This Month in the *Journal*

What Is Causation?, *by Page et al.* **(***p. 711***)**

This month in the *Journal*, Grier Page and colleagues discuss their views on concluding causation in complex disease. Because biological causation can often not be proven in these diseases, it can be hard to move beyond a finding of association between a marker and a complex disease to a conclusion that the polymorphism actually causes disease. They believe that it is the responsibility of investigators to systematically remove confounders and sources of error, bias, and disequilibria before genetic causation is suggested. They also encourage the reporting of all relevant data to better allow biases to be identified and meta-analyses to be performed so that conclusions on causation are nearer at hand.

Multiple Origins of Ashkenazi Levites, *by Behar et al.* **(***p. 768***)**

Membership in three male castes in the Jewish community—the Cohanim, Levites, and Israelites—is determined by paternal descent. The Cohanim are considered to be the descendants of Aaron, Moses's brother, whereas the Levites are the descendants of Levi, a son of Jacob. Behar et al. find evidence of an unexpected event in the history of the Ashkenazi Levites, through an investigation of their paternal genetic history. Using the nonrecombining portion of the Y chromosome, they compare this population with other Jewish groups and neighboring non-Jewish populations. They find a haplogroup, R1a1, in over half of the Ashkenazi Levite samples that is at similarly high frequencies in Slavonic populations but at low frequencies in other Jewish populations. When compared in terms of genetic similarity, the Ashkenazi Levites cluster more with the Slavonic populations than with other Jewish populations, including Sephardi Levites. The clustered pattern of haplotypes within R1a1 is consistent with a founding event that occurred fairly recently and involved a small number of individuals. On the basis of these results, one could speculate that not all Levites are descendants of Levi but, rather, that there was a non-Jewish introgression of a small number of European individuals into the Ashkenazi Levite population and that their children were given Levite status. Modern-day descendants of these converts make up a large proportion of the Ashkenazi Levites today.

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CMG2 ***Mutations Cause JHF and ISH,*** *by Hanks et al.* **(***p. 791***),** *and* **CMG2** ***Mutations in JHF and ISH,*** *by Dowling et al.* **(***p. 957***)**

Juvenile hyaline fibromatosis (JHF) and infantile systemic hyalinosis (ISH) share many clinical features, including the deposition of an amorphous, hyaline (glassy and transparent) material of unknown origin. Both present with joint contractures, gingival hypertrophy, and papulonodular skin lesions, although ISH is a more severe disease that is often associated with death in infancy. Hanks et al. and Dowling et al. report that these diseases both result from mutations in capillary morphogenesis protein 2 (*CMG2*). Little is known about the physiological role of CMG-2, other than the fact that it seems to be involved in binding extracellular matrix proteins, such as laminin, and the fact that it can serve as an anthrax toxin receptor. Because of the potential role of CMG-2 in cell-cell and cell-matrix interactions, Dowling et al. examined the ability of patient fibroblasts to attach and grow on different substrates. They found that, in contrast to wild-type cells, fibroblasts from affected individuals were unable to attach to a laminin matrix. In the body, a disruption of cell-matrix interactions such as this could be the cause of JHF and ISH, but a definitive molecular explanation for the difference between ISH and JHF has not been found.

Alu ***Repeats and Human Duplications,*** *by Bailey et al.* **(***p. 823***)**

Compared with the genomes of other organisms that have been sequenced, the human genome is enriched for large blocks of segmental duplications. These duplications are biased toward genic sequences and are generally separated by at least 1 Mb of intervening sequence, rather than being tandemly arranged. To gain insight into the mechanism that might have generated this pattern of duplications, Bailey et al. did a comprehensive, genomewide survey of the duplication sequences and their junctions. They realized that the segmental duplications were enriched for *Alu* elements compared with the genome average and that many of the duplications terminated within *Alu*s. This finding, along with the fact that the *Alu* elements at the duplication junctions show higher levels of divergence than those internal to the duplicated sequence, suggests that the *Alu*s may have played a role in the origin and expansion of segmental duplications in the human genome through an *Alu*-mediated recombination mechanism. The observed enrichment was almost entirely accounted for by the younger *Alu* subfami-

lies, leading the authors to propose that the primate-specific burst of *Alu* retroposition activity that occurred 35–40 million years ago may have been responsible for the initial excess of segmental duplication events and that this kicked off cycles of nonallelic homologous recombination that led to the expansion of segmental duplications and resulted in the pattern of duplications we see today.

Four BP1-BP2 Genes in the PWS/AS Domain, *by Chai et al.* **(***p. 898***),** *and* **NIPA1** ***Mutations Cause SPG6 HSP,*** *by Rainier et al.* **(***p. 967***)**

Prader-Willi (PWS) and Angelman syndromes (AS) are caused by parent-of-origin–specific loss of expression of genes at chromosome 15q11-q13. Whereas PWS results from the loss of a set of paternally inherited alleles in this region, AS is associated with the loss of maternally inherited alleles. Because the full extent of the imprinted region is not known, Chai et al. examined 15q11-q13 and found four additional genes, two known and two unknown. These are *CYFIP1, GCP5, NIPA1,* and *NIPA2* (for nonimprinted in PWS/AS). As their names imply, *NIPA1* and *NIPA2* were found not to be imprinted, although the mouse orthologs of these genes, along with *Cyfip1,* show asynchronous replication that was random with respect to parental origin, a property generally associated with monoallelic gene expression. The *NIPA* genes are highly conserved in vertebrate species, although it appears that a transposition has altered the relative position of this four-gene block in humans. In addition to PWS/AS, this region is associated with other chromosomal rearrangements, including duplications, triplications, and inverted duplications. These genes are therefore candidates for involvement in the phenotypes associated with these rearrangements, as well as with other disorders that map to this region, including hereditary spastic paraplegia (SPG6).

In fact, Rainier et al. used the original *SPG6*-linked family to determine whether *NIPA1, NIPA2, GCP5,* or *CYFIP1* plays a role in hereditary spastic paraplegia (HSP). They found a missense mutation (T45R) in *NIPA1* that segregated with disease in this large pedigree. The mutated residue is conserved in mouse, chicken, and fish, and it is located at the end of the first of nine transmembrane domains in the protein. *NIPA1* was also sequenced in probands from an additional 68 families with HSP, as well as 13 suspected cases of sporadic HSP. The T45R mutation was found in an additional kindred, although the two mutation-carrying families do not appear to share ancestry, nor is there a shared haplotype in the region, so it appears that the mutation arose independently in the two families. Because the function of NIPA1 is not yet known, it is unclear how this mutation might lead to HSP. The fact that individuals with PWS or AS often have deletions that include *NIPA1* but do not exhibit progressive spastic paraplegia indicates that *NIPA1* haploinsufficiency does not cause this phenotype.

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