This Month in the *Journal*

This month in the *Journal,* Wang et al. describe how mouse-human comparative genetics can be used to identify human genes associated with a complex trait, specifically atherosclerosis. There are at least 27 unique human QTLs for atherosclerosis, but few genes have been reliably associated with this trait. However, about half of the QTLs found in mouse models of atherosclerosis have concordant human QTLs. Wang et al. explain how this overlap can be used to identify the causative genes within these QTLs and the types of mouse crosses that will facilitate gene identification. In fact, the authors have successfully used the general approach they describe to identify the *TNFSF4* gene as being associated with the risk of heart attack and coronary artery disease in humans.

Mutations in* SLC19A3 *Cause BBGD, *by Zeng et al.* (*p. 16*)

In this issue of the *Journal,* two articles report transporter defects that are associated with neurological phenotypes. The first, by Zeng et al., is an investigation of biotin-responsive basal ganglia disease (BBGD). This disorder first appears in children as a subacute encephalopathy, with confusion and vomiting. It progresses to acute encephalopathy, with speech difficulties, inability to swallow, seizures, and partial or complete paralysis. These symptoms can be completely reversed if treatment with high doses of biotin is started at an early stage; without continuous treatment, there is progressive encephalopathy and, ultimately, death. The dramatic improvements with treatment placed biotin metabolism as a key player in this disorder. Unfortunately, no defects in the enzymes that require biotin were found. Linkage analysis placed the critical region on chromosome 2, and Zeng et al. focused on *SLC19A3* as a candidate gene because it belongs to a family of transporter proteins. They found mutations in *SLC19A3* in all four families they examined. Because BBGD is so effectively treated with biotin, the authors speculate that *SLC19A3* encodes a biotin transporter, a hypothesis supported by the recent finding that people with induced biotin deficiency have reductions in *SLC19A3* mRNA levels in their blood. Curiously, the presentation of BBGD seems to have neurological specificity. Affected individuals do not have evidence of a generalized biotin deficiency; therefore, the biotin insufficiency appears to be limited to the brain.

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Allan-Herndon-Dudley Syndrome, *by Schwartz et al.* (*p. 41*)

The second article that reports a transporter defect is by Schwartz et al., who found a transporter defect in Allan-Herndon-Dudley syndrome. This is a severe form of X-linked mental retardation that is associated with hypotonia, delayed motor development, and muscle hypoplasia. Linkage studies had placed the candidate gene in the region of Xq13–Xq21. Schwartz et al. realized that *MCT8* was a good candidate gene in this region because mutations in this gene have recently been reported in males with mental retardation, hypotonia, and thyroid abnormalities. Schwartz et al. studied six kindreds and found that some of the affected individuals did, in fact, have thyroid abnormalities, and all of them had mutations in *MCT8*. This gene encodes the monocarboxylate transporter 8, which has recently been shown to be a thyroid-hormone transporter. The association with thyroid abnormalities could help to prioritize individuals with X-linked mental retardation for *MCT8* mutation screening. As with the *SLC19A3* mutations above, there is specificity for the presentation of the transporter defect, because individuals with *MCT8* mutations don't show the effects of a general thyroid disturbance. Dumitrescu et al. (74:168–175) speculated that the severe neurological phenotype coupled with mild evidence of a thyroid disturbance in people with *MCT8* mutations could suggest a brain-specific function for MCT8 beyond its action as a hormone transporter.

Segmental Duplication Array CGH, *by Sharp et al.* (*p. 78*)

Segmental duplications have been associated with several recurrent genomic disorders and are thought to be prone to instability. With recent reports that there is normal copy-number variation in the human genome, it seemed likely that segmental duplications might also mediate the generation of some of this variation. To test this hypothesis, Sharp et al. developed a microarray of BACs containing regions of segmental duplication and analyzed the DNA of 47 individuals from different populations to assess normal copy-number polymorphism (CNP) in these genetic regions. This approach was certainly successful in identifying CNPs; 119 regions of CNP were found, 73 of them novel. Compared with control BACs, CNPs were enriched in regions that were flanked by or contained segmental duplications, supporting the theory that these duplications mediate the generation of normal genetic variation. Not only did

these duplications seem to generate CNPs, but they were also often variant in copy number themselves. Sharp et al. have created a Web-based database that includes their results and that they hope will serve as a resource for facilitating further studies of structural polymorphisms.

AR *Is the Major Determinant of AGA,* *by Hillmer et al.* **(*p. 140*)**

Hillmer et al. report that a major determinant of male-pattern baldness (androgenetic alopecia) is the androgen receptor (*AR*) gene. In a sample of families with at least two affected brothers, they found linkage to the X chromosome in a region containing *AR*. This finding led the authors to do an association study of markers in the area, and they report a 1-Mb region that is strongly associated with baldness in both a case-control and a family-based association analysis. The only known gene within this region is *AR*, and a GGN repeat is the only specific feature in this gene that shows a strong association with baldness. Previously, it was shown that there is allele-specific variation in protein and activity levels for the GGN repeat, so this association may have functional significance. Alternatively, the GGN repeat could instead be in linkage disequilibrium with the actual but as-yet-undetected causal variation. Although it appears to contribute significantly to male-pattern baldness, *AR* is obviously not the whole story behind this phenotype, because its location on the X chromosome cannot explain the fact that many sons resemble their fathers in terms of baldness.

KATHRYN GARBER
Deputy Editor