Charcot Marie Tooth type 2B (CMT2B) disease is an autosomal dominant peripheral neuropathy whose onset is in the 2nd or 3rd decade of life, thus in adolescence or young adulthood. CMT2B is clinically characterized by severe symmetric distal sensory loss, reduced tendon reflexes at ankles, weakness in the lower limbs and muscle atrophy, complicated by ulcerations that often lead to amputations.

Four missense mutations in the gene encoding the small GTPase Rab7 cause the CMT2B neuropathy. Rab7 is a ubiquitous protein that regulates transport to late endosomes and lysosomes in the endocytic pathway. In neurons Rab7 is important for endosomal trafficking and signaling of neurotrophins, and for retrograde axonal transport. Recent data on CMT2B-causing Rab7 mutant proteins show that these proteins exhibit altered K\textsubscript{off} and, as a consequence, they are mainly in the GTP-bound state and bind more strongly to Rab7 effector proteins. Notably, expression of CMT2B-causing Rab7 mutant proteins strongly inhibit neurite outgrowth in several cells lines and alter NGF trafficking and signaling. These data indicate that Rab7 plays an essential role in neuronal cells and that CMT2B-causing Rab7 mutant proteins alter neuronal specific pathways, but do not fully explain why only peripheral neurons are affected in CMT2B. Here we discuss the current understanding of the molecular and cellular mechanisms underlying CMT2B, and we consider possible hypotheses in order to explain how alterations of Rab7 function lead to CMT2B.