This Month in the *Journal*

Is the Transportation Highway the Right Road for Hereditary Spastic Paraplegia?, *by Crosby and Proukakis* (*p. 1009*) and ***Kinesin Heavy Chain Mutation in SPG10,*** *by Reid et al.* (*p. 1189*)

Hereditary spastic paraplegia (HSP) encompasses a group of disorders, characterized by progressive spasticity of the lower extremities, that are due to degeneration of motor and sensory axons in the spinal cord. HSP is a heterogeneous condition, and, although a few HSP genes have been identified, a common underlying disease mechanism has not been obvious. Crosby and Proukakis review the known HSP genes and outline potential mechanisms that tie the HSP pathologies together. With the recent identification of new HSP genes, including the discovery by Reid et al. that the SPG10 form of HSP is caused by mutations in the kinesin gene *KIF5A*, Crosby and Proukakis develop a model whereby some forms of HSP may be caused by cellular transport defects.

Digenic Diseases and Holoprosencephaly, *by Ming and Muenke* (*p. 1017*)

Incomplete penetrance and variable phenotypic expressivity are two phenomena suggesting there are modifiers affecting phenotypic expression of "simple" genetic disorders. Using several examples, including holoprosencephaly, deafness, and retinitis pigmentosa, Jeffrey Ming and Max Muenke explore, in a review article, the evidence for these modifiers. They discuss the increasing data that digenic inheritance—where mutations in each of two unlinked genes can, in combination, cause a phenotype—plays a role in a variety of disorders. Further, they discuss additional modifiers, such as the environment, that may influence the expression of a phenotype. Ming and Muenke point out that there is overlap between Mendelian and multifactorial disorders and that, as we learn more about the factors behind variable expression of genetic disease, these types of disorders may be seen as opposite ends of a continuum of disease causation.

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Structure of Interphase Chromosomes, *by Lemke et al.* (*p. 1051*)

In school, we all learned that chromosomes in interphase are decondensed and not readily seen under a light microscope, but, as cells enter mitosis, their chromosomes compact into a form we can easily recognize. Using high-resolution multicolor banding (MCB) of chromosome 5, Lemke et al. examine the structure of interphase chromosomes, and their results bring into question these views of chromosome condensation during the cell cycle. They find that chromosomes in interphase are similar in length to metaphase chromosomes, rather than longer. The interphase chromosomes are, however, wider. Condensation may therefore influence chromosomes in terms of their width and volume, rather than their length. The MCB technique also reveals similar banding patterns in interphase and metaphase chromosomes, indicating that chromosome bands are not a feature of mitotic chromosomes but can be visualized at other stages of the cell cycle. This feature could make interphase chromosomes useful for diagnoses, as was demonstrated by Lemke et al., who were able to detect structural aberrations in cells from two cases with known abnormalities of chromosome 5.

Fingerprint of Phantom Mutations in mtDNA, *by Bandelt et al.* (*p. 1150*)

"Mutations" can sometimes be generated during the sequencing process itself. Bandelt et al. call such mutations "phantom mutations." In some cases, phantom mutations are so prevalent in mtDNA that phylogenetic analysis of the sequences is not meaningful. Bandelt et al. determine this through use of a filtering procedure that allows them to remove likely phantom mutations and to generate new phylogenetic networks without them. The procedure they use filters out well-established frequent mutations, which were inferred from other data sets, with the idea that, once these are removed, patterns of incompatibilities generated by phantom mutations will be more easily recognized as "commotion" in reduced median networks. The sites that are responsible for the links in the networks can then be reread or resequenced to determine whether the sequences at these positions are correct. Using as examples sequences published elsewhere, Bandelt et al. find that removing phan-

tom mutations reduces the number of reticulations in the phylogenetic networks, leaving behind a more tree-like structure. This procedure provides a quality check for mtDNA sequences before they are analyzed and interpreted.

Gene Identification in Nephronophthisis Type 4, *by Otto et al.* (*p. 1161*)

Nephronophthisis (NPHP) is the leading cause of chronic renal failure in young people. There are four known *NPHP* loci, and the disease variants can be distinguished from each other phenotypically, on the basis of the age at onset of end-stage renal disease. An exception to this is NPHP4, which is associated with a broad range of ages of onset and is linked to a recently identified locus on chromosome 1p36. To further refine this locus, Otto et al. used 16 affected families with evidence of linkage to *NPHP4*, and this enabled them to identify the *NPHP4* gene. Eleven distinct mutations, many of them loss-of-function mutations, were found in eight of the families. *NPHP4* is a widely expressed gene encoding a novel protein, dubbed "nephroretinin," that shows some conservation in a wide range of species, but its sequence does not reveal clues as to its function. NPHP can co-occur with retinitis pigmentosa in a disease called "Senior-Loken" syndrome. Two families affected by Senior-Loken syndrome were also found to have mutations in *NPHP4*, although these mutations do not suggest an explanation behind the presence of retinitis pigmentosa in these families and the absence in the others.

Demographic History and Haplotype Blocks, *by Wang et al.* (*p. 1227*)

Haplotype blocks, or block-like patterns of linkage disequilibrium, are thought to hold promise for the identification of complex disease genes in association studies. Careful choice of a limited number of markers based on the haplotype block structure could reduce the number of markers necessary to capture the genetic variation in a particular region. Although a great deal of interest has recently been directed at haplotype blocks, little is known about the mechanisms that have shaped their structure. Wang et al. provide data on these mechanisms. First, they developed a less ambiguous method of identifying haplotype blocks, which they did using a four-gamete test. From there, they were able to examine the effects of population parameters on haplotype block size. Through coalescent simulation and comparison of these results with published chromosome 21 data, Wang et al. show that, even in the absence of recombination hot spots, randomly distributed recombination events can lead to the formation of haplotype blocks. The structure of these blocks is affected by the demographic history of a population, so a reference haplotype map may not be useful across populations.

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