Penetrance of LHON, *by Hudson et al.* **(*p. 228*)**

Three mtDNA mutations are responsible for the majority of known cases of Leber hereditary optic neuropathy (LHON), but the reason for the variable penetrance of these variants is not completely understood. Whereas some work has suggested that different factors, including environmental interaction, genetic modifiers, and levels of heteroplasmy, have an effect on the disease, evidence also points to a role for the mtDNA haplogroup background on which the mutations are found. Hudson et al. collected data from a large number of families harboring one of the LHON mutations, to examine an association between mtDNA haplogroup and disease penetrance. They found significant differences in disease risk that depended on mtDNA background. In addition, 99% of the families with one of the mutations belonged to haplogroup J. Because the general European frequency of haplogroup J is 3%–15%, the authors suggested that, with other haplogroups, the mutation rarely causes LHON, so families with the mutation and that belong to another haplogroup would not be ascertained in such a study. Increased insight into the importance of haplogroup background will not only assist in better genetics counseling information but also suggests relationships between the LHON variants and the gene variants specific to each mtDNA haplogroup.

A Coding Function for the FSHD Repeat, *by Clapp et al.* **(*p. 264*)**

It is known that a reduction in the number of tandem repeats of the D4Z4 array causes facioscapulohumeral muscular dystrophy (FSHD). What remains a mystery is how a low copy number of the repeats leads to disease. One clue may reside within the ORF for *DUX4,* which resides within the repeats. Previous work has suggested that *DUX4* is not expressed, but it has been difficult to be certain because of the high number of paralogues in humans. Clapp et al. sought to provide evidence that the product of the ORF is indeed important. By first analyzing the D4Z4 orthologues in a wide range of mammals, they revealed that the array structure is the same among all the species examined but that the sequence outside the *DUX* ORF is divergent. In contrast, the *DUX* ORF shows evidence of conservation due to selection, suggesting an important role for the sequence. Because the authors discovered that mice do not have multiple D4Z4 family members as seen in humans, they hypothesized that an analysis of *Dux* expression in various tissues would be more straightforward. They found convincing evidence of bidirectional expression and evaluated the localization of the product via in situ hybridization. Their data support the importance of the *DUX4* ORF and provide new knowledge that may contribute to understanding the mechanism linking the D4Z4 arrays with FSHD.

Case-Control Association Testing with Related Samples, *by Thornton and McPeek* **(*p. 321*)**

A number of power advantages can be gained by combining family data into case-control studies. Various statistics have been proposed to account for pedigree information, to avoid an increase in false-positive results but also to retain the power gained from use of related individuals. Thornton et al. built on these statistics to develop a new quasi-likelihood score test, M_{QLS}. The M_{QLS} incorporates two new features that serve to improve it over other methods. First, it differentially considers unaffected controls and general-population controls, to take advantage of the assumption that the frequency of causative alleles is lower in controls known to be unaffected than in controls of unknown status. Additionally, M_{QLS} also assigns weights to data from individuals with affected relatives, even if genotyping data of the affected relatives are missing. This feature is based on the hypothesis that having affected relatives suggests an increased risk of carrying the causative allele. The authors demonstrate the utility of their method with simulations of various multilocus disease models with related individuals, and, when applied to data from the Collaborative Study of the Genetics of Alcoholism, M_{QLS} identified four SNPs that were significantly associated with alcohol dependence.

BDB Due to NOG Mutations, *by Lehmann et al.* **(*p. 388*)**

Brachydactyly (BDB), or shortness of the digits, is genetically heterogeneous and has been broken into subgroups on the basis of skeletal features. Mutations in *ROR2,* the gene that encodes the receptor tyrosine kinase–like orphan receptor 2 (ROR2), have been identified in some patients with BDB type B1 (BDB1), but other patients with BDB do not have *ROR2* mutations. Lehmann et al. chose to search for sequence variants in genes that encode proteins related to BMPR1B, because of a known interaction between ROR2 and BMPR1B. These included BMP1RB, its substrate GDF5, and NOG, an inhibitor of GDF5. In six BDB-affected families, the authors identified several heterozygous missense mutations in *NOG.* The authors showed how one of the mutations disrupts dimerization of NOG, whereas another mutation may interfere with the binding of substrates to the BMP receptors. Because of the unique

Am. J. Hum. Genet. 2007;81:i–ii. 0002-9297/2007/8102-0001$15.00
DOI: 10.1086/520725

nature of the shortness of the phalanges in these families with *NOG* mutations, the authors proposed that a new type of BDB, termed "BDB2," be used to describe the condition with such a phenotype.

A Functional SNP Affects an miRNA Target, *by Sethupathy et al.* **(*p. 405*)**

The binding of microRNAs (miRNAs) to sites within the 3′ UTR of genes has been shown to affect gene expression. Additional evidence demonstrates that SNPs within 3′ UTRs can influence expression through the disruption or creation of miRNA-binding sites. Sethupathy et al. chose to analyze the effects of one such SNP within the miR-155–binding site downstream of the gene *AGTR1*. Because it was known that miR-155 binding decreased *AGTR1* expression, a reporter assay was used to compare the expression effects of the intact binding site with those of the binding site containing the SNP and those of the deleted binding site. With the intact binding site, miR-155 decreased expression, but the miRNA had no effect on expression levels of vectors containing the SNP or in which the binding site was deleted. miR-155 is encoded on chromosome 21, so the authors hypothesized that, in cases of trisomy 21, miR-155 levels would be increased, leading to decreased *AGTR1* expression. They used MZ twins discordant for trisomy 21 to demonstrate that an extra copy of chromosome 21 did, in fact, lead to repression of *AGTR1*. The minor allele has been associated with hypertension, and increased *AGTR1* expression has been linked to cardiovascular disease. The effect of the SNP on the binding of miR-155 may be responsible for the SNP's association with disease.

This Month on the Cover

In 1977, Richard J. Roberts (Cell 12:1–8) and Phillip A. Sharp (Proc Natl Acad Sci USA 74:3171–3175) each reported a discovery for which they would later share the 1993 Nobel Prize in Physiology or Medicine. By hybridizing adenovirus late mRNA to DNA encoding the gene and visualizing with electron microscopy, they realized that the mRNA sequence was homologous to discontinuous segments of the DNA. This led to the conclusion that, unlike genes in prokaryotes, eukaryotic genes were made up of separate pieces of sequence that were spliced together. Shortly thereafter, in 1978, Walter Gilbert proposed that the regions of sequence that had been removed be called "introns" for "intragenic regions," whereas the sections of sequence that were retained in transcripts be called "exons" because they were expressed (Nature 271: 501). On the cover is an electron micrograph showing that, when mRNA is hybridized to DNA, the intron sequence forms loops, whereas the exon sequence binds to the mRNA. Special thanks to Margarita Siafaca and Phillip Sharp for the image.

Robin E. Williamson
Deputy Editor