***A SNP Can Neutralize Splicing Mutations,* by *Nielsen et al.* (*p. 416*)**

There is increasing evidence that mutations can significantly affect splicing even when they are not located directly at the splice site. On this basis, Nielsen et al. examined the effects of a missense mutation within exon 5 on the expression of *MCAD*. The mutation was found previously in patients with medium-chain acyl-CoA dehydrogenase deficiency. Here, the mutation was shown to decrease mRNA levels through a disruption of splicing that led to skipping exon 5, early termination, and nonsense-mediated decay. Through various minigene experiments, the authors demonstrated that the mutation disrupted an exonic splicing enhancer (ESE). They then went on to measure the effects of a second variant in exon 5, a synonymous polymorphism. This variant was predicted to alter an exonic splicing silencer (ESS). Additional minigene experiments revealed the complex interplay between these two changes, and of splicing control in general, by demonstrating that the introduction of the SNP disrupting the ESS renders the transcript immune to the detrimental effects of the loss of the ESE.

***Selection on* ADH1B, *by Han et al.* (*p. 441*)**

During alcohol metabolism, alcohol is broken down to acetaldehyde by alcohol dehydrogenase, and the subsequent acetaldehyde is oxidized to acetate by acetaldehyde dehydrogenase 2. The essential nature of these genes in the body's processing of alcohol has made them interesting candidates in the search for variants associated with alcohol dependence. One such association has been identified between a SNP in *ADH1B* and protection against developing alcoholism. Because of the high frequency of which this variant is found in East Asian populations, there has been speculation that selection has occurred at this locus. Han et al. decided to examine this hypothesis by evaluating the selection signatures of SNPs across the *ADH* region. Their results support the hypothesis that a protective *ADH1B* haplotype underwent positive selection in various populations from East Asia.

***Phosphate Carrier Deficiency,* by *Mayr et al.* (*p. 478*)**

Disruptions of mitochondrial metabolism can cause a variety of disorders with a wide range of severities. During energy metabolism in mitochondria, adenosine diphosphate (ADP) is combined with inorganic phosphate to create adenosine triphosphate (ATP). This inorganic phosphate is transported into the organelle by the mitochondrial phosphate carrier, PiC. Muscle-biopsy samples from a pair of sisters presenting with cardiomyopathy and muscle hypotonia revealed that, although the respiratory chain was functioning normally, ATP synthesis was disrupted. Because none of the genes known to be mutated in the disruption of ATP synthesis were found to be affected, the authors decided to check the PiC. A mutation was identified in an exon specific to the isoform expressed only in heart and muscle. To further evaluate the effects of this mutation, yeast deficient for phosphate-carrier activity were produced. The knockout yeast were able to grow only on glucose. Those cells were then transformed with wild-type human PiC as well as with the mutant human PiC. Whereas the introduction of the wild-type protein enabled growth on other types of media, the mutant protein did not.

***Gene-Expression Variation in Humans,* by *Storey et al.* (*p. 502*)**

Sequence variation within and among populations has been studied, but little is known about how gene-expression levels differ among humans. To examine this issue, Storey et al. examined the expression patterns of >5,000 genes in eight CEPH individuals and in eight individuals from Yoruba. The changes that they observed were small, but 83% of the genes showed expression-level variation among individuals, and the levels of 17% of the genes were different between the two populations. It was also determined that most of the variation in expression levels for specific genes was due to the component from differences among individuals. A closer look at the pathways to which these genes belong suggested that the expression of genes in the inflammatory pathway may significantly differ among populations. To evaluate the mechanisms behind this variation, allelic expression was analyzed, and the differential expression of the alleles suggested *cis*-regulation.

This Month on the Cover

In 1901, Landsteiner recognized that normal blood agglutinized when mixed with serum. By analyzing which type of serum led to the agglutination, he was able to categorize blood into three groups: A, B, and C, which later became known as "O" (Wienerklinische Wochenschrift 14:1132–1134). His discovery was supplemented by that of von Decastello and Sturli, in 1902, with their identification of a fourth group, which eventually became known as "AB" (Munch Med Wsch 49:1090–1095). For a time, there was a bit of confusion with the nomenclature when the blood

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groups were also identified and named independently by Jansky in 1907 (Sborn Klincky 8:85–139) and Moss in 1910 (Bull Johns Hopk Hosp 21:63–70). Not only was the discovery of the blood groups critical for effective and safe blood transfusions, but blood type was also the first trait recognized to follow Mendelian inheritance, by Bernstein, in 1925, when he suggested that the inheritance pattern could best be explained by the presence of three alleles at the blood-type locus (Z Induct Abstamm VererbLehre 37: 237–270). This finding identified the A, B, and O alleles as the first genetic markers to use in linkage-mapping studies. On the cover is a modern-day test for ABO typing. In the top row, the blue solution contains antibodies against the A antigen, and the yellow solution contains antibodies against the B antigen. Blood of type A has been mixed with each solution, and a precipitate has formed in the blue solution as the antibodies bind the A antigens in the blood. In contrast, no agglutination occurs in the yellow solution, and a diffuse orange solution results. In the bottom row, the reverse reaction is shown as a control. The type A blood was mixed with type A cells (left) and type B cells (right). Whereas no agglutination is observed on the left, clumping is evident on the right as the anti-B antibodies from the added blood bind the B antigens on the type-B cells. Special thanks to Laura Kolaneci from the blood bank at Brigham and Women's Hospital in Boston for her assistance with the photograph. Photograph by Robin Williamson.

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