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Review

Distortion of the normal function of synaptic cell adhesion molecules by genetic variants as a risk for autism spectrum disorders

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ABSTRACT

Synaptic cell adhesion molecules (SCAMs) are a functional category of cell adhesion molecules that connect pre- and postsynapses by the protein-protein interaction via their extracellular cell adhesion domains. Countless numbers of common genetic variants and rare mutations in SCAMs have been identified in the patients with autism spectrum disorders (ASDs). Among these, NRXN and NLGN family proteins cooperatively function at synaptic terminals both of which genes are strongly implicated as risk genes for ASDs. Knock-in mice carrying a single rare point mutation of NLGN3 (NLGN3 R451C) discovered in the patients with ASDs display a deficit in social interaction and an enhancement of spatial learning and memory ability reminiscent of the clinical phenotype of ASDs. NLGN4 knockout (KO) and NRXN2α KO mice also show a deficit in sociability as well as some specific neuropsychiatric behaviors. In this review, we selected NRXNs/NLGNs, CNTNAP2/CNTNAP4, CNTN4, ITGB3, and KIRREL3 as strong ASD risk genes based on SFARI score and summarize the protein structures, functions at synapses, representative discoveries in human genetic studies, and phenotypes of the mutant model mice in light of the pathophysiology of ASDs.

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1. Introduction

Synaptic cell adhesion molecules (SCAMs) are a functional category of cell adhesion molecules that are localized at synaptic terminals at which they connect pre- and postsynapses during the process of synapse formation, maturation and modification by homophilic or heterophilic interaction through their extracellular cell adhesion domains. The typical example of their structure is, like many other cell adhesion molecules, single-pass transmembrane protein containing a single or multiple cell adhesion domains in the extracellular region and a short cytoplasmic tail. Many SCAMs have a PDZ binding motif at the carboxy-terminus where they bind to a PDZ domain of the synaptic scaffolding proteins. G protein coupled seven-pass transmembrane proteins, such as Celsrs (cadherin EGF LAG seven-pass G-type receptors) and Adgrbs (adhesion G protein-coupled receptor Bs), and Glycophosphatidylinositol (GPI) anchor proteins that lack cytoplasmic tails, such as Glypicans and Contactins, are also known as SCAMs. SCAM's function is not restricted to physical adhesion of synapses but also involved in the induction of intracellular signaling.

For the past decade, human genetic studies have implicated SCAMs in neuropsychiatric disorders, such as autism spectrum disorders (ASDs). ASDs are neurodevelopmental disorders characterized by persistent deficits in social communication and interaction across multiple contexts, and restricted and repetitive patterns of behavior. The prevalence of ASDs is more than 1% of all population (Christensen et al., 2016; Elsabbagh et al., 2012). While behavioral interventions, such as Applied Behavior Analysis (ABA), Floortime therapy derived from the Developmental Individual-difference Relationship-based model (DIR), and Relationship Development Intervention (RID) have been proven to be effective in ameliorating the symptoms of ASDs (Wieder and Greenspan, 2003; Gutstein et al., 2007; Goldson, 2016), at present, no pharmacological treatment is available for ASDs. About 15–25% of ASD cases are syndromic, and the rest of them are non-syndromic (Zuko et al., 2013). Countless studies have identified nucleotide changes, short insertions or deletions, and copy number variations (CNVs) in SCAM genes as candidate risks for ASDs. Many of them are rare mutations but some are common variants. The degree of risk for ASDs is variable among each genetic variant and the effects of common variants are generally milder (Bourgeron, 2015). Most of the genetic variants identified in SCAM genes cause or increase susceptibility for non-syndromic ASDs, but a few of them cause syndromic ASDs. Given the complexity of genetic variants, tremendous effort is needed when evaluating the strength of linkage of each gene to ASDs. SFARI GENE (https://sfari.org/resources/sfari-gene) run by SIMON FOUNDATION AUTISM RESERCH INITIATIVE (SFARI) and AutismKb (http://autismkb.cbi.pku.edu.cn/) run by Pekin University are online databases that collect information on ASD risk genes and are used to evaluate strength of linkage with ASDs in each candidate gene. SFARI GENE scores each candidate gene based on the strength of evidence after evaluation of each literature and classified into the following seven categories; category 1: high confidence, category 2: strong candidate, category 3: suggestive evidence, category 4: minimal evidence, category 5: hypothesized, category 6: not supported, and category s: syndromic. The criteria for category s is that the genes are consistently associated with additional features not required for an ASD diagnosis. Thus, genes in category s should be judged separately when discussing the strength of association with ASDs. If genes in category s have an independent evidence of non-syndromic ASDs, they are indicated with score before s. Table 1 shows SCAM genes listed on SFARI Gene Database. In the list, NRXN and NLGN family genes are generally highly scored. These proteins work cooperatively in synapses and the functions at synapses have probably been best studied among all SCAMs. CNTNAP family genes encode proteins structurally resembling Neurexin family proteins and they interact with a member of Contactin family protein encoded by CNTN gene, which are also listed with high scores. These evidences indicate that the structure and function of SCAMs more or less correlate with the strength of linkage with ASDs.

Table 1
Synaptic Cell Adhesion Molecules listed on SFARI Gene Database.

Gene Symbol	Protein	Chromosomal Locus	SFARI Score
NLGN1	Neuroligin-1	3q26.31	4
NLGN2	Neuroligin-2	17p13.1	NA
NLGN3	Neuroligin-3	Xq13.1	2
NLGN4X	Neuroligin-4X	Xp22.32-p22.31	3
NLGN4Y	Neuroligin-4Y	Yq11.221	4
NRXN1	Neurexin-1	2p16.3	2
NRXN2	Neurexin-2	11q13.1	4
NRXN3	Neurexin-3	14q24.3-q31.1	3
CNTNAP2	Caspr-2	7q35-q36.1	2S
CNTNAP3	Caspr-3	9p12	NA
CNTNAP4	Caspr-4	16q23.1	3
CNTNAP5	Caspr-5	2q14.3	4
CNTN3	Contactin-3	3p12.3	NA
CNTN4	Contactin-4	3p26.3-p26.2	2
CNTN5	Contactin-5	11q22.1	NA
CNTN6	Contactin-6	3p26.3	NA
ITGA4	Integrin, alpha 4	2q31.3	5
ITGB3	Integrin, beta 3	17q21.32	3
ITGB7	Integrin, beta 7	12q13.13	5
KIRREL3	Kin of IRRE-like protein 3	11q24.2	3
CDH8	Cadherin-8	16q21	4
CDH9	Cadherin-9	5p14.1	4
CDH10	Cadherin-10	5p14.2-p14.1	4
CDH11	Cadherin-11	16q21	NA
CDH22	Cadherin-like-22	20q13.12	4
PCDH8	Protocadherin-8	13q14.3	NA
PCDH9	Protocadherin-9	13q21.32	4
PCDH10	Protocadherin-10	4q28.3	4
PCDH15	Protocadherin-related-15	10q21.1	4
PCDH19	Protocadherin-19	Xq22.1	S
IL1RAPL1	Interleukin-1 receptor accessory protein-like 1	Xp21.3-p21.2	4
IL1RAPL2	Interleukin-1 receptor accessory protein-like 2	Xq22.3	4
CADM1	SynCAM-1	11q23.3	4
CADM2	SynCAM-2	3p12.1	NA
MDGA2	MAM domain-containing GPI anchor protein 2	14q21.3	4
SDK1	Sidekick-1	7p22.2	NA
NTNG1	Netrin G1	1p13.3	4Ss
SDC2	Syndecan-2	8q22.1	4
GPC6	glypican-6	13q31.3-q32.1	4
EPHA6	EPH receptor A6	3q11.2	5
EPHB2	EPH receptor B2	1p36.12	NA
EPHB6	EPH receptor B6	7q34	5
CLSTN3	Calsyntenin-3	12p13.31	5
SLITRK5	SLIT and NTRK-like family, member 5	13q31.2	NA
NRG1	Neuregulin-1	8p12	5

*SFARI score indicates as follows; 1: High Confidence, 2: Strong Confidence, 3: Suggestive Evidence, 4: Minimal Evidence, 5: Hypothesized, S: Syndromic, NA: not available.

In this review, we focus on SFARI listed SCAM genes of which scores are higher than 3 with special emphasis on NRXNs and NLGNs, and summarize the knowledge on these molecules from the aspect of the protein structures, synaptic functions, representative finding in human genetic studies, and phenotypes of these mutant model mice in light of the pathophysiology of ASDs.

1.1. NRXNs and NLGNs

Neurexins (NRXNs) are a family of single-pass transmembrane proteins that have originally been isolated as a black widow spider venom, α-Latrotoxin, receptors (Ushkaryov et al., 1992). Mammals have three NRXN genes (NRXN1, NRXN2, and NRXN3) all of which