Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions, and axon guidance.

We report that eight heterozygous missense mutations in TUBB3, encoding the neuron-specific beta-tubulin isotype III, result in a spectrum of human nervous system disorders that we now call the TUBB3 syndromes. Each mutation causes the ocular motility disorder CFEOM3, whereas some also result in intellectual and behavioral impairments, facial paralysis, and/or later-onset axonal sensorimotor polyneuropathy. Neuroimaging reveals a spectrum of abnormalities including hypoplasia of oculomotor nerves and dysgenesis of the corpus callosum, anterior commissure, and corticospinal tracts. A knock-in disease mouse model reveals axon guidance defects without evidence of cortical cell migration abnormalities. We show that the disease-associated mutations can impair tubulin heterodimer formation in vitro, although folded mutant heterodimers can still polymerize into microtubules. Modeling each mutation
in yeast tubulin demonstrates that all alter dynamic instability whereas a subset disrupts the interaction of microtubules with kinesin motors. These findings demonstrate that normal TUBB3 is required for axon guidance and maintenance in mammals.

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