This Month in the *Journal*

Gene-Gene Interaction Testing Framework, *by Millstein et al.* **(***p. 15***)**

As the search for gene variations that are associated with disease becomes more commonplace, the development of methods to identify genes that interact to cause an effect is crucial. Looking at the effects of single genes alone can be complicated by genetic heterogeneity or by the fact that the single effects simply are not large enough to be observed. Millstein et al. propose a new testing strategy that efficiently determines epistatic interactions of genes, both in the presence and in the absence of main effects. With simulations, this method—the focused interaction testing framework (FITF)—outperforms marginal tests and the multifactor dimensionality reduction (MDR) when dealing with additive, dominant, or recessive gene interactions. The usefulness of the strategy is demonstrated through analysis of an asthma cohort from the Children's Health Study. From a case-control comparison of polymorphisms in 12 candidate genes from pathways involving oxidative stress and inflammation, the marginal method identified a protective effect for a rare allele of *NQO1*. But, only FITF was able to significantly establish an association between asthma and a gene set consisting of *NQO1, MPO,* and *CAT*. Importantly, this association was also replicated in a new group of asthma patients from other ethnic backgrounds.

Human* LUNATIC FRINGE *Mutation, *by Sparrow et al.* **(***p. 28***)**

Spondylocostal dysostoses (SD) is a disorder in which somitogenesis is disrupted and vertebral segmentation is affected. Previously, mutations in two genes of the Notch pathway, *DLL3* and *MESP2,* were linked to SD1 and SD2, respectively. The Notch signaling pathway is critical in proper somite formation, and several mouse models that highlight this role have been made. Here, after recognizing the phenotypic similarities between mice deficient in *Dll3* and those lacking a third Notch gene, *Lfng,* Sparrow et al. sequence and identify a mutation in *LFNG* in a Lebanese family with recessive SD. *LFNG* encodes a fucose-specific β 1,3 *N*-acetylglucosaminyltransferase that posttranslationally modifies the Notch receptors. The mutation in exon 3 affects a residue conserved from *Drosophila melanogaster* to humans and is hypothesized to interfere with an aromatic ring in the predicted structure. Although this change does not destabilize the protein, it does render the enzyme inactive and disrupts the protein's proper localization to the Golgi apparatus. Accordingly, a cell-based system demonstrates that Notch signaling is not modulated by mutant *Lfng*.

Determinants of* SMN2 *Splicing, *by Cartegni et al.* **(***p. 63***)**

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder caused by mutations in the *SMN1* gene, which encodes the survival motor neuron (SMN) protein. A paralog of *SMN1, SMN2,* is nearly identical in sequence but has a T instead of a C at position 6 of exon 7, leading to an increased level of exon 7 skipping and the production of an unstable protein. Researchers hope to learn more about the mechanisms regulating this alternative splicing, in an effort to selectively increase the amount of full-length transcript produced by *SMN2* in patients lacking functional *SMN1*. Previous work has suggested that the splicing enhancer, SF2/ASF, has enhanced affinity for the sequence containing a C at position 6, resulting in the increased inclusion of exon 7 in *SMN1* transcripts. Alternatively, other experiments have demonstrated that it is actually increased binding of the splicing suppressor, hnRNP AI, to the *SMN2* sequence that leads to the skipping of exon 7. Cartegni et al. reevaluate the situation with the use of RNA affinity chromatography, in an effort to remove any experimental bias from the data. They conclude here that hnRNP A1 binds both sequences with equal strength but that SF2/ASF more preferentially binds to the *SMN1* sequence. This work provides new insight into the complex interactions that are involved in the regulation at splice sites.

D-*Bifunctional Protein Deficiency,* *by Ferdinandusse et al.* **(***p. 112***)**

D-bifunctional protein (DBP) is a homodimeric enzyme consisting of a dehydrogenase unit, a hydratase unit, and a sterol carrier protein 2-like unit. The protein is involved in the oxidation of fatty acids, and patients deficient in DBP are often severely affected with neonatal hypotonia and seizures. Although most patients with DBP deficiency die before the age of 2 years, there is a spectrum of phenotype severity, and there are some reported cases in which children survived several years longer. Ferdinandusse et al. present here a careful *in sil-*

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ico examination of the structural effects of 61 mutations and relate them to the severity of the phenotype observed. The deficiency can be broken down into three groups, depending on which DBP unit is affected. The DBP in type I–deficient patients does not have any dehydrogenase or hydratase activity. Type II–deficient patients lack a functional hydratase unit, and type III–deficient patients are deficient for dehydrogenase activity. Whereas type I–deficient patients all have insertions, deletions, or nonsense mutations that affect the overall structure of DBP, type II and type III mutations are usually missense mutations that uniquely alter one subunit of the protein. Changes in the active sites or in substrate and cofactor binding sites abolish activity, whereas changes in other sites have less of an effect on activity. Some mutations specifically alter the protein folding of one subunit or the sites of dimerization. From this collection of data, the authors are able to create a genotype-phenotype spectrum for DBP mutations that may be useful in predicting the disease outcome of new patients with DBP deficiency.

This Month on the Cover

In 1866, Gregor Mendel published his observations of hereditary traits in pea plants. His recognition of the dominant and recessive nature of variation in seed shape, seed color, seed coat color, pod shape, pod color, flower position, and plant height laid the groundwork for modern genetics.

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