This Month in the *Journal*

Mutations in a Novel Transmembrane Protein Cause vLINCL, *by Gao et al. (p. 324); and* **CLN6** ***Encodes a Novel Predicted Transmembrane Protein (Report),*** *by Wheeler et al. (p. 537)*

The neuronal ceroid lipofuscinoses (NCLs) are a group of neurodegenerative disorders that are inherited in an autosomal recessive manner and that are characterized by progressive blindness, cognitive problems, and seizures. One form of NCL is variant late-infantile neuronal ceroid lipofuscinosis (vLINCL), which has symptom onset at 5–7 years of age and leads to death during the mid 20s. The locus for vLINCL, *CLN6,* has been mapped to chromosome 15q21-23. Gao et al. and Wheeler et al. use samples of affected families to narrow the *CLN6* locus and to identify a novel gene that is mutated in these families. In the study by Gao et al., 13 Costa Rican families share a haplotype, in the *CLN6* region, that includes a truncating mutation in exon 3 of the novel gene; Wheeler et al. find the same mutation in 7 Costa Rican families in their sample; and additional mutations, including missense mutations, small insertions, and small deletions, are identified in 9 additional families. A spontaneous mutation in mice, *nclf,* causes NCL-like disease and is identified, by both studies, as a single-base insertion mutation in the mouse homolog of *CLN6*. The mouse gene is highly identical to the human gene, and homologs are also found in a variety of other species, including chicken and *Xenopus*. The function of the encoded protein, dubbed "linclin" by Gao et al., is unknown, because it does not have any obvious protein relatives or functional domains. However, because mutations in *cln8* cause a phenotype in mice that is identical to that seen in *nclf* mice, it is likely that linclin works in the same functional pathway as does the protein encoded by *cln8*.

IL12 Deficiency, *by Picard et al. (p. 336)*

Familial cases of susceptibility to mycobacterial infection have been described, and, although there is more than one underlying genetic defect in these people, all result in impaired interferon-γ (IFNγ)–mediated immunity. Affected individuals are susceptible to bacille Calmette-Guérin (BCG) vaccine, nontuberculous mycobacteria, and *Salmonella* species. Mutations have been found in the genes for IFNγ receptor 1, IFNγ receptor 2, the β1 chain of IL12R, signal transducer and activator of transcription–1 (STAT1), and the p40 subunit of IL12, the last of which is encoded by *IL12B* and causes the only known human inherited cytokine deficiency. Only one person with IL12B deficiency has been described, and that individual carried a large homozygous deletion in *IL12B*. To find additional people with IL12 deficiency, Picard et al. use IL12 production as a screen and identify three patients, with a history of either BCG or nontuberculous myobacterial infections, who do not produce detectable amounts of the IL12p40 subunit or of p70, the full-sized heterodimer of IL12. One of these patients has a deletion identical to the one found previously. The other two, unrelated patients have the same one-base insertion in *IL12B,* which leads to a premature stop codon. Sequence analysis of additional affected families identified two further kindreds with the same insertion mutation. Not only are all of these individuals deficient for IL12, but they also may be deficient for IL23, a heterodimeric cytokine that is partially composed of the p40 subunit of IL12. Further studies will help to dissect the roles of these cytokines in immunity to mycobacteria.

Selection at the **FY** ***Locus,*** *by Hamblin et al. (p. 369)*

Because the major alleles of the Duffy blood group locus (*FY*) have striking patterns of geographic differentiation, *FY* is widely believed to be a target of natural selection. A force for this selection is thought to be provided by vivax malaria, because the *FY*O* allele confers resistance to this parasite. Through examination of the patterns of variation at *FY*—and comparison of these patterns to those at neutral loci—Hamblin et al. find further support for past selection at *FY* and evidence that there are previously unrecognized signatures of positive selection in this region. A sample from sub-Saharan Africa, in which the *FY*O* allele is fixed, shows evidence—based on two independent measures, the level of sequence variation and the frequency of nonancestral alleles—of directional selection. The variation in this sample is consistent with directional selection involving recombination. However, in a Chinese sample, in which *FY*A* is nearly fixed, and in an Italian sample, in which allele fixation has not occurred, there are unusual patterns of variation, particularly in the region 3′ to *FY.* The departures from neutrality in these samples do not fit a simple model of directional selection, as do the African samples, but they may represent a previously unrecognized signature of positive selection in the *FY* region. The identity of this selective force is unknown, because the function of the Duffy antigen receptor is not fully understood.

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Gdnf *and HSCR Haploinsufficiency,* *by Shen et al.* (*p. 435*)

Hirschsprung disease (HSCR) is a gastrointestinal (GI) disorder with symptoms including vomiting, severe constipation, and intestinal obstruction, and the main diagnostic criterion is the congenital absence of intrinsic ganglion cells in the GI tract. Mutations in the genes for endothelin 3 and its receptor, endothelin receptor type B, have been associated with HSCR, as have mutations in *c-RET* and its ligand *GDNF*. Mouse models have given some insight into the disease mechanism for HSCR, but they do not recapitulate the incomplete penetrance and variable expressivity of HSCR symptoms that are seen in affected people. Shen et al. identify *Gdnf* haploinsufficiency in mice as a better model to represent the expression of the HSCR-like phenotype. By crossing *Gdnf*+/− mice with strains that express β-galactosidase in enteric ganglion cells, they were able to accurately quantify the density of these cells along the GI tract in each strain. *Gdnf*+/− mice exhibit general hypoganglionosis that is more severe in the terminal gut and that is present as early as embryonic day 10. Strain-dependent differences in mortality associated with *Gdnf*+/− suggest that modifying loci play a role in the outcome of *Gdnf* mutations. Although the functional impairment of *Gdnf*+/− mice is variable, hypoganglionosis is associated with gut dysmotility and appears to be a defect that renders the mice susceptible to these HSCR-like symptoms. Therefore, the degree of hypoganglionosis in human HSCR may be an important determinant of the disease phenotype, although it is not currently possible to accurately assess the level of ganglion-cell density in the human GI tract.

Detection of Errors in Nuclear-Family Data, *by Douglas et al.* (*p. 487*)

In gene-mapping studies, inconsistencies with Mendelian inheritance are often used as the only means of screening for genotyping errors. Douglas et al. examine the accuracy of this screening procedure, through calculations of the expected probability of detecting a genotyping error or mutation in nuclear-family data. These probabilities are a function of the number of genotyped parents and offspring and of the marker-allele frequency distribution. Even under the best circumstances, a substantial fraction of genotyping errors are not detected with analysis of Mendelian-inheritance inconsistencies; these errors are especially difficult to detect when biallelic markers are used. Douglas et al. suggest that additional error-checking procedures, such as multipoint analysis or partial duplicate genotyping, may be used to ensure better error detection. Because both genotyping errors and pedigree errors can result in inheritance inconsistencies in nuclear families, distinguishing between the two sources of error can be difficult, especially in the early part of a study. The work of Douglas et al. enables researchers to estimate the expected number of inheritance inconsistencies. If any families in a study exceed the expected number, then pedigree error, rather than genotyping error, is the likely culprit, and these cases can be dealt with appropriately.

KATHRYN BEAUREGARD
Deputy Editor