This Month in the *Journal*

Robin E. Williamson[1]

PDE8B as a TSH and Thyroid Modulator

Arnaud-Lopez et al., 1270
The thyroid's regulation of metabolic pathways is maintained by the interaction of several factors that control the release of thyroxine (T4) and triiodothyroxine (T3). One of these factors, thyroid-stimulating hormone (TSH), is involved in activating the release of T4 and T3, and TSH levels are often measured as a means of monitoring thyroid function. Arnaud-Lopez et al. use individuals from a large data set from Sardinia to perform a genome-wide association study looking for genetic variants that affect TSH levels and thyroid function. Their strongest signals are from markers in *PDE8B*, which encodes a cAMP-specific phosphodiesterase that is highly expressed in the thyroid, and the authors predict that *PDE8B* may control TSH levels through modulation of cAMP levels in the thyroid. The significantly associated variants are in strong LD with each other, and their association is replicated in several independent datasets. Fine-mapping analysis suggests that the functional variant(s) responsible for the association signal resides within or around intron 1.

Detection and Imputation of Deletions

Franke et al., 1316
A variety of methods have been developed to detect copy-number variations (CNVs) in the genome, but resolution issues can limit the findings. With the increasing cost-effectiveness of SNP genotyping technology and the wealth of SNP data already generated from a large number of data sets, efficient ways of identifying CNVs from SNP data would be beneficial. Established methods require that a sequence of SNPs be affected by the CNV or that related samples be used. Here, Franke et al. describe their method, TriTyper, which is capable of using SNP data from unrelated individuals to detect deletions that encompass only one SNP. The method works by identifying SNPs that have an "extra" allele, which can be a third nucleotide or a deletion. By first using raw data to denote those SNPs with three alleles, the authors then determine that the majority of triallelic variants can be imputed from genotype calls of other SNPs in the region. The next step is to determine whether the triallelic data can be effectively used in association studies. Franke et al. use simulations to demonstrate the power of TriTyper, and a reanalysis of celiac disease genotype data further supports the advantages of the method.

Genetic Architecture of AITD

Vieland et al., 1349
With the identification of an increasing number of genetic variants that contribute a small amount of risk to the development of complex diseases, the idea that the perturbation of multiple interacting pathways is involved in disease etiology has become well accepted. However, being able to map out the relationships between these factors is another thing entirely. Vieland et al. approach this problem by studying a large dataset of families with Autoimmune Thyroid Disease (AITD). Patients with AITD present with high levels of thyroid antibodies (T_{AB}), and T_{AB} levels are often used to predict a person's risk of developing AITD. The authors use their PPL method to model the genetic factors controlling the development of AITD and high levels of T_{AB} and the cause-effect relationship between the two. They identify several regions linked to the different outcomes and find that there are independent risk loci for each. Previous work has indicated that *CTLA4* genotype is a risk factor for AITD, and epistatic analysis reveals that some of the risk loci interact with *CTLA4* variants in an allele-specific manner.

Allelic Expression Differences in MZ Twins

Cheung et al., 1357
Although we are commonly taught that, in general, humans have two alleles of each gene and that each of those alleles contributes equally to the overall expression of that gene, there is accumulating evidence that a large number of genes exhibit differential allelic expression (DAE). The mechanisms controlling allele choice for genes that undergo monoallelic expression as a result of X-inactivation or imprinting have been well studied, but the factors determining the expression ratios in other genes with moderate DAE are only beginning to be examined. Recent work has reported that the choice of which allele is expressed is random and most likely controlled via epigenetic means. Cheung et al. analyze this phenomenon further by assessing DAE in unrelated individuals and in a dataset of monozygotic twins. They report that, in their group of unrelated individuals, more than half of the genes studied showed

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evidence of significant DAE. In an effort to determine whether genetic factors are involved in DAE regulation, the authors then compare allele expression in monozygotic twins. They find that, within the twin pair, the magnitude and direction of the allelic imbalance was correlated at about 30% of the assessed genes. These findings suggest that germline factors contribute to the choice of allele expressed from genes with DAE.

CC2D2A Is Mutated in Meckel Syndrome

Tallila et al., 1361

Meckel syndrome (MKS) is a recessive lethal disorder affecting the kidney, liver, and nervous system. All four of the genes already known to be mutated in MKS are ciliary genes, and the syndrome is part of a large collection of disorders known as ciliopathies. Previous work identified *MKS1* mutations in the majority of Finnish MKS patients, and, here, Tallila et al. study *MKS1*-mutation-negative patients to determine additional genetic factors contributing to the disease. Because of the severity of MKS, linkage methods are difficult to pursue, so the authors take advantage of the homogeneity of the Finnish population and look for regions of homozygosity in ten unrelated MKS fetuses. A gene within one region shared by six patients, *CC2D2A*, is part of the ciliary proteome, and sequencing of this candidate gene reveals a missense mutation that affects splicing and results in a 4 bp deletion. Comparisons of mutant cells with control cells indicate that centriole migration, a process that is necessary for cilia formation, is normal in MKS cells but that cilia structures are absent.