This Month in the *Journal*

This month in the *Journal,* Jay Gargus contributes a review on monogenic channelopathies. Therein, he details the current understanding of this class of disorders, which may involve a range of organ systems, including the heart, skeletal muscle, or CNS. Dr. Gargus also argues that the genes involved in these channelopathies be considered as candidate genes for a range of polygenic disorders of the CNS.

Geography of Ashkenazi Mutations, *by Risch et al.* (*p. 812*)

Four lysosomal storage disorders (LSDs) affecting glycosphingolipids are found at an elevated frequency in the Ashkenazi Jewish population. Many have argued that this must be due to a carrier advantage that leads to maintenance of the causative mutations in the population. Others have suggested that the increased frequency is simply due to a founder effect and genetic drift. Risch et al. tease this apart through comparisons of LSDs with non-LSDs, in terms of their mutation frequency, coalescence times, and geographic distributions. No obvious differences were found between the groups for any of these parameters, as would have been expected if an LSD mutation were under different selective forces than the other mutations. Highly disparate geographic distributions can be found for mutations within single disease entities, which further supports a role for random genetic drift, rather than selection, in the distribution of these mutations.

PKCγ Mutations in SCA, *by Chen et al.* (*p. 839*)

Expansions of coding and noncoding repeat tracts are responsible for nine different forms of spinocerebellar ataxia (SCA), but there are additional forms of SCA for which no underlying genetic explanation has yet been found. Chen et al. recently mapped a locus for a new form of cerebellar ataxia to chromosome 19q13.4-qter in one family. Among the >300 genes in this region, *PRKCG,* which encodes PKCγ, was a compelling candidate gene for several reasons, including the fact that it is highly expressed in Purkinje cells of the cerebellar cortex, the major component of the CNS that exhibits degeneration in this disorder. Missense mutations were found in two affected families, including the one used to define the locus, and one sporadic case of SCA. Protein modeling studies predict that two of the three mutations, which were all found at conserved residues in exon 4, would affect protein function. Immunohistochemical studies on cerebellar tissue from an affected individual indicate that, in addition to low levels of PKCγ, there is a reduction in expression of *ATX1,* the gene involved in SCA1. Although these results support a new mechanism for the development of SCA that does not involve repeat tract expansions, they also suggest a possible link between the pathway leading to this form of SCA and those associated with other forms of this disorder.

Phenotypes Associated with Deletions of 17p13.3, *by Cardoso et al.* (*p. 918*)

Deletions of 17p13.3 cause a range of phenotypes, from isolated lissencephaly sequence (ILS) to the more complex phenotype Miller-Dieker syndrome (MDS). Although ILS generally does not include dysmorphic features beyond lissencephaly, individuals affected with MDS have facial dysmorphism and a range of congenital anomalies, in addition to a more severe grade of lissencephaly than is generally seen in ILS. Although haploinsufficiency for *LIS1* is involved in both disorders, it cannot explain the more severe grade of lissencephaly, nor the additional components of the MDS phenotype. To uncover the genetic differences between ILS and MDS, Cardoso et al. characterized 34 individuals with deletions of 17p13.3, including some with ILS, MDS, or no lissencephaly. They generated a detailed physical map of the region and used it to compare deletions from individuals with different phenotypes. This allowed them to define a 400-kb critical region that differentiates ILS from MDS. Within this region are eight genes that are consistently deleted in MDS, including two genes, *CRK* and *14-3-3ε,* that are deleted in individuals with the most severe grade of lissencephaly. Because a mouse model has implicated *14-3-3ε* in cortical development, Cardoso et al. speculate that deletions of this gene, possibly in combination with *CRK,* contribute to the more severe form of lissencephaly.

hTERT ***Haploinsufficiency in CdCS,*** *by Zhang et al.* (*p. 940*)

The telomerase reverse transcriptase (*hTERT*) gene is located in the same general region of chromosome 5p that is deleted in Cri-du-Chat syndrome (CdCS), a syndrome characterized by such things as psychomotor and mental retardation, microcephaly, and a characteristic catlike cry in newborns. Zhang et al. found that, indeed, one copy of *hTERT* was deleted in all 10 individuals with CdCS whom they examined. This haploinsufficiency was associated with decreased *hTERT* expression and accel-

0002-9297/2003/7204-0001$15.00

erated telomere shortening in lymphocytes from the affected individuals. Because progressive loss of telomeres limits cellular replication in vitro, Zhang et al. examined the proliferation potential of cells from the individuals with CdCS and found that they did have impaired replicative capacity, as indicated by a reduced number of population doublings before the cells became senescent. This loss of replicative capacity was rescued through expression of *hTERT* from a viral vector. In addition to premature senescence, CdCS-derived cells exhibited an age-dependent increase in chromosomal abnormalities, specifically chromosome fusions, that seem likely to result from the loss of telomeres. These *hTERT*-haploinsufficient cells should serve as a useful model for studies of in vivo telomerase function, as well as the role of the *hTERT* deficiency in the phenotype of CdCS.

The mtDNA Mutation A3243G, *by Torroni et al.* **(***p. 1005***)**

The mtDNA mutation A3243G is associated with a wide range of phenotypes, from maternally inherited diabetes and deafness to the severe MELAS syndrome. The factors influencing phenotypic expression of this mutation are unknown. Torroni et al. studied 35 unrelated Spanish carriers of A3243G, who had a range of phenotypes, to determine whether the mtDNA background on which this mutation is found influences the phenotypic expression of the mutation. In this group, the A3243G mutation was found on 34 individual haplotypes, indicating that the mutation arose independently in almost all cases. The lack of evidence for a founder mutation in this population suggests that A3243G is a severely deleterious mutation that is under negative selection. There was also no evidence that groups of individuals with a particular phenotype had mutations that clustered on a specific haplogroup, suggesting that the haplogroup on which A3243G is located does not influence the phenotypic expression of this mutation.

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