Review

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Mutation Watch

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As the year 1997 progresses, the cloning of classical mammalian mutations and the generation of new mutants continue at a breathtaking pace. The association of complex phenotypes with specific molecular defects is generating fascinating insights into basic biological processes and improved understanding of human genetic disease. This column will highlight new developments that may be of particular interest to the readers of *Mammalian Genome.*

Holoprosencephaly and Sonic Hedgehog

Three recent papers describing mutations in sonic hedgehog demonstrate a simple molecular basis for a syndrome of great morphological complexity, and provide a glimpse into the molecular events that comprise the developmental pathway from notochord to floorplate to adult organs. The mammalian genome contains three unlinked paralogs closely related to hedgehog, a segment polarity gene in Drosophila. Hedgehog proteins undergo an unusual autocatalytic proteolytic cleavage that transfers a cholesterol moiety to the active signalling protein (Porter et al. 1996). Targetted mutation of mouse sonic hedgehog locus (*Shh*) resulted in homozygous mice with severe malformations of forebrain and cranium characteristic of human holoprosencephaly, including single midline eye and nasal structures (Chiang et al. 1996). The morphological abnormalities are preceded by loss of bilateral symmetry in the expression pattern of three PAX genes. Human holoprosencephaly is a major malformation syndrome observed in spontaneously aborted fetuses at the frequency of 1/250 and as an inherited disorder with a frequency of 1/16,000. Five dominant HPE loci have been mapped. HPE3 on Chr 7q36 was isolated as a result of the mapping of SHH into the nonrecombinant region defined in a positional cloning project (Belloni et al. 1996). Identification of five independent mutations established SHH as the gene responsible for HPE3 (Roessler et al. 1996). Human HPE3 is inherited as a dominant disorder, apparently due to haploinsufficiency, while the mouse mutation is recessive. Translocations upstream of SHH are associated with mild phenotypes in human patients, apparently another example of position effects.

Of Tottering Mice and Persons

The voltage gated calcium channel alpha subunits are typical four domain ion channels and are encoded by a family of at least six mammalian genes. During a recent three month period, mutations in the alpha 1A gene were identified in two mouse mutants and three human neurological syndromes, providing classic examples of allelic heterogeneity in both species. Mutations at the mouse tottering locus result in ataxia, motor seizures, and absence seizures resembling petit mal epilepsy. A successful positional cloning effort identified a missense mutation leading to a proline-to-leucine substitution in the tottering allele and a splice site mutation in the allelic mutant, leaner (Fletcher et al. 1996). Analysis of these two mutants is also in press in this journal (Doyle et al. (1997)). Two human disorders, Familial Hemiplegic Migraine (FHM) and Episodic Ataxia Type-2 (EA-2), had previously been mapped to overlapping regions of chromosome 19p13. Exon trapping from a cosmid contig yielded two exons from the human gene CACNL1A4, and patient mutations were detected by SSCP and denaturing HPLC (Ophoff et al. 1996). Identification of a polymorphic CAG repeat in the CACNL1A4 gene and examination of repeat length in patients with spinocerebellar ataxia led to the discovery of an expanded repeat in patients (n = 21–27) compared with controls (n = 4–16) (Zhuchenko et al. 1997). Cerebellar dysfunction and ataxia is a common feature of four of the disorders associated with CACNL1A4, but the severity and time of onset vary considerably. The discovery of common molecular bases for clinical syndromes previously viewed as unrelated is becoming a familiar pattern. The critical role of ion channels in the CNS, and the heterogeneity among the five CACNL1A4 disorders, suggest that a broad spectrum of neurological syndromes may in the future be associated with different mutations in the voltage gated ion channels.

Inactivation of IsK Generates a New Shaker/Walzer Mouse

The close phenotypic similarity between a recently described induced mutant and the classical category of shaker/walzer mice is a reminder of the continuity underlying experimental work on the two types of models. The mouse *isk* gene encodes a 129 amino acid protein with a single transmembrane domain. When expressed in oocytes, the IsK protein has a low level of potassium channel activity with slow kinetics and atypical pharmacological properties. Among other sites, IsK is expressed in the inner ear, in the stria vascularis and vestibular dark cells where it is thought to contribute to regulation of the composition of the endolymph. Targetted inactivation of *isk* (Vetter et al. 1996) generated homozygous null mice with typical shaker/walzer behavior including bidirectional circling, hyperactivity, head bobbing, and inability to swim. The loss of Pryor's reflex suggests that these mice are also deaf. Degenerative changes were observed in a variety of cells of the inner ear. The two previously cloned spontaneous circling mutants, shaker1 and Snell's walzer, both result from mutations in members of the nonconventional myosin gene family. The *isk* null mice provide the first example of an ion channel mutation with specific effects on the inner ear.

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