This Month in the Journal

Identification of the Cohen Syndrome Gene, by Kolehmainen et al. (p. 1359)

Cohen syndrome is a multifactorial disorder that exhibits phenotypic variability. In Finland, where this syndrome is overrepresented, the phenotype is highly homogeneous and includes microcephaly, developmental delay, retinal dystrophy, intermittent neutropenia, joint laxity, and a characteristic dysmorphic appearance. Kolehmainen et al. find that the homogenous phenotype in this population can be explained by a founder mutation in a novel gene, *COH1*. Only 1 of 27 Finnish cases did not carry the founder mutation, a 2-bp deletion that leads to premature protein truncation. In addition, one missense and seven truncating *COH1* mutations were found in Finnish and non-Finnish people with Cohen syndrome. The *COH1* protein is predicted to contain conserved N- and C-terminal domains that share homology to the yeast VPS13 protein, which is involved in membrane protein trafficking. Also sharing the VPS13 domains is chorein, a protein that is altered in another disorder that includes psychomotor deficiency and a hematological abnormality, choreoacanthocytosis. Although the functions of *COH1* and chorein are not yet clear, their homologies to VPS13 implicate vesicle-mediated sorting and intracellular protein transport pathways in the development of mental retardation syndromes.

Icelandic Matrilineal and Patrilineal Genealogies, by Helgason et al. (p. 1370)

In anthropological genetic studies, certain assumptions must be made about the evolutionary processes in the populations of interest. Helgason et al. examine the validity of these assumptions by determining how much a real population deviates from the expectations of the standard demographic models. They do this by using the Icelandic genealogy database to calculate demographic parameters that could be compared to the model expectations. Contemporary Icelanders were traced back to two cohorts of ancestors, one born between 1698 and 1742 and one born between 1848 and 1892. Although the Icelandic population increased five-fold during this period, which might be expected to be associated with low levels of genetic drift, the majority of contemporary Icelanders are actually descended from a minority of ancestors. This genetic drift has contributed to the differences, between Icelanders and their source populations, in terms of their haplotype frequency spectra for

mtDNA and the Y chromosome. The Icelandic population also exhibits a faster rate of evolution for mtDNA than for Y haplotypes, and this can be attributed to a shorter matrilineal generation interval. Also contributing to this matrilineal/patrilineal difference is a higher matrilineal intergenerational correlation in offspring numbers and generation intervals. Not only do these results give us insight into the development of the modern population of Iceland, they verify that this population deviates from standard demographic models. This deviation has implications for calculations, such as coalescent date estimates, that use these demographic models.

Hyperdeletion at Minisatellite MS1, Berg et al. (p. 1436)

Studies of minisatellite MS1 instability in yeast have previously suggested that this minisatellite is unusual in that it shows both meiotic and mitotic instability. In order to determine whether this is normally the case in humans, Berg et al. analyzed sperm DNA from men with MS1 allele sizes suitable for analysis. As with other minisatellites, high levels of germline instability were seen with MS1. This was not the case in blood samples from one of the sperm donors, indicating that, in contrast to the finding in yeast, this instability is restricted to meiosis. Two classes of instability were seen in the germline; the larger mutational changes appeared to arise by intra-allelic rearrangements that were complex, biased towards expansion, and fairly randomly scattered along the alleles. The smaller deletions, on the other hand, were clustered in homogeneous stretches of C-repeats, and the longer the C-repeat, the greater the instability. These results bring up some interesting questions, including: why are there differences in MS1 instability between yeast and humans? And how do long C-repeat arrays arise if they are prone to deletion?

Hand Osteoarthritis and *matrilin-3*, by Stefánsson et al. (p. 1448)

Stefánsson et al. suggest the first mutation that may contribute to a common form of osteoarthritis. This missense variant in *matrilin-3* was identified in a sample of Icelandic families affected by osteoarthritis of the hand. Genome scans yielded the strongest evidence for linkage on chromosome 2, and six genes were located in the region centered on the linkage peak. Included in these is *matrilin-3*, which shows increased expression in joint cartilage of people with osteoarthritis and which recently has been implicated in multiple epiphyseal dysplasia,

a disorder characterized by early-onset osteoarthritis. The *matrilin-3* variant identified by Stefánsson et al., T303M, was first identified when the gene was screened for variation in a small subset of the osteoarthritis sample. When the full sample was screened for T303M, an estimated relative risk of 2.12 was found for hand osteoarthritis. If this missense change is indeed a mutation, it does not appear to be the only variation in this genetic region that is involved in osteoarthritis; when carriers of T303M were removed from the linkage analysis, the chromosome 2 peak LOD score remained significant.

mtDNA Analysis of Dutch Pedigrees with LHON, by
Howell et al. (p. 1460)

Three primary mutations in the mitochondrial genes encoding the respiratory chain complex I account for ~95% of cases of Leber hereditary optic neuropathy (LHON) in people of European descent. Despite this fact, LHON does not present with a simple pattern of maternal inheritance but rather with a variable penetrance that is not fully understood. To better understand

this phenomenon, Howell et al. present the complete mtDNA sequences of 63 Dutch pedigrees with LHON. Almost 90% of these pedigrees carry one of the three primary LHON mutations. Sequence comparisons of pedigrees carrying the same mutation allow the authors to construct lineages of related families, and this information is used to estimate how often the major LHON mutations have independently occurred. Analysis of pedigrees containing the 14484 mutation revealed a group of four closely related genotypes that probably result from the same founder. A predominance of the 14484 mutation has been reported in French Canadian families with LHON, resulting from a founder effect, and the mtDNA sequences from these families indicate that they result from the same founder sequence as in the Dutch. It previously has been proposed that the 14484 mutation exhibits a higher penetrance when it is present on a haplogroup J background. The strong founder effect for this mutation may have influenced this association.

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