This Month in the *Journal*

Haplotype Analysis of Drug-Related Genes, *by Kamatani et al.* **(***p. 190***)**

The use of haplotype-tagging SNPs (htSNPs) has been advocated by many as a way to minimize the genotyping required in a linkage-disequilibrium study. An htSNP is a SNP that can be used to mark the majority of haplotypes in a segment of limited haplotype diversity. It has been unclear, however, to what extent htSNPs represent uncommon variation. Kamatani et al. study this in the context of 199 genes involved in drug transport and/or metabolism. They report that most uncommon SNPs (those with minor-allele frequencies <0.1) can be identified by htSNPs if the minor-allele frequencies of the uncommon SNPs are >.03. This fact can be exploited to detect uncommon, phenotype-associated SNPs by use of the haplotype-tagging method, provided the uncommon SNPs are located within a haplotype block—which was the case for >60% of the uncommon SNPs in their study—and provided the allele frequencies of the SNPs differ between cases and controls. In their particular study, this means that Kamatani et al. need to genotype only 1,147 of 3,244 SNPs to perform a thorough case-control association analysis within their set of 199 genes.

Ancient-DNA Statistics, *by Spencer and Howe* **(***p. 240***)**

One need only follow the Letters to the Editor section of the *Journal* to know that the results of ancient-DNA analyses are often controversial. Despite attempts to set criteria for authentication, the results of these studies are often disputed. Spencer and Howe advocate the use of statistical methods to analyze the results of ancient DNA studies. They propose one way to do this: a maximum-likelihood method that allows them to calculate the probability that a positive result from a sample is authentic. They can also calculate CIs for this probability. During the study-design phase, their methods can be used to determine the sample size necessary to achieve a given level of confidence. In fact, Spencer and Howe show that it is essential to have more than a single sample to reject the possibility that a positive result is due to contamination. In these cases, even in the absence of positive results from negative controls, the lower 95% CL is zero. With five positive samples, on the other hand, the lower CL goes up to 0.96. Their methods can also be used to analyze results that have already been obtained. They find that positive results in negative control samples do not necessarily lead to rejection of the experiment. Instead, these data can be taken into account when the probability is calculated that a result is due to contamination.

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GJA12 ***Mutations Cause PMLD,*** *by Uhlenberg et al.* **(***p. 251***)**

Some people with a phenotype that is pretty much identical to Pelizaeus-Merzbacher disease (PMD) don't have mutations in the PMD gene *PLP1* and have been lumped in the category of having PMD-like disease (PMLD). Both PMD and PMLD are characterized by such symptoms as rapid, involuntary movements of the eye (nystagmus), impaired motor development, ataxia, and difficulty articulating. Uhlenberg et al. now report that at least some people with PMLD have mutations in the gene encoding the gap junction protein α12 (*GJA12;* connexin 46.6). So what is the connection between *PLP1* and *GJA12*? *PLP1* encodes the major component of myelin in the CNS. PMD-associated deletions of *PLP1* lead to length-dependent axonal degeneration, probably due to disruptions of axonal-glial interactions (Garbern et al. [2002] Brain 125:551–561). In mice, *Gja12* is expressed specifically in oligodendrocytes in a pattern similar to *Plp1* and other myelin-related genes (Menichella et al. [2003] J Neurosci 23:5963–5973). It is largely colocalized with Cx32 in oligodendrocytes, and these proteins appear to have a similar and at least partially redundant function. Mice that are double knockouts for *Gja12* and *Cx32* exhibit tremors and seizure due to demyelination and oligodendrocyte cell death. The phenotype in these mice was used to argue that gap-junction communication is required for proper myelination. Not only does this finding begin to explain that the underlying connection between PMD and PMLD is due to defects in myelination in the CNS, but it also brings another nervous system disorder into the picture, X-linked Charcot-Marie-Tooth (CMTX). CMTX is caused by mutations in the gene for GJA12's gap junction partner, CX32. Further highlighting the intertwined nature of these disorders is the finding by Uhlenberg et al. that some of their patients with *GJA12* mutations had peripheral neuropathy, which is a feature of CMTX and is only sporadically found in PMD.

MCPH1 ***Regulates Chromosome Condensation,*** *by Trimborn et al.* **(***p. 261***)**

Beyond the fact that it is mutated in some cases of primary microcephaly, little is known about the function of microcephalin, *MCPH1*. The reduction in brain size in affected individuals is believed to reflect a reduction in

neural cells, as a result either of reduced cell proliferation or of increased cell death. The phenotypic resemblance between primary microcephaly and premature condensation syndrome (PCC) led Trimborn et al. to postulate that the disorders might be allelic. In fact, this turned out to be true; they found a truncating *MCPH1* mutation in a family with PCC. An examination of the cellular phenotype of cells from patients with MCPH1 also supported the similarity of the disorders, which both show low-quality metaphases with poor banding resolution, a high proportion of prophaselike cells, and a considerable delay in chromosome decondensation after mitosis. Loss of microcephalin is sufficient to cause this cellular phenotype, as demonstrated through RNAi (RNA interference)–mediated depletion of *MCPH1*. This work reveals an early role for microcephalin in the regulation of chromosome condensation. The authors propose, because of the homology between microcephalin and other cell-cycle checkpoint proteins, that microcephalin may act as an intermediary between cell-cycle control and the chromosome-condensation apparatus. Ultimately, the role that microcephalin plays in neurogenesis and the explanation for the specificity of the primary microcephaly and PCC phenotypes will need to be teased apart as the precise function of microcephalin in these pathways is determined.

PTPN22 *and Rheumatoid Arthritis,* *by Begovich et al.* **(***p. 330***)**

Genetic linkage of various autoimmune disorders to the same loci and clustering of different autoimmune disorders within families suggest that there are common genetic underpinnings for autoimmunity. Along with a recent paper by Bottini et al. (see reference in Begovich et al.), Begovich et al. present evidence that one of the "autoimmunity genes" may be *PTPN22*. This story started when Bottini et al. reported a polymorphism in *PTPN22,* which encodes a suppressor of T-cell activation, that is associated with type I diabetes (T1D). The altered residue in the protein R620W lies in an N-terminal proline-rich motif that interacts with Csk, which in turn is a suppressor of Src kinases that mediate T-cell–receptor signaling. A tryptophan residue in this motif interferes with binding to Csk and would presumably lead to increased T-cell activity. In this issue, Begovich et al. show that the association of *PTPN22* is not limited to T1D but can also be seen with another autoimmune disorder, rheumatoid arthritis (RA). In two separate cohorts, the same allele of *PTPN22* was associated with increased risk of RA. The authors further demonstrated, through use of RNAi experiments, that PTPN22 does function as a negative regulator of T-cell activation and, through immunoprecipitations, that W620 PTPN22 may not function properly because it does not bind Csk. Although this would suggest a nice model for the development of autoimmune disease on the basis of T-cell hyperreactivity, *PTPN22* is expressed in all subtypes of peripheral-blood mononuclear cells, so the association with RA may be multifactorial. Together, the results of Bottini et al. and Begovich et al. suggest a common genetic variant that contributes to the development of at least two different autoimmune disorders.

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