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Diverse molecular mechanisms of de novo TBR1 variants in au3()

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Keywords

Mice; Autistic Disorder; Intellectual Disability; Speech; Brain

Abstract

Heterozygous de novo variants in the TBR1 cause a rare form of autism called TBR1 Syndrome, which involces intellectual disability, behavioral disturbances, and speech and motor delays. TBR1 encodes a neuronally expressed transcription factor with a conserved T-box DNA-binding domain (T-box) and a T-Box transcription factor-associated domai (T-box_assoc) of unknown function. We sought to identify how TBR1 variants impacting different domains contribute to shared autism risk as well as clinical heterogeneity in TBR1 Syndrome. Using in vivo mouse models and in vitro functional assays, we demonstrate that TBR1 variants fall into at least three distict functional subclasses: (1) early-truncating variants that reduce TBR1 dosage in the developing brain; (2) missense variants in the T-box that increase TBR1 protein levels but impair DNA and protein binding; and (3) late-truncating variants that impair TBR1 protein function in a distinct manner from the T-box_assoc domain. These TBR1 variant subclasses lead to convergent and divergent brain morphological phenotypes in developing mice. Importantly, all heterozygous Tbr1 mutant mice show thinning of he anterior commissure (AC) axon tract in the brain, recapitulating a frequent MRI finding in TBR1 Syndrome patients and supporting the AC's role in broader autism etiology. Preliminary RNA-seq analysis indicates dysregulation of extracellular matrix, neurotrophin, and Wnt signaling genes in mutant Tbr1 embryonic cortex, and we identify chromatin accessibility signatures unique to mutant cortical glutamatergic neurons. These findings point to potential biological pathways that converge from different autism-associated variants and demonstrate the importance of modeling clinically relevant variants for understanding disease processes.