genes on

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that same allele. This allelic variation of *cis*-regulation can be due to X chromosome inactivation, imprinting, or polymorphism. Recent studies have associated allelic variation with common disease phenotypes, including asthma. Asthma is a chronic condition in which the airways of the lungs, or bronchi, become inflamed and cause constriction. Though there are environmental factors that may trigger an asthma attack, there is also a genetic component to this disease. In this issue, Verlaan and colleagues analyze the 17q12-q21 locus to uncover mechanisms of transcriptional control of asthma-related genes, because SNPs within this locus have been associated with risk for asthma, type 1 diabetes, primary biliary cirrhosis, and Crohn disease. Individual differences in allelic expression make up one reason that associated alterations in genes may affect a certain disease phenotype in one person but not in another. This group identifies a haplotype exerting allelic expression of at least three asthma-related genes. Additional functional studies show that *cis*-regulation of chromatin organization and binding properties of CTCF, a DNA insulator protein, are associated with this haplotype. They further associate SNPs within this *cis*-regulatory haplotype with risk of asthma in three independent cohorts. Together, these data provide insight into the mechanism of transcriptional control of genes likely to be involved in asthma and several autoimmune disorders.

Positive Modifier of Spinal Muscular Atrophy

Prior et al., page 408

The two *SMN* genes on 5q13 have an interesting collaborative relationship that can affect whether or not a person develops spinal muscular atrophy (SMA). The two genes, *SMN1* and *SMN2*, are almost completely identical, except that *SMN2* contains a variant that affects splicing and leads to high levels of transcript that lacks exon 7 and to corresponding low levels of full-length message. Because of this, when a mutation affects *SMN1*, *SMN2* is, in general, unable to compensate for the loss of *SMN1*, and SMA is the result. There have been, though, recent findings that have demonstrated that patients who have a higher copy number of *SMN2* have a less-severe disease and, in some cases, are completely unaffected. This is presumably due to the additive effect of having several *SMN2* copies producing low levels of functional full-length transcript. Here, Prior and colleagues describe three SMA patients who have a shared genotype-phenotype relationship, which adds a bit of complexity to the story. Each of the cases has a milder form of SMA than expected by their *SMN2* copy number. Sequence analysis of *SMN2* in these patients identifies a single base pair change that is shown to alter splicing and increase the inclusion of exon 7. This finding underscores the importance of understanding the effects of each variant in these genes and highlights the possible benefits to be achieved by increasing full-length *SMN2* expression in SMA patients.