Molecular Regulation of SCN1A Splicing, *by Heinzen et al.* (*p. 876*)

There is evidence that response to certain antiepileptic drugs may be influenced by a splice-site variant in *SCN1A*. Patients with the AA genotype at this site have been shown to require a higher dose for the drug to be effective. A link between this genotype and the functional consequences has been suggested by data showing that the alternative splicing induced by this SNP increases the amount of the neonatal transcript produced. In such a scenario, those patients with the AA genotype would have a higher ratio of neonatal-to-adult transcript than do those with fewer copies of the polymorphism. In addition to modifying a consensus splice site, the SNP may also modify a putative binding site for the splice-modifier protein Nova2. Heinzen et al. evaluated how the variant might influence the response to antiepileptic drugs. After confirming that the AA variant does cause lower levels of the neonatal transcript, Heinzen et al. then demonstrated that an increase in Nova2 was able to alter the transcript ratio, so that it was similar to that present in cells with the GG genotype. The authors hypothesized that such elucidation of the splicing control of the *SCN1A* transcripts would contribute to future endeavors to improve epilepsy therapy.

Y Chromosomes across the Himalayas, *by Gayden et al.* (*p. 884*)

Geographically, the Tibetan plateau is bounded by the Kunlun Mountains on the north, the Karakoram range on the west, and the Himalayas on the south. It has been speculated that such geographic barriers would lead to genetic isolation, and previous work has focused on the historic origins of the populations in the region. Results have been a source of significant controversy, since conflicting data have suggested various routes of dispersal. Gayden et al. sought to shed light on the situation with an analysis of Y-chromosome haplogroup diversity in the region. Their goal was not only to learn more about the genetic structure of the populations involved but also to evaluate the role the Himalayas have played in restricting the gene flow into and out of the Tibetan plateau. The authors found evidence that, although the Himalayas seem to have restricted movement from the south into Tibet, gene flow appears to have occurred in the opposite direction: out of the Tibetan plateau. The directionality of the barrier is hypothesized to be due to the inability of those from lower altitudes to effectively cope with the strenuous conditions associated with living at higher elevations.

FA-D2 Phenotype and* FANCD2 *Mutations, *by Kalb et al.* (*p. 895*)

Patients with Fanconia anemia (FA) are predisposed to the development of malignancies and bone-marrow failure. Several of the proteins in which mutations are known to cause FA assemble into a "core complex" that is required for the proper ubiquination of FANCD2. Although the function of FANCD2 is incompletely understood, it is thought that the protein is involved in the cellular response to DNA damage. The importance of the gene is highlighted by the severe phenotype of *Facd2*-deficient mice, but few human patients with FACD2 have been studied. Kalb et al. assembled a data set of 29 patients with FACD2, to analyze the molecular basis of the disease in each and to search for genotype-phenotype correlations. One significant finding was the presence of congenital abnormalities in all studied patients, which is in contrast to the expectation that 30% of patients with FA will not present with such phenotypes. Also, as has been observed in other types of FA, reverse mosaicism was seen in the hematopoietic system of a fraction of the patients with FACD2. Of particular note, all patients, including the large proportion in whom reversion was not identified, produced residual levels of protein. This suggested that the complete absence of the FACD2 protein was lethal and was in concordance with the phenotype observed in the knockout mice.

Simple Correction for Stratification, *by Epstein et al.* (*p. 921*)

Allele-frequency differences between two populations can be misinterpreted as significant differences in disease-causing variants. The presence of this population stratification can significantly confound results in case-control association studies. Current methods of avoiding spurious positive associations include use of homogeneous populations and/or correction for allele-frequency heterogeneity through statistical manipulation of data gathered from panels of population markers. But there remains evidence that suggests that such statistical methods are not yet able to always remove the effects of population stratification. Epstein et al. worked to develop a new approach that, by incorporating a stratification score into the testing, allowed them to accurately detect an association, even in the presence of population structure. The power of this computationally simple method was demonstrated through an application to simulated data, as well as to data from the classic stratification example of the association between height and the *LCT* locus.

Am. J. Hum. Genet. 2007;80:i–ii. © 2007 by The American Society of Human Genetics. All rights reserved. 0002-9297/2007/8005-0001$15.00
DOI: 10.1086/518009

TCF4 *Mutations in Pitt-Hopkins Syndrome,* by *Amiel et al.* (*p. 988*)

TCF4 *Mutations Cause Pitt-Hopkins Syndrome,* by *Zweier et al.* (*p. 994*)

Pitt-Hopkins syndrome (PHS) is a severe psychomotor disorder characterized by epileptic encephalopathy and episodes of hyperventilation. Although it was previously suspected that PHS was an autosomal dominant disease, the genetic etiology of the disease was unknown. Here, two different groups have used the detection of copy-number differences to identify candidate regions, the loss of which causes PHS. In the report, by Amiel et al., the authors used a BAC array to screen four patients and found that one had a de novo microdeletion that encompassed 11 genes. Sequencing of two of these genes in each of the remaining patients identified a missense mutation in *TCF4*. Similarly, Zweier et al. used SNP arrays to screen two patients with PHS and found that one had a deletion that contained three known genes, including *TCF4*. Further sequence analysis identified five more patients, each of whom had a mutation in *TCF4*. Further functional work with luciferase assays supported the hypothesis that the subsequent mutant proteins were unable to function in the same way as did the wild-type protein.

This Month on the Cover

Chediak-Higashi syndrome (CHS) and Griscelli syndrome (GS) are two types of syndromic albinism. Although the name for CHS credits Chediak with the first discovery of a case of CHS in 1952 (Rev Hematol 7:362–367) and Higashi for similar findings in 1954 (Tohoku J Exptl Med 59: 315–332), the first description was actually by Beguez-Cesar in 1943 (Bol Soc Cubana Pediat 15:900–922). Griscelli et al. later defined the independent syndrome, GS, in 1978 (Am J Med 65:691–702). Mutations in the CHS1 gene *LYST* were identified in 1996 by Nagle et al. (Nat Genet 14:307–311). The genes *MYO5A* and *RAB27A* are each associated with a type of GS (Nat Genet 16:289–292; Nat Genet 25:173–176). Each disease is caused by defects in melanosome transport. One way to properly distinguish CHS from GS is to analyze patient hair with light microscopy. The differences in the size and distribution of the melanin granules in these diseases can be appreciated in the images on the cover. From left to right are a hair from an unaffected individual and a hair each from individuals with CHS6, CHS4, and GS. Special thanks to Heidi M. Dorward of the Section on Human Biochemical Genetics, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, for the image.

Robin E. Williamson
Deputy Editor