# Pleiotropic Effects of Trk Receptor Mutations

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Signaling through the RPTK family, Trk neurotrophin receptors activate multiple pathways and produce pleiotropic effects throughout the nervous system. In recent years, several human genetic diseases have been associated with loss-of-function mutations in specific Trk receptors (Reichardt, 2006). The phenotype is specific to the Trk receptor, based on the neurons that are normally dependent on a given Trk, as well as on the stage of development in which expression is critical and, potentially, on the genetic site of the mutation.

Several different types of mutation have been observed in the TrkA gene, including nonsense, missense, frame shift and splice site mutations. The mutations are distributed throughout the various domains of the TrkA receptor. These loss-of-function mutations have been associated with a syndrome of congenital insensitivity to pain with anhidrosis (CIPA) (Indo, 2010). CIPA is a hereditary sensory and autonomic neuropathy, presenting as an autosomal recessive genetic disorder that is characterized by recurrent episodic fever, anhidrosis, absence of reaction to noxious stimuli, self-mutilating behavior, and mental retardation. Loss of pain sensitivity is particularly pernicious, because serious injuries can occur without being detected. Phenotypes associated with CIPA result in large part from embryonic loss of NGF-dependent neurons in the PNS, including nociceptive sensory and sympathetic neurons, and in the CNS, including cholinergic neurons in the forebrain.

Mutations in the TrkB receptor gene present a very different phenotype. TrkB null mice die shortly after birth, whereas mice with haploinsufficiency survive and exhibit a distinctive set of phenotypes (Chao, 2003). These include expected phenotypes such as impaired LTP and loss of specific neuronal populations, but also less obvious changes. These include elevated striatal

dopamine, loss of mechanosensitivity, and obesity. These mouse phenotypes are consistent with human disease. For example, a dominant mutation in TrkB (Y722C) that impairs TrkB kinase signaling has been described in a patient with severe hyperphagic obesity and severe impairments in nociception, learning and memory (Yeo et al., 2004). Interestingly, point mutations in specific signaling motifs of TrkB can lead to different phenotypes. Thus, the Y816F mutation abolishes signaling through the PLCγ1 pathway (Ch. 25), leading to reductions in synaptic plasticity, but not affecting neuronal survival or the set of transcription responses that are mediated by the Ras/MAPK and PI3K pathways, because these are activated by a different domain (Minichiello, 2009) (see Figure 26-9A). Knowledge of the molecular architecture of the Trk receptors and delineation of distinct signaling modalities provide a molecular basis for understanding the phenotypes of mutations in mouse and human.

## References

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