This Month in the *Journal*

CAPN10 ***Gene and Type 2 Diabetes,*** *by Song et al.* (*p. 208*)

There have been many follow-up studies (with mixed results) to the first report of an association between the calpain-10 gene *CAPN10* and type 2 diabetes (T2D) (see Horikawa et al. reference in Song et al.). Overall, the *CAPN10*-T2D association, if it is found at all, appears to be modest. In the hope of generating a more concrete conclusion regarding the role of *CAPN10* in T2D, Song et al. collected the data from all of these population- and family-based association studies for use in a meta-analysis. Although, individually, none of the previous studies had sufficient power to provide a robust estimate of the effect of *CAPN10* on T2D risk, the pooled population-based data indicate that the G/G genotype at UCSNP-43 confers modest susceptibility to T2D, with an odds ratio of 1.19. The pooled family-based data have little power to detect a modest genetic effect and do not provide support for this association. Horikawa et al. also reported that the 112/121 haplotype combination in *CAPN10* is associated with increased susceptibility to T2D. A pooled analysis indicates that this association may have been overestimated in subsequent underpowered studies and that a significant association with the haplotype combination is not seen when these small studies are disregarded. In addition to the lack of power in the individual studies, Song et al. suggest several other reasons for difficulties in confirming the *CAPN10*-T2D association. These include the fact that population-specific linkage disequilibrium patterns have been overlooked, the presence of population stratification, and the scarcity of prospective study designs. Although no definitive conclusion about the role of *CAPN10* in risk of T2D can be made yet, this study does make it possible to more critically evaluate the data at hand and to better plan future studies in this area.

Selection and Human mtDNA Evolution, *by Elson et al.* (*p. 229*)

When mtDNA is used to trace human evolution, the assumption is made that divergence obeys a molecular clock and that selection has been negligible. If these assumptions were false, it would mean that our estimates of the rate of mtDNA evolution—and therefore our dating of events on the basis of this technology—are inaccurate. Some analyses of selection in mtDNA have been performed, largely with limited stretches of mtDNA. Since complete mtDNA coding-region sequences are now becoming available, it was possible for Elson et al. to do a more thorough analysis of selection in mtDNA, by use of both gene-by-gene and whole-genome approaches. Although the evidence for selection was not consistent throughout their comparisons, the gene-by-gene analysis of substitutions in protein-coding genes shows that sets of older sequence changes have relatively fewer nonsynonymous changes than do sets of younger sequence changes, which is most simply explained by the action of negative selection. Also supporting the existence of mtDNA selection are differences between the observed and predicted numbers of nonsynonymous changes in the sequences. Additional work will be needed to determine the exact consequences of these selective forces on rates of mtDNA evolution.

ETHE1 ***Mutations in Ethylmalonic Encephalopathy,*** *by Tiranti et al.* (*p. 239*)

The metabolic disorder ethylmalonic encephalopathy (EE) is associated with developmental delay and death, usually by age 10 years. The gastrointestinal system and peripheral vessels are also involved, as indicated by chronic diarrhea, acrocyanosis, and petechiae. Although it is known that high levels of ethylmalonic acid in the body fluids and low cytochrome c oxidase activity in skeletal muscle are features of EE, the underlying defect in this disorder has remained a mystery—that is, until Tiranti et al. did a linkage study and mapped the EE locus to chromosome 19q13. Although >100 genes were present in the critical region, Tiranti et al. were able to zero in on the causative gene, *ETHE1,* using an integrative genomics approach. The features of EE led Tiranti et al. to suspect the involvement of a protein involved in mitochondrial metabolism, so they narrowed the list of candidate genes on the basis of the similarity of their expression profiles to those of known mitochondrial genes. Sixteen mutations were found in a gene formerly known as "*HSCO,*" in both families and singleton cases. All mutations, even missense, led to a loss of detectable protein. A series of fractionation and localization experiments suggests that the ETHE1 protein is localized to the mitochondrial matrix, a finding that contradicts a previous report. Although the protein has high homology with glyoxalase II, no enzymatic activity could be detected in isolated mitochondria. Further studies are needed to clarify the role of this putative enzyme in mitochondrial homeostasis.

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Bias in Conventional Linkage Analysis, *by Schork and Greenwood* (*p. 306*)

Schork and Greenwood have identified a potentially serious bias in nonparametric linkage (NPL) analysis methods that may be partly responsible for the difficulties in using these methods to identify complex disease loci. This bias toward the null hypothesis of no linkage arises when expected allele-sharing values are assigned to relative pairs when marker information is uninformative; the amount of bias varies on the basis of several aspects of the study design, including the markers used, the sample size, and the type of relative pairs. There are several potential ways to lessen or eliminate this bias, such as removing uninformative relative pairs from the analysis, identifying genomic areas for which marker data are uninformative, and using a denser genetic map to reduce uninformativeness; their usefulness should be studied further. For now, Schork and Greenwood suggest that it may be beneficial for researchers to re-evaluate their NPL results with this bias in mind.

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