Ontogeny of Autism: altered developmental trajectories of dimensional features of autism in genetic mouse models of 22q11.2 copy number variants

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The precise mechanisms of autism spectrum disorders (ASDs) remain elusive. However, recently discovered genetic variants have provided an unprecedented entry point to delve into the genetic mechanisms of this developmental neuropsychiatric disorder. Chromosomal deletions and duplications, termed copy number variants (CNVs), are robustly and reproducibly associated with ASDs. While CNVs at human chromosome 22q11.2 are associated with high rates of ASDs, how 22q11.2-encoded genes contribute to this developmental neuropsychiatric disorder is still poorly understood. Gene dose alterations of small segments and individual genes in mice have identified several 22q11.2 genes that contribute to various dimensional aspects of developmental neuropsychiatric disorders. Our studies have identified the T-box transcription factor 1 (Tbx1) and Catechol-*O*-methyltransferase (COMT) as potential causative genes for dimensional aspects of ASDs. *Tbx1* heterozygous pups emit individually invariable call sequences as early as postnatal day 8 and such call sequences are ineffective in eliciting maternal approach. Moreover, *Tbx1* heterozygosity impairs reciprocal social interaction and working memory and enhances a repetitive behavioral trait. COMT over-expression selectively impairs the developmental maturation of working memory capacity during adolescence in mice. Our *in vivo* and *in vitro* data show that *Tbx1* heterozygosity and COMT over-expression affects postnatal neurogenesis. Taken together, defective postnatal neurogenesis is a potential neuronal mechanism through which various dimensional features of ASDs developmentally emerge.

References:

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