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REVIEW

MONOGENIC MOUSE MODELS OF AUTISM SPECTRUM DISORDERS: COMMON MECHANISMS AND MISSING LINKS

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Abstract—Autism spectrum disorders (ASDs) present unique challenges in the fields of genetics and neurobiology because of the clinical and molecular heterogeneity underlying these disorders. Genetic mutations found in ASD patients provide opportunities to dissect the molecular and circuit mechanisms underlying autistic behaviors using animal models. Ongoing studies of genetically modified models have offered critical insight into possible common mechanisms arising from different mutations, but links between molecular abnormalities and behavioral phenotypes remain elusive. The challenges encountered in modeling autism in mice demand a new analytic paradigm that integrates behavioral analysis with circuit-level analysis in genetically modified models with strong construct validity.

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Key words: autism mouse models, Mecp2, Fmr1, Ube3a, Pten, Shank3.

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INTRODUCTION

Autism spectrum disorders (ASDs) are a group of conditions primarily characterized by impairments in social communication and engagement in restricted, repetitive behaviors (American Psychiatric Association, 2013). Common comorbidities include intellectual disability, epilepsy, anxiety, sleep disturbances, abnormal sensory processing, motor impairments, and gastrointestinal complaints (Argyropoulos et al., 2013). ASDs are heterogeneous in nature, as patients display a wide range of symptom severity and prognosis (Lord et al., 2000; Howlin et al., 2004), which is mirrored by hundreds of identified causal or potentially causal genetic variants (Persico and Napolioni, 2013; Willsey and State, 2015). Unfortunately, most genetic mutations are rare or private (i.e. observed only in a single family). Both the phenotypic and genetic heterogeneity present significant obstacles to understanding the disorders and attempts to associate phenotypic severity with genetic differences have had mixed results (Chaste et al., 2014; Chang et al., 2015). While genetics undoubtedly play a substantial role in ASD pathophysiology, the inexplicable phenotypic heterogeneity and incomplete concordance rates between monozygotic twins (Hallmayer et al., 2011), suggest that non-genetic factors may also contribute to the etiology.

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Abbreviations: ASDs, Autism spectrum disorders; CNV, copy number variant; eIPSC, evoked IPSC; FMRP, fragile X mental retardation protein; FXS, fragile X syndrome; LOH, loss of heterozygosity; LTD, long-term depression; LTP, long-term potentiation; mEPSCs, miniature excitatory postsynaptic currents; mGluRs, metabotropic glutamate receptors; mIPSCs, miniature inhibitory postsynaptic currents; MSNs, medium spiny neurons; PHTS, PTEN hamartoma tumor syndromes; TSC, tuberous sclerosis complex.

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A recent survey indicates that 1 in 68 children in the United States are diagnosed with ASDs, a drastic increase from previous estimates over the last few decades (Centers for Disease Control and Prevention, 2014). While there is considerable debate regarding the degree to which the increase in prevalence can be explained by broadened diagnostic criteria (King and Bearman 2009), increased awareness (Liu et al., 2010), or changes in environmental factors (Nevison, 2014), there is nevertheless an ever-increasing urgency to determine the underlying pathophysiology and develop safe, cost-effective interventions for ASDs to improve patient outcomes. Regardless of the source of the rising prevalence, it is an issue of great public health concern, as the lifetime cost of ASD-related care ranges from approximately $1.4 million to $2.2 million per individual (Buescher et al., 2014).

Studies in human clinical populations have been and continue to be critical for understanding the genetic and non-genetic contributions to ASDs (Willsey and State, 2015). However, animal models are needed determine the mechanisms leading to abnormal functioning. Although human brain imaging techniques have identified regions and circuits involved in the disorders (e.g. Karten and Hirsch, 2014), animal models provide opportunities for direct manipulation of these brain regions and circuits to test their precise functions. In current clinical practice, ASDs are defined by behavioral symptoms that are uniquely human and there is no singular neuropathological hallmark identified so far that is pathognomonic, so it is challenging to determine the validity of an animal model of autism. Nevertheless, recent successes in identifying genes implicated in ASDs have paved the way to explore the neurobiology underlying the disorders using animal models.

GENETIC MUTATIONS IMPLICATED IN ASDS

Substantial progress has been made to understand the genetic causes of ASDs. Genes implicated in syndromic forms of autism were first identified in the 1990s. Subsequent genomic copy number variant (CNV) analysis in the 2000s generated a list of rare but highly penetrant CNVs associated with ASDs. Pathogenic CNVs are estimated to account for ~10% of non-syndromic ASDs (Devlin and Scherer, 2012). Most recently, whole exome and whole genome sequencing techniques have been utilized to identify rare *de novo* and inherited sequence variants in hundreds of genes from ASD subjects. Despite the inability to establish a causal role for the majority of these sequence variants, a subset of new genes have emerged as strongly causal because *de novo* loss-of-function and likely-gene-disrupting mutations are found in multiple affected patients and are absent in a large number of controls (Table 1). In other cases, mutations that likely disrupt protein function are found in genes that are implicated in other neuropsychiatric disorders. Functional annotation of these genes immediately suggests the following molecular features: (1) neuronal ion channels and receptors; (2) synapse-related cytoskeleton and scaffolding proteins; (3) epigenetic and transcriptional regulators; (4) post-translational protein modifiers and regulators. An important question is whether or not the mutations in these genes share a common molecular and/or circuit-level mechanism underlying the pathophysiology of ASDs. Modeling these mutations in animal models is essential to address this question.

Table 1. List of genes with strong evidence for syndromic and non-syndromic ASDs

Syndromic ASDs		Non-syndromic ASDs	
Gene name	Locus	Gene name	Locus
ADNP	20q13.13	ASH1L	1q22
ADSL	22q13	ASXL3	18q11
AHI1	6q23.3	CACNA1H	16p13.3
ALDH5A1	6p22	CACNA2D3	3p21.1
ANKRD11	16q24.3	CHD2	15q26
ARID1B	6q25.1	CHD8	14q11.2
ARX	Xp22.	CNTN4	3p26
ASXL3	18q11	CNTNAP2	7q35
CACNA1C	12p13.3	CUL3	2q36.2
CDKL5	Xp22	DEAF1	11p15.5
CHD2	15q26	DSCAM	21q22.2
CHD7	8q12.2	DYRK1A	21q22.13
CNTNAP2	7q35-q36	GABRB3	15q12
DHCR7	11q13	GRIN2B	12p12
DYRK1A	21q22.13	GRIP1	12q14.3
EHMT1	9q34.3	KATNAL2	18q21.1
FMR1	Xq27.3	KDM5B	1q32.1
HDAC4	2q37.3	KMT2A	11q23
KMT2A	11q23	KMT2C	7q36.1
MECP2	Xq28	MED13L	12q24.21
NIPBL	5p13.2	MET	7q31
PTEN	10q23.3	MSNP1AS	5p14.1
RAI1	17p11.2	MYT1L	2p25.3
SCN1A	2q24.3	NRXN1	2p16.3
SYNGAP1	6p21.3	POGZ	1q21.3
TSC1	9q34	PTCHD1	Xp22.11
TSC2	16p13.3	RELN	7q22
UBE3A	15q11.2	SCN2A	2q23
VPS13B	8q22.2	SETD5	3p25.3
		SHANK2	11q13.3
		SHANK3	22q13.3
		SUV420H1	11q13.2
		SYNGAP1	6p21.3
		TBR1	2q24

WHAT CONSTITUTES A VALID ANIMAL MODEL FOR ASDS?

Animal models of psychiatric disorders have classically been evaluated on three criteria, which were first applied to mouse models of depression: construct, face, and predictive validity (Willner, 1984). Ever since these criteria were articulated, they have been interpreted in a variety of ways (Belzung and Lemoine, 2011), making it worth elaborating on their precise meanings and their relationships to animal models of ASDs.

Construct validity, for our purposes, refers to the rationale behind the creation of the model and its ability to recapitulate the etiology of the disorder. For instance, a model of ASD with high construct validity mimics a

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