# This Month in the *Journal*

This month in the *Journal,* Robert Hegele (p. 1161) contributes a review on monogenic dyslipidemias. After presenting an overview of lipoprotein metabolism, Dr. Hegele describes known defects in these pathways and the phenotypic outcomes of these defects. These outcomes include disorders that affect the levels of LDL, HDL, triglycerides, and remnant lipoproteins. He also touches on whether common variation in the components of these metabolic pathways will be useful for the determination of cardiovascular risks in the general population.

***Mutations in* FKRP *Cause a Form of CMD,*** *by Brockington et al.* (*p. 1198*)

The congenital muscular dystrophies (CMDs) are a group of autosomal recessive disorders that are characterized by hypotonia, muscle weakness, and dystrophic changes of skeletal muscle. Although genes involved with some types of CMD are known, there are forms of CMD for which no underlying defect has been identified. Individuals with Fukuyama CMD (FCMD) have mutations in the *FCMD* gene, which encodes fukutin, and a secondary reduction in the expression of laminin $\alpha 2$. FCMD is rare outside Japan, but there are other forms of CMD that have secondary laminin $\alpha 2$ deficiencies. This led Brockington et al. to look for *FCMD*-like genes that might be mutated in other forms of CMD. Using the mouse *FCMD* sequence, they found a fukutin-related gene, in mice, and its human ortholog. As with fukutin, human fukutin-related protein (FKRP) contains motifs suggestive of a sugar transferase. Seven families with both a common, severe CMD phenotype and a secondary laminin $\alpha 2$ deficiency were found to have *FKRP* mutations. Muscle from affected individuals shows a severe reduction in $\alpha$-dystroglycan expression. The $\alpha$-dystroglycan that is expressed is of reduced molecular weight, and Brockington et al. believe that this is due to a different pattern of glycosylation in these patients and that this altered processing plays a major role in the pathology of the disorder. Normal expression of other glycosylated proteins in muscle suggests that this disorder does not result from a generalized defect of glycosylated proteins, although as-yet-unidentified alterations of other glycosylated proteins cannot be ruled out as participating in the phenotype.


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***Association-Based Substance-Abuse Genome Scan,*** *by Uhl et al.* (*p. 1290*)

Although drug-abuse vulnerability has a significant genetic component, it has been very difficult to localize genes for complex behavioral disorders. Uhl et al. tackle this problem with a genomewide-association approach. Because the number of markers required for such a study is large, the authors pooled samples and genotyped them in a high-throughput gene-chip assay. By first combining the cases (individuals with a history of drug abuse) and unrelated controls in separate pools, the researchers reduced the labor involved for this study, because they could identify and individually examine only the interesting markers: those that exhibited the largest allele-frequency differences between the original pools of cases and controls. The replication of allele-frequency differences between cases and controls in a second sample of a different race allowed the authors to limit their attention to 42 markers that were reproducibly positive in the two samples. Of these 42 markers, 2 were <0.2 Mb from each other, and one pair corresponded to the same SNP, thus decreasing the likelihood that the associations were spurious. A third pair of markers flanked a strong candidate-gene locus, *BDNF.* This gene encodes brain-derived neurotrophic factor, which influences both the development and survival of certain classes of neurons and the expression of the dopamine $D_3$ receptor. A polymorphism in *BDNF* shows association with drug-abuse vulnerability in this sample.

***Bias in Locus Effect-Size Estimates,*** *by Göring et al.* (*p. 1357*)

Why is it so hard to replicate linkage and association for complex traits, and why do most follow-up studies give lower locus-specific effect-size estimates than are seen in the original studies? Göring et al. demonstrate, through simulation and analytical results, that, if you estimate the size of a locus-specific effect—such as phenotypic variance—at genomewide LOD-score peaks, the result will tend to be grossly inflated. Because LOD scores and locus-specific effect sizes are not independent, if the LOD score is maximized across the genome, then the locus-specific effect size is also maximized, and this generates the upward bias. The conditions used for the simulations include a fairly large data set, fully informative markers across the genome, and error-free data. These conditions are unlikely to be met in a real genome scan for complex disease, and the bias is likely to be even greater. In fact, the bias in locus-specific effect-size

estimation is inversely related to the power of a study. The power to replicate gene-mapping results is likely to be overestimated if inflated locus-specific effect-size estimates from an initial study are believed, and this could lead to failure to replicate. There is no obvious correction for the bias in locus-specific effect estimates. The authors urge that, to get around the bias, readers should use independent data sets for locus mapping and for estimation of locus-specific effect size.

**CASQ2 *Mutation in Autosomal Recessive PVT,* by *Lahat et al.* (*p. 1378*)**

Catecholamine-induced polymorphic ventricular tachycardia (PVT) is a stress-related ventricular tachycardia—in the absence of structural heart disease—that usually presents as fainting episodes, seizures, or sudden death in response to emotional or physical stress. Autosomal dominant catecholamine-induced PVT has been ascribed to mutations in *RYR2,* encoding a cardiac sarcoplasmic–reticulum calcium-release channel that couples excitation of myocardial cells to the cardiac contractile apparatus. Lahat et al. previously localized the gene for an autosomal recessive catecholamine-induced PVT to chromosome 1p13-p21. Now, they have refined this interval and have discovered that therein lies a gene that encodes another protein, calsequestrin 2, involved in the control of calcium in the sarcoplasmic reticulum. A D307H mutation segregates with disease in all of the affected families. On the basis of a model of rabbit skeletal-muscle calsequestrin, the mutated residue protrudes into an interdomain space that is thought to play an important role in sequestration of calcium ions. The replacement of a negatively charged residue by a positively charged one, as is seen with the mutation, would likely disrupt calcium binding to this region. Further supporting the association of D307H with disease is the fact that mice overexpressing calsequestrin 2 have cardiac abnormalities, features of which are similar to those seen in patients carrying the D307H mutation.

***Histone Methylation at the PWS-IC,* by *Xin et al.* (*p. 1389*)**

Evidence of genetic imprinting at chromosome 15q11-q13 is revealed when a copy of this genetic region is not inherited from each parent. Because some genes in this region are exclusively expressed from the maternal or paternal chromosome, loss of the allele from one parent results in altered gene expression. Loss of the paternal copy of the region, either through deletion or through uniparental disomy, leads to Prader-Willi syndrome (PWS), whereas loss of the maternal copy leads to Angelman syndrome (AS). The mechanism governing differential gene expression from homologous chromosomes is not understood. Xin et al. attempt to identify the epigenetic mark distinguishing the maternal from the paternal alleles in this region. They examine histone methylation in this region because histone modifications are known to affect transcription and heterochromatin assembly and because histone methylation exhibits a low turnover rate. Chromatin from individuals with PWS, from individuals with AS, and from controls was immunoprecipitated with antibodies either to histones methylated at the lysine 9 residue or to those methylated at the lysine 4 residue. Precipitated DNA was then assayed, by PCR, for specific sequences in the imprinted chromosome 15 region. Maternal-specific methylation of lysine 9 of histone H3 was identified in a region surrounding *SNRPN* exon 1, the maternal allele of which is inactive; paternal-specific methylation of lysine 4 of histone H3 was seen for the promoters of *SNRPN* and *NDN*, genes that are both paternally expressed. Thus, these markers distinguish the parental alleles of these genes from each other. These results suggest that histone modification may be the imprint marker in this region, and Xin et al. propose a model by which this marker could be transferred in a sex-specific manner during gametogenesis.

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