

## INVITED REVIEW

# Genetics and genomics of autism spectrum disorder: embracing complexity

Silvia De Rubeis<sup>1,2</sup> and Joseph D. Buxbaum<sup>1,2,3,4,5,6,\*</sup>

<sup>1</sup>Seaver Autism Center for Research and Treatment, <sup>2</sup>Department of Psychiatry, <sup>3</sup>Department of Genetics and Genomic Sciences, <sup>4</sup>Department of Neuroscience, <sup>5</sup>Friedman Brain Institute and <sup>6</sup>The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, 1468 Madison Avenue, New York, NY 10029, USA

\*To whom correspondence should be addressed. Tel: +1 2122410200; Fax: +1 2128284221; Email: joseph.buxbaum@mssm.edu

## Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder (NDD) characterized by impairments in social communication and social interaction and the presence of repetitive behaviors and/or restricted interests. ASD has profound etiological and clinical heterogeneity, which has impeded the identification of risk factors and pathophysiological processes underlying the disorder. A constellation of (i) types of genetic variation, (ii) modes of inheritance and (iii) specific genomic loci and genes have all recently been implicated in ASD risk, and these findings are currently being extended with functional analyses in model organisms and genotype–phenotype correlation studies. The overlap of risk loci between ASD and other NDDs raises intriguing questions around the mechanisms of risk. In this review, we will touch upon these aspects of ASD and how they might be addressed.

## Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder (NDD) characterized by persistent deficits in social communication and interaction and the presence of repetitive behaviors and/or restricted interests. ASD manifests with broad phenotypic variability and evolves along heterogeneous developmental trajectories (1). Severity of ASD symptoms is variable and inversely correlates with adaptive functioning (2). Language abilities and cognitive function, two domains strongly affecting adaptive behavior (2,3) and predicting later outcome (4), also have a broad range in ASD. For example, ~30% of individuals with ASD remain minimally verbal throughout life (5) and ~60% have co-occurring intellectual disability (ID) (3). Other NDDs [e.g. attention deficit hyperactivity disorder (ADHD) and schizophrenia], neurological disorders (e.g. motor deficits, sleep disturbances and epilepsy) and medical conditions (e.g. gastrointestinal problems, congenital anomalies and allergy) are also common in ASD although highly variable (6). Here, we will discuss recent findings on the genetic architecture of ASD and its complex relationship to phenotype.

## Etiological heterogeneity

Studies making use of twin pairs (7–11), families (12) and populations (11,13) have provided estimates that over half of risk of developing ASD resides with genetic variation, which explains the elevated recurrence risk of ASD and associated phenotypes observed in families (13).

Diverse forms of genetic variation, differing in frequency (i.e. common, rare and very rare variation), mode of inheritance (i.e. autosomal inherited, X-linked and *de novo* variation), type of variation [i.e. structural—including aneuploidy, copy number variation (CNV), indel, and single-nucleotide variation] and mode of action (additive, recessive, dominant and hemizygous), all shape risk architecture (11,14,15). Common variation in the form of single-nucleotide polymorphisms (SNPs) has a very weak effect when a given SNP is considered individually (16). As a result, genome-wide association studies carried out to date have been underpowered due to the weak effect of individual SNPs (16) and, hence, insufficient sample size [the largest study has analyzed 2,705 families (16)], and have failed to identify reproducible SNP

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associations (16–20). However, polygenic risk due to a large number of SNPs is a major determinant of the variance for ASD (11,12,16) (Fig. 1).

Rare genetic risk variation identified to date, in contrast, has a very substantial effect on individual risk. Recent whole-exome sequencing analyses of large ASD cohorts (21–29) have expanded the repertoire of known genes harboring ASD-linked mutations that were previously identifiable only by traditional genetic approaches and targeted sequencing (14,15).

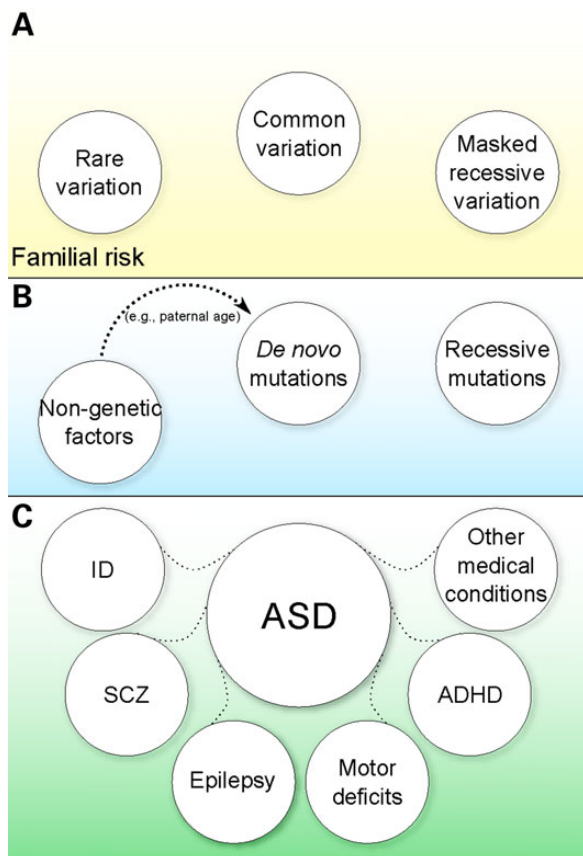
At this point, it is clear that rare microscopically detectable chromosomal rearrangements (14,15), submicroscopic deletions or duplications (CNV or smaller structural variation) (27,29–32), single-nucleotide variation (SNV) and small deletions and duplications (indels) (21–26,33–35) all contribute to risk.

Rare variants can be inherited from unaffected parents (26,28,34,35) or arise as *de novo* mutations during the meiotic divisions of gametogenesis (21–27,30–32,36,37). Autosomal *de novo* loss-of-function SNV has been identified that acts in a dominant manner and carries a large burden for individual risk, with odds ratios of 20 or above for genes identified to date (24,26). Transmitted variants that disrupt protein function can also have a strong influence on risk when inherited and acting dominantly (odds ratios ~3) (26) or if resulting in biallelic

disruption and acting in a recessive (34,35) or X-linked (34) manner (odds ratio above 2).

Beyond genetic factors, there is evidence for a role of non-genetic sources of risk in ASD, although the mechanisms underlying these associations are still unclear. Paternal (38–41) and maternal (41,42) age have been independently associated with ASD risk. In the case of paternal age, one mediating mechanism lies in the increased rate of *de novo* SNV and CNV with advancing paternal age (22,24,25,43,44). The factors contributing to the maternal age effect, in contrast, have been less explored, but advancing maternal age is a known risk factor for chromosomal aberrations (45).

These findings are consistent with a model whereby inherited variation, both common (11) and rare (26,28), defines a substrate of susceptibility, and additional high-risk genetic (including *de novo*, recessive and X-linked variation) and/or non-genetic factors then act on this substrate to surpass the liability threshold that results in ASD (Fig. 1). Gaugler *et al.* (11) provide a clear example by estimating the probability for carriers of *de novo* mutations (CNV or SNV) to be affected if they were not carriers of these mutations, using a well defined ASD cohort (11). They found that ~80% of the individuals with a *de novo* CNV and an ASD diagnosis would not be affected if they did not have the CNV, and 57% of the individuals with a *de novo* loss-of-function SNV and an ASD diagnosis would not be affected if they did not have the SNV, but common variation, in the form of SNPs, contributes in either case. The model helps in the understanding of the relatively high risk for siblings of individuals diagnosed with ASD (13,46), the increased mutational burden in ASD probands compared with their unaffected siblings (22,28), etiological heterogeneity even within pairs of affected siblings (47,48) and, as we shall discuss further, the variable expressivity of certain loci (49,50) (Fig. 1).



**Figure 1.** Genotype–phenotype model in ASD. Heritable common and rare variation (A) define familial risk and a liability index. When additional risk variation, for example in the form of rare variation in autosomal recessive or X-linked genes (the latter in males) and/or *de novo* deleterious variation, occurs in this familial risk environment (B), the liability is increased over a threshold resulting in disease. Non-genetic factors can contribute as well, and some such factors are now beginning to be understood (e.g. paternal age increasing the likelihood of *de novo* variation). The concerted action of familial background (A) and high-risk events (B) defines the varying clinical manifestations of ASD (C).

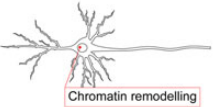
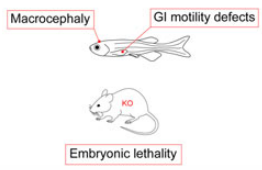
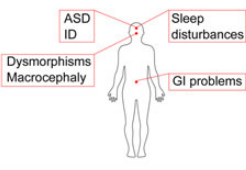
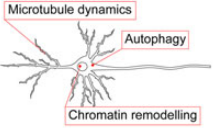
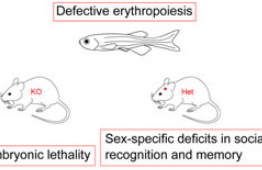
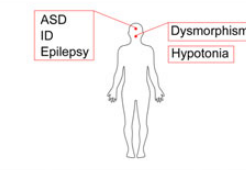
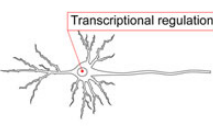
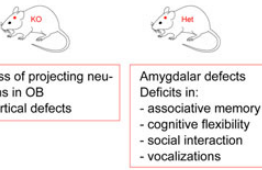
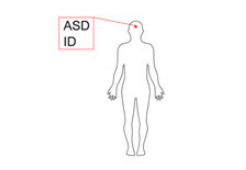
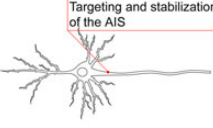
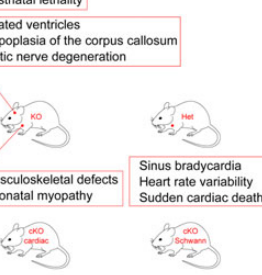
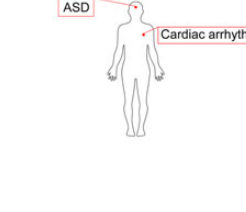
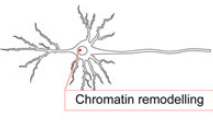
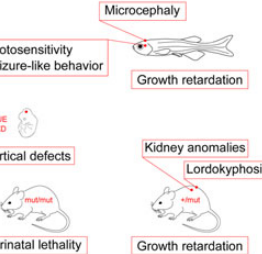
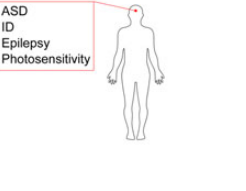
## From gene discovery to model organisms and human phenotypes

Simulations based on the observed number of recurrently disrupted genes have estimated that there are some 600–1200 ASD risk genes (21,24,26,51). Studies to identify additional ASD risk genes are ongoing, but as these genes are distributed along a gradient of effect size, it will become increasingly difficult to identify new genes. To date, in addition to causal and highly penetrant genes and genomic loci identified before whole-exome sequencing (15,30), over 50 high-risk genes have emerged from the large-scale sequencing studies (21–26), most under a model of autosomal dominant variation. Genetic manipulations of these genes in model organisms and subsequent functional analyses are beginning to provide insights into their biology and are highlighting complex phenotypic associations with these genes.

Looking at even just a handful of the top genes reveals an unexpected complexity (Fig. 2, see legend for a detailed discussion). For example, although *ADNP* is essential for brain development (64) and *Adnp*<sup>+/-</sup> mice display a sex-related impairment in learning and memory behaviors (66), the most prominent phenotype of *ADNP* knockdown in zebrafish is defective erythropoiesis (63).

*ANK2* has been consistently associated with ASD (22,26,80) and also with cardiac arrhythmia (OMIM no. 600919) (78). Consistently, neurological (76) and cardiac (77,78) phenotypes have been described in mouse models with a disruption of this gene. As most *ANK2* missense mutations in patients with cardiac arrhythmia map to both cardiac and neuronal isoforms (88), ASD and cardiac arrhythmia might be common manifestations of a distinct nosological entity.

Mutations in *CHD2* have been detected in individuals with a diagnosis of ASD (22), ID (73) or epilepsy (82,83,87,89), as have

	Functions in the NS	Model organisms	Clinical spectrum
CHD8			
ADNP			
TBR1			
ANK2			
CHD2			

**Figure 2.** Characterization of newly discovered ASD genes. The figure summarizes, for the indicated genes, what is known about the function in the nervous system, phenotypes in animal models (KD, knockdown; KO, knockout; Het, heterozygotes) and association with human disorders. *CHD8* is involved in chromatin remodeling and affects transcriptional regulation (52–54) (a postmitotic neuron is shown, but *CHD8* functions in neural progenitor cells as well). In cell models, *CHD8* is also implicated in apoptosis (55) (not shown). Both zebrafish (52,56) and mouse models have been generated (55,57). *Chd8*<sup>+/-</sup> mice have not been fully characterized. Deep phenotyping of 15 patients with *CHD8* mutations has led to the identification of a proposed ASD subtype (56), although for this and many such studies the ascertainment was primarily from samples ascertained on the basis of phenotypes of interest, likely introducing biases. *ADNP* is involved in chromatin remodeling (58,59), autophagy (60) and microtubule dynamics at synapses through its active peptide (NAP) (61). *ADNP* is also expressed in glial cells (not shown) (62). *ADNP* knockdown in zebrafish results in no major brain anomalies but defective erythropoiesis (63). *ADNP* knockout in mice is embryonic lethal (64), and *Adnp* heterozygotes show deficits in spatial learning and memory (65) and sex-specific deficits in novel object recognition, social recognition and social memory (66). Deep phenotyping of 10 patients with *ADNP* mutations has led to the identification of a potential new syndrome (67). *TBR1* encodes a transcription factor essential for neural stem cell fate and cerebral cortex development (68–70). *TBR1* knockout in mice (71) results in the loss of projection neurons in the olfactory bulbs and olfactory cortex (71) and severe defects of cortical lamination (68,72). *Tbr1*<sup>+/-</sup> mice do not show gross lamination defects, but have defective axonal projections in the amygdala and a behavioral phenotype (72). *TBR1* has been implicated in ASD (21,22,25,26) and ID (73). *ANK2* encodes for a protein regulating the assembly of the submembranous cytoskeleton at the axonal initial segment (AIS) in unmyelinated axons (74) and acting as a glial paranodal scaffolding protein in Schwann cells (75) (not shown). *ANK2* knockout in mice reduces survival postnatally (premature death by postnatal day 21) and causes lateral ventricle dilation, hypoplasia of the corpus callosum and pyramidal tracts, degeneration of the optic nerve (76) as well as musculoskeletal defects and neonatal myopathy (77). *Ank2*<sup>+/-</sup> mice display a cardiac phenotype (78), but their neurological phenotype has not yet been exhaustively assessed. Two conditional models have also been established: a conditional knockout of the cardiac isoforms (cKO cardiac) not fully characterized yet (79) and a knockout in Schwann cells only (cKO Schwann), with no obvious defects in paranodes of the peripheral nervous system (75). *ANK2* has been associated with ASD (22,26,80) and cardiac arrhythmia (78). *CHD2* is involved in chromatin remodeling [a postmitotic neuron is shown, but *CHD2* functions in neural progenitor cells as well (81)]. *CHD2* knockdown in zebrafish causes pericardial edema, microcephaly, body curvature, absent swim bladder, growth retardation, seizure-like behavior (82) and photosensitivity (83). *CHD2* knockdown in mice by *in utero* electroporation causes defective cortical development by affecting neural progenitor cells proliferation (81). Homozygous mice for a *CHD2* lacking the DNA-binding domain (mut/mut) have perinatal lethality (84,85). Heterozygosity (+/mut) attenuates lethality, but results in a complex phenotype (84–86). *CHD2* has been associated with ASD (22,23), ID (73), epilepsy (82,87) and photosensitivity (83).

many of the known and novel ASD genes, and individuals carrying gene deletions in *CHD2* display ID, epilepsy and autistic-like behaviors (90). However, in addition to postnatal growth retardation, zebrafish and mouse models share some unexpected phenotypic traits, including cardiovascular and renal defects, and lordokyphosis (82,84–86). Broad phenotyping of model systems, beyond social and repetitive behaviors, is clearly important (91).

## Genotype–phenotype relationships

The scenario emerging from these few examples shows how ASD risk loci and genes identified to date rarely map exclusively to ASD (Figs 1 and 2), raising questions about pleiotropy or other mechanisms of action and rendering genotype–phenotype correlations complex. Chromosomal microarray and sequencing studies have found remarkable genetic overlap between ASD and other neurodevelopmental and neurological conditions, including ID, epilepsy and schizophrenia (92,93). Genetic commonalities might extend beyond NDD. In fact, recent discoveries indicate shared genes and pathways between ASD and congenital heart disease (CHD) (26,93,94).

Using a genotype-first approach, studies reporting the comprehensive clinical characterization of cohorts of patients with shared etiology have shown a high degree of variability in the expressivity of recurrent CNVs and mutations in single genes (95). Among the best examples are 22q11.2 deletions and 16p11.2 deletions. Both deletions are in fact associated, with variable severity, with various neuropsychiatric disorders, including ASD, ID and schizophrenia, among others (50,96). The deletions can also be detected in healthy individuals, an observation consistent with incomplete penetrance (50,96), which is true for most of the genes and loci that have been identified. One intriguing hypothesis is that common variation may be a factor determining the expression of specific traits when a highly penetrant mutation occurs (Fig. 1), and recent findings in both 22q11.2 and 16p11.2 deletion syndromes provide some support of this. A study focussing on the variable expressivity of CHD in carriers of 22q11.2 deletion has identified a common CNV that could act as a modifier on the cardiac phenotype in individuals with the syndrome (49). Also, by analyzing quantitative cognitive, social, motor and anthropometric traits that are highly heritable, a study on 56 individuals with *de novo* 16p11.2 deletions has shown the importance of family background (which in turn might be mediated by common variation and/or non-genetic factors) on clinical variability and shown the value of using quantitative rather than dichotomous measures to better assess and account for such familial influence (50).

Among the most studied connections is that between ASD and ID. In addition to the high co-occurrence, there is also interdependence between cognitive function and response to social cues. Recent observations in the Simons Simplex Collection (SSC) suggest that ASD risk architecture might differ in individuals with lower and higher IQ, although this must also be examined in additional cohorts. In the SSC, individuals with ASD and IQ < 100 have an excess of *de novo* loss-of-function mutations in comparison to their higher functioning counterparts (97,98), whereas individuals with ASD but not ID have a higher rate of family history of psychiatric disease and thus a greater familial burden (98). Stratifying patients by IQ, as well as other clinical variables, has been proposed as an approach to reduce phenotypic variability (99–103) and to enhance genetic discoveries. However, in one recent study, grouping by ASD diagnostic category, IQ, ASD severity, insistence on sameness and symptom profiles did not

significantly increase genetic homogeneity, at least as defined by SNPs nor does it yield more discoveries for common variation (104,105).

All of these observations may complicate the validity of ASD as a specific construct and support a shared risk between diverse NDDs. To capture this complexity, Ledbetter and co-workers have proposed returning to the term ‘developmental brain dysfunction’ to harmonize and merge classically defined categorical diagnoses, including minimal brain disorders (learning disabilities, language disorders, developmental coordination disorder and ADHD), NDDs (ID, ASD and cerebral palsy) and some neuropsychiatric disorders (schizophrenia and major affective disorders to a certain extent) (50), whereas Gillberg (105,106) has proposed the ESSENCE prospective. Extending these perspectives, cognitive, motor, neurobehavioral and neuroanatomical/neurophysiological traits would ideally be expressed as quantitative measures that account for familial background, and penetrance and expressivity will be considered for a specific trait.

## Conclusions

The integration of genetic discoveries and clinical observations in ASD is delineating a scenario whereby common and rare variations combine to produce a diagnosis, and, possibly, common variation (genetic or familial background) defines the specific phenotypes that are manifested. Genotype–phenotype correlation analyses would thus benefit from quantitative analyses of specific traits that take into account the common and rare genetic variation.

The observations on disease co-occurrence in ASD and the emerging evidence of shared risk across NDDs from genetic studies stress the importance of future studies that can determine whether specific gene signatures exist for a given disorder, while also making it clear that aggregating data from multiple NDDs are an efficient means to enhance power for gene discovery.

Finally, deep phenotyping studies of patients sharing highly penetrant mutations, accompanied by functional analyses in model organisms, will also clarify the pathobiological mechanisms of specific genetic loci, lead to the identification of ASD subtypes and novel syndromes and enhance the potential for novel therapeutics.

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