RNA polymerase (Pol) III is a ubiquitously-expressed 17 subunit enzyme responsible for the synthesis of abundant small non-coding RNAs that function in protein synthesis and secretion, pre-mRNA splicing, and other important cellular processes. Despite the essential function of the enzyme, pathogenic mutations in multiple subunits cause a spectrum of neurodegenerative diseases. These Polr3-related disorders include a prevalent form of leukodystrophy with hypomyelination, hypodontia and hypogonadotropic hypogonadism (4H leukodystrophy) as distinguishing features along with cerebellar atrophy, myopia and short stature. Disease mechanisms are poorly understood and no treatment options are available. Recently developed mouse models of Polr3-related disease exhibit phenotypes consistent with the clinical features seen in patients and have provided important insights into the cellular and molecular bases of neurodegeneration. I will present our findings and discuss hypotheses concerning disease pathogenesis and the largely selective effects of Polr3 mutations on the central nervous system.