This Month in the *Journal*

Epigenotype–Phenotype Relationships in BWS, *by DeBaun et al.* (*p. 604*)

Through a registry-based case-cohort study, DeBaun et al. make epigenotype-phenotype correlations in Beckwith-Wiedemann syndrome (BWS). The cardinal features of this syndrome are midline abdominal-wall defects, macrosomia, and macroglossia (enlargement of the tongue) in neonates. Affected individuals are also at increased risk of specific types of cancer. Several genetic and epigenetic alterations in the chromosome 11p15 region have been associated with BWS, including abnormal methylation of a region upstream of *H19* and loss of imprinting of *IGF2,* but associations between these alterations and specific aspects of the BWS phenotype have not been thoroughly dissected. DeBaun et al. discover an association between abnormal methylation of *H19* and embryonal cancer. Bliek et al. (see reference in DeBaun et al.) previously had found evidence suggestive of this association, but DeBaun et al. show that this association is specific to the *H19* methylation defect and not to uniparental disomy of the region. DeBaun et al. also find associations between abnormal methylation of *LIT1* and macrosomia and midline abdominal-wall defects and between paternal uniparental disomy of 11p15 and hemihypertrophy, cancer, and hypoglycemia.

Mutation Studies, *by Huang et al.* (*p. 625*)

The simplest model invoked to describe mutations at microsatellite loci is the stepwise mutation model (SMM). This model assumes that microsatellites change by only one repeat unit per mutation and that the probabilities of addition and deletion are constant across alleles. Huang et al. directly detect mutation events, in pedigree genotypes, to investigate mutation patterns at >300 autosomal dinucleotide microsatellite loci in humans. They find evidence that microsatellite mutation events are actually much more complex than is suggested by the SMM. To begin, most (63%) mutation events are actually multistep rather than one-step. This is in contrast to results in previous studies, in which 15% of the mutations were multistep. In addition, longer alleles tend to lose repeat units, whereas shorter alleles tend to gain them. Overall, there was, in the study, a net loss of 59 repeat units, and the authors suggest that this size-dependent mutation bias may serve as a potential mechanism for allele-size constraint.

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TRIM32 ***Mutation Associated with LGMD2H,*** *by Frosk et al.* (*p. 663*)

Frosk et al. believe that they have identified a causative mutation for limb-girdle muscular dystrophy type 2H (LGMD2H). This relatively mild form of autosomal recessive muscular dystrophy, which has both an onset during the 2d or 3d decade of life and slow progression, has so far been identified only in the Hutterite population of North America. Fine mapping was used to limit the LGMD2H critical region, on chromosome 9q31-33, to a segment containing only four genes, which were then analyzed by single-stranded conformational analysis and DNA sequencing. Four polymorphisms were identified, but only one segregated with the disorder and was predicted to have an effect on the encoded protein. This polymorphism results in an aspartate-to-asparagine substitution in *TRIM32* and is found in all 35 affected individuals in the study. *TRIM32* is expressed in a variety of tissues, including skeletal muscle, and the mutation occurs at a conserved residue. On the basis of presence of a RING-finger domain, TRIM32 is thought to be an E3-ubiquitin ligase. This led the authors to speculate about potential disease mechanisms, including one based on the pathogenesis of Parkinson disease in individuals with mutations in *PARK2,* which also encodes an E3-ubiquitin ligase. There, neuronal death is believed to result from accumulation of proteins that are no longer ubiquitinated and that therefore are not directed to the proteasome for degradation. Similar toxic accumulations of proteins in muscle tissue may result from mutations in *TRIM32.*

Gene Defects in **LMNA** ***Cause AR-CMT2,*** *by De Sandre-Giovannoli et al.* (*p. 726*)

De Sandre-Giovannoli et al. have discovered in *LMNA* a mutation that is associated with Charcot-Marie-Tooth disorder, a group of peripheral neuropathies with muscle wasting, foot deformities, and walking difficulties due to reduced or absent tendon reflexes. This R298C missense substitution, seen on the same haplotype in three Algerian families, is the first mutation associated with autosomal recessive axonal Charcot-Marie-Tooth type 2 (CMT2). Further support for its involvement in CMT is the fact that homozygous *Lmna*-knockout mice show a peripheral-nerve histology similar to that seen in individuals affected with CMT, including a reduction in axon density and an increase in the presence of nonmyelinated axons. *LMNA* encodes lamin A/C, a nuclear-envelope protein. Mutations in this gene have also been

associated with limb-girdle muscular dystrophy, dilated cardiomyopathy, Emery-Dreifuss muscular dystrophy, and a lipodystrophy. The authors propose that distinct functional domains essential for the integrity of different cell lineages may exist in lamin A/C and that these domains may be the explanation for the range of disorders resulting from *LMNA* mutations. The domain in which a particular mutation falls may determine the resulting phenotype. The CMT2-associated mutation is located in the rod domain of lamin A/C, a highly conserved domain essential for protein/protein interactions, and it is, in fact, predicted to disrupt protein interactions. It seems likely that this domain is normally fundamentally involved in axon development or survival.

Agouti Signaling Protein and Human Pigmentation, *by Kanetsky et al. (p. 770)*

In mice, the agouti signaling protein (ASP) is known to influence, through its interaction with melanocyte-stimulating hormone receptor (MSHR), the relative production of the pigments eumelanin and pheomelanin. In humans, variation in the gene for MSHR, *MC1R,* is associated with pigmentation variation and with risk of melanoma and nonmelanoma skin cancers, but similar associations for agouti signaling protein have not been identified. In a sample of white individuals, Kanetsky et al. characterize genetic variation in *ASIP,* the gene for agouti signaling protein. Although the *ASIP* coding regions lacked variation, a polymorphism, g.8818A→G, was found in the 3′ UTR. The G allele at this position was significantly associated with dark hair and with brown eyes but not with susceptibility to melanoma. This report provides the first evidence of a role for *ASIP* in human pigmentation. Because ASP and MSHR interact, at least in mice, the authors note that a combination of *ASIP* and *MC1R* may show a stronger association with pigmentation than do the individual genotypes, although this has not yet been examined.

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