This Month in the *Journal*

At least 12 loci are involved in the various forms of familial amyotrophic lateral sclerosis (ALS), which can have dominant, recessive, or X-linked patterns of transmission. There are also sporadic forms of ALS that are associated with variation in additional genes and that almost certainly are influenced by the environment. Catherine Kunst reviews the genetics of ALS in this issue of the *Journal*. In addition to a discussion of the genes involved, she discusses animal models for the disease and current hypotheses regarding potential disease mechanisms.

SOST *Polymorphisms and Osteoporosis,* *by Uitterlinden et al.* (*p. 1032*)

Sclerostin is a negative regulator of bone formation that is expressed in osteogenic cells. This bone-morphogenetic-protein antagonist initiates apoptosis of osteoblasts through a mechanism that involves caspase 3. Mutations in the gene that encodes sclerostin, *SOST,* cause sclerosteosis, which is a bone-overgrowth disorder. This finding led Uitterlinden et al. to postulate that *SOST* might underlie some of the genetic component of variation in bone-mineral density (BMD) or risk of fractures in a normal elderly population. In their sample of >1,900 subjects aged $\geqslant$55 years, two polymorphisms were associated with BMD, one in men and one in women. In women, the effect on BMD of an indel polymorphism 5′ to *SOST* became stronger with age and had an additive effect with another polymorphism known to affect BMD, *COL1A1* Sp1. *SOST* did not appear to have an effect on risk of bone fracture in either sex, although a larger sample size would be needed to rule out a small effect. The indel is located in a region that is conserved between humans and mice; it may have a repressive effect on the activity of the *SOST* promoter, but further work is needed to establish the exact mechanism of the association of this polymorphism with BMD.

Genetics of Gene Expression in Humans, *by Monks et al.* (*p. 1094*)

Monks et al. report that gene expression is a heritable trait for a large number of genes and that QTLs related to these traits can be identified. Their experiments began with microarrays that were performed on lymphoblastoid cell RNA from CEPH families. Of the genes on the microarray, ~10% were differentially expressed between people; this set of differentially expressed genes was enriched for certain functional classes, particularly those involved in the immune and inflammatory responses. There is a heritability component for the differential expression of approximately one-third of these genes, and these heritability estimates are similar to those measured for complex traits. An attempt to find the loci governing this differential expression led to the identification of several QTLs. In fact, the QTLs for some of these genes overlap with the physical locations of the genes themselves. Clusters of genes that were generated on the basis of genetic-correlation measures corresponded well to biological pathways, so it is possible that these clusters could give insight into the biological relationship among genes that together might underlie a complex trait.

Genetics of Descent Groups, *by Chaix et al.* (*p. 1113*)

Many societies are organized into descent groups, in which the population is divided into tribes, then clans, then lineages. The majority of these are patrilineal, with each descent group able to trace its heritage to a common male ancestor. Chaix et al. were interested in whether (1) this type of organization is actually genetically demonstrable or (2) the lineages are socially reconstructed. They studied this through use of Y-chromosome data for five patrilineal populations from Uzbekistan. The genetic relationship within each descent group was measured through estimation of mean kinship coefficients. Individuals from the same lineage and from the same clan were, in general, more related than individuals taken at random from the population, a result that supports their claim of a common ancestor. In contrast, however, tribes do not appear to represent genetic relatedness but rather a grouping of unrelated clans. This is consistent with previous speculation that clans sometimes fused for economic or military reasons and that, to promote group cohesiveness, the "tribe" genealogy was subsequently connected through the creation of a fictitious common ancestor.

Sex-Specific Linkage Signals in Autism, *by Stone et al.* (*p. 1117*)

The male:female ratio for idiopathic autism is 4–10:1, and a male bias is generally found in the pervasive developmental disorders. Stone et al. wondered if the incorporation of this sex bias into their linkage analysis would help them identify autism loci. They subdivided their affected-sib-pair sample from the Autism Genetic Resource Exchange (AGRE) on the basis of the sex of the affected individuals in the family; one subsample

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contained affected males only, whereas families with affected females were placed in a second group. Stone et al. hoped that this sample stratification would reduce genetic heterogeneity in the sample and allow them to identify genetic risk factors that were sex specific. To assess the statistical significance of the sex-stratified results, they compared their results with those obtained by randomly splitting the full sample 1,000 times into size-matched groups. A linkage peak with genomewide significance was found on chromosome 17q11 in the male-only subsample. Although suggestive linkage to this region was found in the original AGRE genome scan, little evidence of linkage is found in the female-containing subset of this sample. Thus, the 17q11 locus is likely to contain a genetic-risk allele that is specific to males. Beyond the identification of this sex-specific autism locus, the methods developed in this work might be useful for study of other complex traits that exhibit sex biases, such as autoimmune disorders.

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