This Month in the *Journal*

TMD Is Caused by Mutations in Titin, *by Hackman et al.* **(*p. 492*)**

Hackman et al. add the gene for titin (*TTN*) to the list of genes involved in muscular dystrophy, with their finding of mutations in individuals with tibial muscular dystrophy (TMD). Titin is a giant, filamentous muscle protein that is essential for muscle structure, development, and elasticity. It also possesses several ligand-binding sites for muscle proteins and may serve as a blueprint for sarcomere assembly. Immunofluorescence, using antibodies to specific epitopes within titin, suggests that, at least for one of the two mutations identified in this work, a large portion of the titin structure is intact but that the C-terminus is disrupted. There are many titin regions that are differentially expressed in different muscle types. This may be one reason behind the localization of muscle weakness and atrophy in TMD to the anterior compartment of the lower leg. However, it does not explain why TMD patients do not have cardiomyopathy, even though the portion of titin that is disrupted by the mutations in this study is expressed in cardiac muscle. Another potential explanation for the muscle specificity of TMD is the loss, in titin, of binding sites for muscle-specific binding proteins. As a protein interaction site for calpain3 is in the mutated region of *TTN* and as calpain3 is not expressed in mature heart muscle, the authors speculate that alteration of the titin-calpain3 interaction may partly explain the TMD disease mechanism and its muscle specificity.

IAHSP and Alsin, *by Eymard-Pierre et al.* **(*p. 518*)**

Eymard-Pierre et al. increase the range of phenotypes associated with mutations in the gene for alsin (*ALS2*), with their finding of *ALS2* mutations in families with infantile early-onset ascending hereditary spastic paralysis (IAHSP). IAHSP is a severe spastic paralysis with an ascending progression. *ALS2* mutations were previously reported in juvenile amyotrophic lateral sclerosis and in familial juvenile-onset primary lateral sclerosis, which are similar neurodegenerative disorders that affect the upper and lower motor neurons, to different extents. The function of alsin is unknown. There are two alternatively spliced variants of the *ALS2* transcript, and it has been proposed that *ALS2* mutations that disrupt only the longer form of the alsin protein result in a milder phenotype. However, Eymard-Pierre et al. did not find evidence for a genotype-phenotype correlation; mutations in either form of alsin gave rise to similar disease phenotypes and progression in their sample.

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HLA Class II Risk Haplotypes in SLE, *by Graham et al.* **(*p. 543*)**

Although associations of the HLA region with systemic lupus erythematosus (SLE) have been found, it has been difficult to dissect this association further, because of extensive linkage disequilibrium (LD) in this region. Graham et al. managed to do this by typing, in a large set of families with SLE, a dense set of microsatellites across the HLA region. Three haplotypes exhibited transmission distortion and were enriched in case individuals compared with control individuals. These haplotypes contain the DRB1*1501/DQB1*0602, DRB1*0801/DQB1*0402, and DRB1*0301/DQB1*0201 alleles. The families that carried one or more of these risk haplotypes accounted for almost all of the transmission distortion observed in this region. By determining the ancestral risk haplotypes containing the risk alleles, the authors were able to limit the risk interval around DRB1*0801 and DRB*0501 to an interval of ~500-kb that contains DRB1 and DQB1 but excludes the class I and class III regions, including TNF-α. In fact, there are only two other genes in this interval, and they are of unknown function. The HLA class II haplotypes containing the DRB1 and DQB1 alleles thus appear to be strong risk factors for SLE.

LD Mapping of BP-1 in Costa Rica, *by Ophoff et al.* **(*p. 565*)**

Ophoff et al. report the results of a genomewide LD mapping study for severe bipolar disorder. They genotyped >1,000 STR markers in a young population isolate from the central valley of Costa Rica (CVCR) that has previously been demonstrated to have extensive LD. The goal was to identify haplotypes that were shared more frequently by affected individuals than would be expected by chance. Several markers were overrepresented in affected individuals, with one region particularly standing out: marker alleles and haplotypes in a 22-cM region on chromosome 8p showed evidence of association(with bipolar disorder, when analyzed using two different statistical methods. At this stage, the development of this LD mapping strategy is still in its infancy, and it is not clear how corrections for multiple testing should be applied to these data to assess the statistical significance of the findings. Rather than using this method to identify statistically significant associations, the authors propose that this type of strategy be

used to prioritize the genetic regions that should be further studied, using additional samples and methods.

BRCA2 *T2722R Is a Deleterious Allele That Causes Exon Skipping,* *by Fackenthal et al.* **(*p. 625*)**

Although a large number of predicted missense polymorphisms have been found in *BRCA1* and *BRCA2,* it has been impossible to characterize most of these variants because of the lack of standard, functional assays for the BRCA proteins. It is therefore not clear whether these variants are deleterious mutations that can lead to breast and ovarian cancer. Fackenthal et al. decided to determine whether they could classify any exonic single-base *BRCA2* substitutions through use of sequence matrices that predict the disruption of exonic splicing–enhancer (ESE) sequences. The analysis predicts that the *BRCA2* T2722R allele, a C→G transversion that segregates with disease in an affected family, disrupts three potential ESE sites, thereby leading to exon skipping. This is confirmed in an individual carrying T2722R, who is found to produce a *BRCA2* transcript that lacks exon 18 and that is predicted to encode a functionally null, truncated protein. The authors hope that this and other predictive models can be used to characterize additional *BRCA1* and *BRCA2* variants, to determine their clinical significance.

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