This Month in the *Journal*

This month in the *Journal,* RNA-mediated pathogenesis is the focus of two review articles, one on myotonic dystrophy by Laura Ranum and John Day and one on the fragile-X premutation by Paul and Randi Hagerman. Evidence is mounting that the expanded CUG and CCUG repeats in DM1 and DM2 alter expression and splicing of genes relevant to the DM phenotype by sequestering repeat-binding proteins. The picture for the newly recognized fragile-X premutation–associated pathologies is not as clear, although parallels with the pathogenic mechanism for DM are being drawn.

In conjunction with the review of the fragile-X premutation, we also have a research report that focuses on one of its associated phenotypes, the fragile-X–associated tremor/ataxia syndrome (FXTAS). Whereas previous reports found that only men are affected with this phenotype, Hagerman et al. report five women with definite or probable FXTAS.

LRP5 and Bone Phenotypes, *by Ferrari et al.* **(***p. 866***)**

As the song goes, short people got little noses and tiny little teeth and wear platform shoes on their little feet. But do they also have a missense change in *LRP5?* Ferrari et al. found variation in *LRP5* that is associated with vertebral bone size and stature, especially in adult males. Carriers of the A allele at this exon 9 polymorphism were, on average, 2 cm shorter than noncarriers. In children and adolescents, who have not reached their peak stature and bone mass, variation at *LRP5* was not strongly associated with static bone-mass and size measurements. Instead, the exon 9 polymorphism was associated with changes in bone mass and size over time, with carriers of the missense variant having smaller gains in these measurements. Again, this association was restricted to males. This is one of the first common genetic determinants reported for vertebral bone size and stature. In addition to its apparent role in normal growth, *LRP5* has also been implicated in two syndromes characterized by aberrant bone mass, osteoporosis pseudoglioma and high-bone-mass syndrome.

Linkage Analysis of Bipolar Disorder with SNP Arrays, *by Middleton et al.* **(***p. 886***)**

There has been a lot of recent interest in the use of SNPs, rather than microsatellites, in genomewide linkage studies. Although, with SNPs, you lose in terms of individual marker informativeness, you gain in terms of marker abundance and the ability to do high-throughput genotyping. Middleton et al. assess the usefulness of a SNP genome array through comparisons with data from a microsatellite-based genome scan. The genome scans were performed on 12 families with bipolar disorder, by use of the GeneChip Human Mapping 10K (HMA10K) array, which has marker spacing of ~0.21 Mb. These families were previously included in a genome scan that used 10-cM and 4-cM microsatellite marker sets. In general, the linkage signals from the two types of marker sets agree, but the HMA10K array raised the linkage scores for loci on chromosomes 6 and 11 over the level of genomewide significance. The addition of 13 families to the study increased the maximum nonparametric linkage score to 4.20 on chromosome 6q22, providing further support for a bipolar-disorder locus in this area. Suggestive loci that were not picked up in the microsatellite scan were also identified. Overall, the increased coverage and information content of the HMA10K marker set yielded more precise linkage information across the genome and make it an attractive approach to consider for genome scans.

Design and Analysis of Admixture-Mapping Studies, *by Hoggart et al.* **(***p. 965***);** ***Dense African American Admixture Map,*** *by Smith et al.* **(***p. 1001***);** ***and High-Density Admixture Mapping,*** *by Patterson et al.* **(***p. 979***)**

Admixture mapping exploits the fact that there are disease-causing genetic variants that differ in frequency between populations. If one looks at a population that arose from fairly recent mixing of two or more parental populations (an admixed population), chromosomal regions that contain a disease gene should show a higher proportion of ancestry from the population with more disease-susceptibility alleles. In theory, this could be a very useful method for mapping complex-disease loci, because it requires far fewer markers than traditional association-mapping methods. To date, admixture mapping has been of more theoretical than practical significance because good tools for its use have not been available. In this issue of the *Journal,* we have three articles that go a long way toward developing admixture mapping into a more feasible approach. Two of these, by Hoggart et al. and by Patterson et al., focus on study design. Between them, they evaluate and improve methods for admixture mapping and describe what they see as the most effective designs for this approach to gene mapping. Smith et al. present a marker map with >3,000 markers that will make possible genomewide admixture

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mapping in African Americans. The SNPs in this map were chosen for even spacing and because of their high allele-frequency differentiation between the African and European parent populations. Now that an appropriate marker map is available and analytical methods are evolving, the real test of admixture mapping can begin: will it actually be able to find a disease gene?

AXIN2 *in Oligodontia and Colorectal Cancer,* *by Lammi et al.* **(*p. 1043*)**

The Wnt signaling pathway is involved in the establishment of the body axis and the development of many organs. In addition, misregulation of Wnt signaling can lead to cancer. Wnt signaling leads to accumulation of β-catenin, which facilitates expression of downstream targets. Without a Wnt signal, β-catenin is phosphorylated and subsequently degraded through the action of a protein complex that includes APC, Axin1, and Axin2. This complex therefore serves as a negative regulator of Wnt signaling. Lammi et al. report a truncating *AXIN2* mutation in a family segregating a phenotype with two components: oligodontia, the congenital lack of several permanent teeth, and colorectal neoplasia. A second truncating *AXIN2* mutation was found in an isolated subject with oligodontia. Both mutations are predicted to cause loss of function and, therefore, increased Wnt signaling. These data suggest that overstimulation of the Wnt pathway leads to failure of the development of permanent but not baby teeth. It had already been reported that somatic mutations in components of the β-catenin degradation complex can be found in various cancers. Perhaps the surprising thing, then, is that the phenotype in the affected individuals reported by Lammi et al. is limited to the teeth and colon, since Wnt signaling is so widely used in the regulation of development and homeostasis. This might give us a clue as to where and when regulation of Wnt signaling by AXIN2 is important.

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