This Month in the *Journal*

Fascioscapulohumeral muscular dystrophy (FSHD) is a progressive disorder characterized by muscle weakness and wasting that generally starts in the upper body and that can be asymmetric. Contractions of a chromosome 4q subtelomeric repeat, called "D4Z4," cause FSHD, but the mechanism by which this happens is not fully understood. This month in the *Journal,* van der Maarel and Frants give us a window into the complexity of this problem. It involves two alleles of the 4q subtelomeric region and a highly homologous repeat on chromosome 10qter, but contractions in only one of these three sequences are found in persons with FSHD. It is likely that the D4Z4 contraction alters the transcriptional control of other genes and that this leads to the FSHD phenotype. There are several models for how this occurs; van der Maarel and Frants discuss the evidence for each.

***Functional Consequences of* PRODH,** *by Bender et al.* (*p. 409*)

The proline dehydrogenase PRODH catalyzes the first step in proline degradation, and its encoding gene is located on chromosome 22q11 in the region deleted in velocardiofacial/DiGeorge syndrome (VCFS/DGS). Linkage of schizophrenia to this region has generated interest that was further fueled by the fact that individuals with VCFS/DGS are at increased risk of schizophrenia. Some groups argue that mutations in *PRODH* that lead to increased proline levels are associated with risk of schizophrenia, but others are not convinced. One difficulty in studying this association is that the key environment in which to study the effects of the *PRODH* variants is probably in the CNS, but plasma proline levels have been used as a proxy. To examine *PRODH* more directly, Bender et al. expressed 16 missense variants of *PRODH* in CHO-K1 cells and measured their functional consequences. Of these alleles, 11 have reductions in PRODH activity that range from moderate to complete, and, although data are limited, it appears that the severity of the mutation on PRODH activity may be correlated with plasma proline levels. The alleles used in this study were identified in people with hyperprolinemia, in people with schizophrenia, and in control individuals. A direct correlation between the severity of the mutation and the phenotype was not found, but the authors find it intriguing that three of four alleles associated with schizophrenia had a severe effect on PRODH activity. Perhaps these direct functional studies will pave the way for more-conclusive studies on the association between schizophrenia and *PRODH*.

Imprinting and Obesity, *by Dong et al.* (*p. 427*)

The need to control intrauterine growth is thought to have given rise to the development of genetic imprinting in mammals. This is supported by the fact that several genes involved in growth, such as *IGF2,* are imprinted. Some imprinting disorders, including Beckwith-Wiedemann and Prader-Willi syndromes, also include altered growth and body composition in their phenotypes. This relationship between genetic imprinting and control of body size and composition, therefore, makes it plausible that genes involved in common obesity might have a parent-of-origin effect. Dong et al. performed genome-wide parent-of-origin linkage analysis that examined obesity as a discrete trait and as a series of quantitative traits. Three regions—chromosomes 10p12, 12q24, and 13q32—appear to influence obesity only when transmitted from a specific parent. None of these regions was known to contain imprinted genes, so, in addition to their relevance to obesity, this type of study could facilitate the identification of additional imprinted regions in the human genome.

Accounting for Decay of Linkage Disequilibrium, *by Stephens and Scheet* (*p. 449*)

The PHASE algorithm has become a popular method for haplotype inference from unphased genotype data. Stephens and Scheet have updated this algorithm so that it takes into account locus spacing and the decay of linkage disequilibrium (LD) with distance. Because LD generally declines with distance but is sometimes punctuated by recombination hotspots, their approach uses a flexible model that allows for either scenario by estimating the recombination rate in each intermarker interval. Their new approach outperforms the previous version of PHASE and other haplotype-inference methods in an autosomal genotype data set and, to a lesser extent, in an X chromosome data set. This method can also be used to impute missing genotypes with a high degree of accuracy and is available in the PHASE (v.2.1.1) software package.

FLCN *and Spontaneous Pneumothorax,* *by Painter et al.* (*p. 522*)

When air is found in the pleural space in the absence of trauma or lung disease, it is known as "primary sponta-

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neous pneumothorax" (PSP), a condition that results in collapse of the lung. PSP can occur as part of an inherited connective tissue disorder, such as Ehlers-Danlos syndrome, but it is also reported as an isolated phenotype. Familial PSP is usually seen as an autosomal dominant trait with reduced penetrance, and most patients have emphysemalike changes called "bullae" in their lungs. Painter et al. made use of this fact to classify individuals in a family affected with PSP. They were able to do high-resolution computed tomography on several members of this family to identify those with bullae, who were then classified as "affected." A genome scan implicated a region on chromosome 17p that contained an interesting candidate gene, *FLCN*. This gene, which encodes folliculin, is a candidate because it is mutated in Birt-Hogg-Dubé (BHD) syndrome, a disorder associated with an increased risk of PSP. A frameshift mutation in *FLCN* was found only in the members of this family who had bullae. Thus, although PSP in general is considered to have fairly low penetrance, the penetrance of bullae in mutation carriers in this family is 100%. Mechanistically, the gene identification doesn't tell us much about the pathogenesis of PSP, because the function of folliculin is unknown. Clinically, though, this finding could have implications; because renal cancer and benign skin tumors are part of the BHD phenotype, Painter et al. argue that the potential for tumors in individuals with PSP needs to be considered.

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