This Month in the *Journal*

Familial Partial Lipodystrophy* (*Dunnigan Variety*),** *by Speckman et al.* (*p. 1192*)*; and* ***Mutations in the LMNA Gene, *by di Barletta et al.* (*p. 1407*)

Once known only to play a role in the maintenance of nuclear structure, the nuclear lamina has lately become a larger field of study. Mutations in the proteins that make up the bulk of the nuclear lamina, the lamins, are involved in Emery-Dreifuss muscular dystrophy (EMD; see the Bonne et al. [1999] entry in the References lists of both articles), Dunnigan-type familial partial lipodystrophy (FPLD; see the Cao and Hegele [2000] entry in the References lists of both articles), and dilated cardiomyopathy and conduction disease (DCM; see the Fatkin et al. [1999] entry in the References lists of both articles). The lamins are a family of highly conserved proteins that form a layer on the nucleoplasmic side of the inner nuclear membrane. They dimerize into coiled coils through a central rod domain and interact with chromatin and integral proteins of the nuclear membrane. Hyperphosphorylation of the lamins is correlated with dissolution of the lamina during mitosis, a process that is necessary but not sufficient for breakdown of the nuclear envelope. Lamins A and C are produced through alternative splicing of the message from *LMNA,* the gene involved in at least some forms of EMD, FPLD, and DCM. Production of lamins A and C is developmentally regulated; although both proteins are eventually found in most tissues, expression is stage specific and tissue specific.

EMD is a disorder characterized by early-onset contractures, progressive weakness in humeroperoneal muscles, and cardiomyopathy with conduction block. There are X-linked, autosomal dominant, and autosomal recessive forms of this disease. The X-linked form of EMD is caused by mutations in the gene for emerin (see the Bione et al. [1994] entry in the References list of the di Barletta et al. article), a protein that associates with the nuclear rim and that colocalizes with lamins A and C. The autosomal dominant form of EMD results from mutations in *LMNA* (see the Bonne et al. [1999] entry in the References lists of both articles). di Barletta et al. have studied several patients with EMD and have found *LMNA* mutations in all of them. Despite having mutations in the same gene, these patients presented with a range of clinical phenotypes, from a slight increase in creatine kinase levels to a severe muscular dystrophy. The inheritance pattern of the disease also differed between families, with some exhibiting autosomal recessive EMD and others exhibiting autosomal dominant forms of EMD with reduced penetrance. Thus, mutations in *LMNA* lead to several forms of EMD, but the distribution of the mutations along *LMNA* does not explain the differences in either phenotype or inheritance pattern.

FPLD, another disease associated with mutations in LMNA (see the Cao and Hegele [2000] entry, in the References lists of both articles, and the Shackleton et al. [2000] entry, in the References list of the Speckman et al. article), is an autosomal dominant disorder in which there is a loss of subcutaneous adipose tissue in the trunk and extremities. Speckman et al. have performed mutational analysis on 15 families with FPLD and have found that 14 had missense mutations in *LMNA,* 12 of these at residue R482. The remaining mutations were a G465D mutation and an R582H mutation, thereby localizing all known FPLD-causing mutations to the globular C-terminal domain of lamin A/C.

It has been proposed that the location of mutations in *LMNA* determines the resulting phenotype. In general, mutations associated with DCM are found in the beginning of the rod domain of lamin A/C; those associated with EMD are found from the C-terminal end of the rod domain into the C-terminal globular domain (although a severely truncated form of the protein leads to EMD); and those leading to FPLD are found only in the C-terminal globular domain. However, data presented in this issue indicate that the causative mutations for EMD, DCM, and FPLD are interspersed along *LMNA* and that none of the lamin A/C domains is specifically associated with any one disorder.

DCM and EMD both affect muscle tissue and may be part of a phenotypic spectrum; some patients with DCM have partial skeletal-muscle involvement, and some patients with EMD have cardiomyopathy. The relationship between these muscular disorders and FPLD, a disease of adipose tissue, is not clear. The varied phenotypic effects of *LMNA* mutations may be due to the tissue-specific and developmentally regulated expression levels and the spatial arrangement of the lamins within cells. Furthermore, mutations may disrupt tissue- or cell-specific interactions of LMNA, leading to localized defects. Additional mutational analyses of *LMNA* will be required in order to determine how mutations that are closely apposed lead to very different disorders.

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Effects of ATP7A Splice-Site Mutations, *by Møller et al.* (*p. 1211*)

Mutations in *ATP7A* lead to one of two copper-deficiency disorders: Menkes disease (MD) or the milder form, occipital horn syndrome (OHS). *ATP7A* encodes a copper-transporting P-type ATPase that moves copper through and out of cells. Mutations in *ATP7A*—and the resulting copper-transport deficiency—yield markedly elevated copper concentrations in the fibroblasts of patients with either disorder, as well as decreased copper levels in their sera and hair. Malfunction of copper-requiring enzymes apparently leads to the clinical manifestations of MD and OHS—namely, connective-tissue abnormalities and neurological degeneration. However, the explanation for the more severe MD phenotype has so far not been clear. Møller et al. have examined this problem through genotype-phenotype correlations for the *ATP7A* locus, using patients with similar splice-site mutations but different clinical outcomes. These patients, one with OHS and two with MD, all have mutations that are found at the same splice donor site of *ATP7A* and that lead to skipping of exon 6. By two different quantitative PCR methods, a small amount of correctly spliced *ATP7A* transcript (2%–5% control) was found in the patient with OHS. Although each patient with MD had *ATP7A* transcripts that were approximately the right length, the use of cryptic splice sites in both patients with MD was predicted to yield a severely truncated and completely nonfunctional protein. These results suggest that a very small amount of full-length *ATP7A* transcript—and the subsequent production of the encoded copper transporter—is sufficient to permit development of OHS, rather than the more severe MD phenotype.

Genetic Effects on Iron Stores, *by Whitfield et al.* (*p. 1246*)

Hemochromatosis is a common, autosomal recessive disorder characterized by excessive iron accumulation that can damage the heart, liver, pancreas, and pituitary gland. Periodic removal of blood can lower iron levels and prevent tissue damage, but early identification of affected individuals is essential for this treatment to be effective. The most common mutation in the gene for hemochromatosis, *HFE,* is C282Y. This tyrosine substitution abrogates binding of the HFE protein to beta-2-microglobulin and disrupts the transport of HFE to the cell surface. There, HFE would normally associate with transferrin receptor and modulate the uptake of transferrin-bound iron by the intestinal crypt. The role that another common *HFE* polymorphism, H63D, plays in hemochromatosis is less clear. Whitfield et al. have assessed the effects of the C282Y and H63D *HFE* genotypes, as well as age, sex, and ethnicity, on iron storage and metabolism. Although neither simple heterozygotes nor C282Y/H63D compound heterozygotes are likely to be affected by hemochromatosis, C282Y and H63D influence iron stores in the heterozygous state. However, their effect on iron stores accounts for only a small percentage of the phenotypic variance, indicating that there are other significant, but unidentified, genetic influences on iron stores. In response to the *HFE* polymorphisms, serum iron and transferrin saturation are altered to a greater extent than are ferritin levels, a result that raises doubt as to which measurement is the best index of body iron stores when one is assessing risk of iron overload or deficiency.

Surnames and the Y Chromosome, *by Sykes and Irven* (*p. 1417*)

For several hundred years, children have been given their father's surname, as a matter of tradition. Along with a last name, sons also inherit a Y chromosome. Since both surname and Y-chromosome haplotype should be inherited together, Sykes and Irven examined the correspondence between the two, using a sample of British individuals with the surname "Sykes." A single haplotype at the nonrecombining segment of the Y chromosome was carried by 43.8% of the Sykes sample, and this haplotype was not found in any of the control individuals. For this haplotype to occur with such prevalence, a single, patrilineal ancestor must have founded the Sykes sample, with little genetic divergence occurring since the lineage was founded. Sykes individuals without the common haplotype probably inherited the name because of nonpaternity, an event that was estimated to occur at an average rate of 1.3%/generation.

Chromosome 3 Cataract and BFSP2, *by Conley et al.* (*p. 1426*)*; and* ***Cataract Associated with BFSP2 Mutation,*** *by Jakobs et al.* (*p. 1432*)

Autosomal dominant congenital cataracts (ADCC) are a genetically heterogeneous group of disorders. Identified in the 15 genetic regions that have shown linkage to ADCC are several causative genes, including those for various crystallin proteins, connexins 46 and 50, gap-junction proteins, and a homeobox protein. Another

possible ADCC locus is found on chromosome 3q21.2-q22.3, and this region includes the gene for beaded filament structural protein 2 (BFSP2). Expression of BFSP2 is restricted to fiber cells of the ocular lens, making it a candidate gene for ADCC. Two articles in this issue of the *Journal* propose that mutations in BFSP2 lead to ADCC, making it the first cytoskeletal protein to be associated with cataracts. Conley et al. found an R287W mutation that alters a highly conserved positive charge in BFSP2. The ΔE233 BFSP2 mutation, identified by Jakobs et al., breaks a repeated, conserved pattern that is required for coiled-coil dimer formation. Although the function of BFSP2 is not yet known, both mutations are predicted to alter intermediate filament assembly in the ocular lens. Despite these predictions, the mutations differ in the age at onset of clinical symptoms. Many of the family members with the ΔE233 mutation developed cataracts in early childhood and had corrective surgery at age 3–5 years. In contrast, the onset of clinical symptoms in the family with the R287W mutation occurred at age 8–25 years.

May-Hegglin Anomaly Maps to 22q12.3-13.1, *by Martignetti et al.* (*p. 1449*)

In this issue of the *Journal,* we are proud to present one of the first studies to use the chromosome 22 sequence to localize a genetic region of interest. Martignetti et al. have studied a large family affected by May-Hegglin anomaly (MHA), a platelet disorder that can lead to bleeding episodes. The gene for MHA was mapped to a 6.6-cM region on chromosome 22q. Using the newly published chromosome 22 sequence, this group was able to order the genetic markers in the region and to determine the physical distance between the boundary markers. This analysis narrowed the region of interest to 700 kb and identified candidate-gene sequences within the region. In addition to greatly narrowing the MHA region, these studies illustrate the direct application of the Human Genome Project.

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