***Multilocus Tests and Interactions,* by *Chatterjee et al.* (*p. 1002*)**

When looking for an association between genetic variants and disease, investigators often use multilocus tests to exploit the fact that several SNPs may be associated or may be in linkage disequilibrium with a causal variant. The effects of these variants can be complicated by interactions with SNPs in other genes or with environmental factors. Allowances for all these interactions can significantly reduce power because of the degrees of freedom needed for the calculations. In an effort to reduce the degrees of freedom, Chatterjee et al. propose that, under the assumption that the multiple SNPs within a gene are related to one another because of a common causal mechanism, Tukey's 1-df model for interaction can be used. This allows the test to account for main effects as well as gene-gene interactions and gene-environment interactions without loss of too much power. The power of the new method, TukAssoc, was compared with a method that measured only main effects and a method that included a saturated interaction analysis. Depending on the model of the joint effects in the simulations, TukAssoc either had the highest power or had power close to that of the main-effects method. The algorithms were then evaluated using data from an association study of colorectal adenoma, *NAT2* SNPs, and cigarette smoke. When an interaction with smoking was accounted for, the evidence of association was strongest when TukAssoc was used.

***Biochemical and Genetic Analysis of ANK,* by *Gurley et al.* (*p. 1017*)**

Familial chondrocalcinosis (CCAL2), the deposition of calcium pyrophosphate dehydrate in the joints, is caused by mutations in the gene encoding ANKH, a transmembrane protein believed to be a pyrophosphate transporter. A contrasting disease, craniometaphyseal dysplasia (CMD), in which patients do not have any joint problems but instead have an abnormal skull and long-bone phenotype, is also caused by mutations in *ANKH*. Previous work has sought to determine the effect that the disease-causing mutations have on the function of the transporter protein, but results have been conflicting. Here, Gurley et al. used a *Xenopus* oocyte system to more directly measure the pyrophosphate transport activity of wild-type ANKH, ANKH with CCAL2 mutations, and ANKH with CMD mutations. They observed that, whereas transport levels were similar between the wild-type proteins and those with CCAL2 mutations, ANKH with CMD mutations had very little activity and had a dominant negative effect on wild-type protein activity. The effects of the mutations were also evaluated by measuring how well BACs containing the different disease mutations could rescue the phenotype of *Ank*-deficient mice. Rescue was observed with the wild-type BAC and with the BAC containing the CCAL2 mutation, but no rescue was seen with the CMD mutation–containing BAC. The different phenotypes caused by the mutations in the same gene can now be predicted on the basis of how the mutations affect the function of the protein-transport activity.

***Mutations of* TRIC *Cause DFNB49,* by *Riazuddin et al.* (*p. 1040*)**

Various proteins are involved in the maintenance of the intricate structures of the inner ear, and the disruption of the genes encoding these proteins can lead to hearing loss. Riazuddin et al. studied multiple families with a recessive, moderate-to-profound hearing loss that was linked to 5q12.3-q14.1. Their analysis of the genes in this locus revealed pathogenic mutations in tricellulin (encoded by *TRIC*), a recently identified tight-junction protein that is expressed at the contacts between epithelial cells of body tissues. TRIC has several splice isoforms and contains a binding domain at its C-terminus that is similar to the C-terminus of the structural protein occludin. Expression analysis done on developmental sections of mouse inner ear revealed that tricellulin concentrates at the tricellular junctions of the cochlea and the vestibular epithelia. To learn more about the function of tricellulin and the possible consequences of the pathogenic mutations, GST-fusion proteins were produced for the wild-type protein and one of the mutants. It was predicted that, because occludin binds to the scaffolding protein ZO-1, tricellulin might similarly interact with ZO-1 through its C-terminus–binding domain. The authors demonstrate that wild-type tricellulin does bind to ZO-1 and that one of the mutations causing hearing loss significantly reduces the interaction.

***HLA and Genomewide Allele Sharing in DZ Twins, by Montgomery et al.* (*p. 1052*)**

There is evidence that genetic factors influencing embryo survival can lead to a higher amount of allele sharing between siblings than would be expected randomly. Because of the careful conditions that must be met for human conceptions to reach full term, it is thought that those embryos that do survive have a selective advantage over those that do not. There are also additional conflicting data regarding whether DZ twins are even more related than regular siblings; the hypothesis is that the survival of two twins might be more difficult than the survival of a singleton pregnancy. This potential oversharing of chromosomal material becomes an issue in genetics studies,

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because DZ twins are usually treated as normal sib pairs, with traditional assumptions about the sharing of alleles identical by descent. If DZ twins are more closely related than normal siblings, twin-study designs would need to be significantly restructured. Here, Montgomery et al. looked at the amount of allele sharing at various loci in three twin data sets and found no evidence of skewing of allele transmission. These results support the customary use of DZ twins in linkage studies.

***Human Adaptive Evolution at Myostatin,* by *Saunders et al.* (*p. 1089*)**

Because of the possible importance of muscle growth and development in species survival, it is predicted that genes involved in these processes are targets of evolutionary selection. Saunders et al. examined the gene sequence of myostatin (*GDF8*), an inhibitor of muscle growth, to see whether any evidence of positive selection exists. Sequencing of the gene in African American and European individuals revealed five nonsynonymous SNPs and three synonymous changes. The higher number of nonsynonymous alterations suggested that the human variation in *GDF8* was due to positive natural selection, so further comparisons were made in other species, and the human ratio was indeed unusual. The authors then focused their analysis on two of the nonsynonymous SNPs, to gain more insight into the pattern of evolution of the gene, and determined that the selection in the region is relatively recent and that the frequency of the polymorphisms has increased quickly. Although the functional consequences of the two variants are not clear, the strong observed signature of selection suggests that the changes were important in the evolutionary history of *GDF8*.

This Month on the Cover

In 1964, Philip Leder and Marshall Nirenberg employed a simple binding assay to begin their quest to crack the genetic code (Proc Nat Acad Sci USA 52:420–427). Their method involved evaluating which di-, tri-, or polynucleotides would cause binding between tRNA molecules and ribosomes. The cover figure shows that the trinucleotide GpUpU and poly UG induces binding of Val tRNA to ribosomes. Further work showed that, whereas poly UG could direct Phe- and Val-tRNA binding, GpUpU was very specific for valine and did not induce binding to any of 17 other amino acids. Additionally, dinucleotides were unable to stimulate binding, so it was determined that code for amino acids was triplet in nature. Other trinucleotides, including the isomers UpUpG and UpGpU, were unable to stimulate binding to valine. This led to the conclusion that it was specifically the sequence GUU that encoded for the amino acid valine. With use of this technique, the rest of the code was eventually revealed. Special thanks to the authors—Philip Leder and Marshall Nirenberg—for the use of their figure.

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