Molecular Motors and Peripheral Neuropathies

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Several inherited peripheral neuropathies have been associated with mutations in molecular motor proteins, such as members of the kinesin family or cytoplasmic dyneins. Curiously, specific neuronal populations appear to be primarily affected in these diseases, despite the fact that the motor proteins are more widely expressed. The first description of a mutation in kinesin associated with a peripheral neuropathy was the report of a loss of function mutation in the *KIF5B* gene in a Japanese family diagnosed with a dominant form of Charcot-Marie-Tooth 2A or CMT2A (Zhao et al., 2001). KIF1B was expressed in motor neurons, consistent with an axonal defect, and the *KIF1B* gene was mapped near the known locus for CMT2A. A similar phenotype was seen with haploinsufficiency of KIF1B in a mouse model, suggesting that partial loss of function for KIF5B is sufficient to produce a neuropathy. However, subsequent studies in other CMT2A lineages failed to find a mutation in *KIF1B*, so there may be more than one gene near this locus associated with CMT2A.

In 2003, a study of patients with congenital fibrosis of extraocular muscles type 1 (CFEOM1) demonstrated that mutations in the gene encoding another kinesin family member, KIF21A, were the most common cause (Traboulsi & Engle, 2004), showing autosomal dominant inheritance and primarily affecting the occulomotor cranial nerve affecting eye movements. At least seven mutations in *KIF21A* have been reported in CFEOM1 and one additional mutation is associated with a different variant, CFEOM3 (Andrews et al., 2006). The seven mutations associated with CFEOM1 affect a set of amino acids implicated in KIF21A stalk formation and may destabilize the motor or affect interaction with specific cargos. KIF21A is widely distributed in the brain and some non-neuronal tissues, but preferentially affects the occulomotor nerve. This

again appears to be a case of haploinsufficiency, but the reason for selective vulnerability in occulomotor neurons remains to be determined.

Mutations in the dynein motor can also produce a selective peripheral neuropathy (Braunstein et al., 2010; Chen et al., 2007; Dupuis et al., 2009; Ilieva et al., 2008; Weedon et al., 2011). A nine-pair deletion in the cytoplasmic dynein heavy chain gene produces a preferential loss of proprioceptive sensory neurons (Chen et al., 2007). In mice with this mutation, motor neurons are spared even at advanced age. Two other mutations in dynein heavy chain similarly preferentially affect proprioceptive sensory neurons (Dupuis et al., 2009; Ilieva et al., 2008) while sparing motor neurons. Curiously, at least one mutation in dynein heavy chain also affects striatal neurons (Braunstein et al., 2010). This variation in phenotype with different mutations in the same gene may allow us to relate the molecular architecture of a protein to specific functional roles of a gene product. In turn, the genetics of disease provide insights into the selective vulnerabilities of different neuronal populations.

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