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Lecture Title: Genetic contributions to autism susceptibility: Disturbance in CAPS2-mediated BDNF secretion is associated with autism

Autism is a relatively prevalent neurodevelopmental disorder characterized by impaired social and communicative behavior. Twin studies and family studies suggested strong genetic contributions to autism susceptibility. Recent application of genome-wide technique has provided evidence that oligogenic interaction of many potentially-important candidate genetic loci is associated with the etiology of autism. My laboratory and colleagues have recently suggested that CAPS2, a gene within an autism susceptibility region on human chromosome 7, influences autism susceptibility. CAPS2 (also called CADPS2) encodes a protein (Ca²⁺-dependent activator protein for secretion 2) that is involved in trafficking of secretory vesicles containing brain-derived neurotrophic factor (BDNF), which modulates neuronal cell differentiation and survival, and synaptic plasticity. CAPS2-deficient mice exhibited no significant abnormalities in basic visual, auditory, olfactory and motor function. However, like autistic humans, CAPS2-deficient mice showed fewer social interactions with other mice, displayed heightened anxiety and reduced exploration in unfamiliar environments, and were hyperactive even in familiar surroundings. Absence of CAPS2 resulted in cellular defects mirroring those observed in the brains of some autistic patients, such as reduced development and impaired survival of certain neuronal cell-types including some GABAergic interneurons and cerebellar Purkinje cells. Application of BDNF rescued some of these cellular abnormalities. Notably, some autistic patients expressed an aberrantly spliced shorter CAPS2 form. The aberrant CAPS2 form expressed in primary cultured neurons was not transported into axons, suggesting a disturbance in local BDNF release from synapses of neurons expressing this aberrant CAPS2. We also identified seven rare non-synonymous single nucleotide polymorphisms (SNPs) within CAPS2 genome from autistic patients. Moreover, recent genetic studies reported several de novo copy number variations (CNVs) around the chromosomal region containing the CAPS2 locus. These findings highlight CAPS2 gene that might contribute to the development and/ or pathology of autism.