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Review Article

Progress towards understanding risk factor mechanisms in the development of autism spectrum disorders

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Autism spectrum disorders (ASD) are a heterogenous set of syndromes characterised by social impairment and cognitive symptoms. Currently, there are limited treatment options available to help people with ASD manage their symptoms. Understanding the biological mechanisms that result in ASD diagnosis and symptomatology is an essential step in developing new interventional strategies. Human genetic studies have identified common gene variants of small effect and rare risk genes and copy number variants (CNVs) that substantially increase the risk of developing ASD. Reverse translational studies using rodent models based on these genetic variants provide new insight into the biological basis of ASD. Here we review recent findings from three ASD associated CNV mouse models (16p11.2, 2p16.3 and 22q11.2 deletion) that show behavioural and cognitive phenotypes relevant to ASD. These models have identified disturbed excitation-inhibition neurotransmitter balance, evidenced by dysfunctional glutamate and GABA signalling, as a key aetiological mechanism. These models also provide emerging evidence for serotoninergic neurotransmitter system dysfunction, although more work is needed to clarify the nature of this. At the brain network level, prefrontal cortex (PFC) dysfunctional connectivity is also evident across these models, supporting disturbed PFC function as a key nexus in ASD aetiology. Overall, published data highlight the utility and valuable insight gained into ASD aetiology from preclinical CNV mouse models. These have identified key aetiological mechanisms that represent putative novel therapeutic targets for the treatment of ASD symptoms, making them useful translational models for future drug discovery, development and validation.

Introduction

Autism spectrum disorders (ASD) are a heterogenous set of syndromes characterised by social impairments and communication deficits, often accompanied by restrictive, repetitive behaviours and interests and altered sensory processing [1]. The prevalence of ASD diagnosis has increased over recent decades. In 2020 prevalence was estimated at ~1 in 34 children in the U.S.A., an increase from 1 in 68 in 2010, with diagnosis being four times more common in males than females [2]. Given the complexity and multifactorial nature of ASD there is no singular disease mechanism that underlies diagnosis. However, research has identified key aetiological mechanisms that contribute to the risk of developing ASD, highlighting some of the central biological mechanisms involved. This review summarises several key ASD risk factor mechanisms, with a focus on recent insights gained from rodent models based on genetic risk for ASD and the impact on neurotransmitter system function.

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The genetic risk basis of ASD

Heritability estimates for ASD range from 40% to 90% [3,4], emphasising the central importance of genetic risk. Environmental risk factors, such as maternal smoking, advanced paternal age and

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prenatal maternal infection are also important [5–7], with at least some of these interacting with genetic risk [8]. Protective modifiable factors in relation to an individual's neurodevelopmental trajectory are also important, and diagnostic outcome is often dissociated from genetic risk. Such protective factors include a healthy maternal body weight (both pre- and during pregnancy), good maternal nutrition and breastfeeding [9–12].

The genetic architecture of ASD risk is highly complex and polygenic in nature. In most cases, ASD results from the interaction of multiple common genetic risk variants, with each variant individually contributing a very small increase in risk. Genome Wide Association Studies (GWAS) with very large sample sizes have been key in identifying common gene polymorphisms that contribute to an increased risk of developing ASD. These studies have provided important new insights into some of the key biological mechanisms contributing to ASD risk, including genetic mutations that impact neuronal gene transcription (*ASH2L*, *BCL11A*, *KANSL1*, *SOX7*, *SRRM4*, *XRN2*), brain development (*BLK*, *BTG1*, *CNTN5*, *DSCAM*, *FOXP1*, *KIZ*, *MMP2*, *NTM*, *WDR73*, *WNT3*, *XKR6*), inflammation (*C2CD4A*, *IFI16*, *MFHAS1*, *NFKB2*), the stress response (*CRHR1*), neuronal cell activity (*DPP10*, *KCNN2*) and synaptic (*CNTNAP5*, *DDHD2*, *SEMA3G*, *SNCA*) and neurotransmitter system (*GABBR2*, *GRIN2A*, *PAFAH1B1*, *RASGEF18B*) function [13–15].

In addition to common gene variants of small effect, single genes and copy number variants (CNVs), wherein chromosomal segments are either deleted or duplicated, that substantially increase the risk of developing ASD have also been identified (Table 1). CNVs have received particular interest following the observation that rare and *de novo* CNVs are more prevalent in ASD populations [16,17]. CNVs result in a gain or loss of genetic material that vary in size from tens of thousands to millions of nucleotides, altering the number of copies of a particular gene (e.g. 2p16.3 deletion, *NRXN1*) or multiple genes (e.g. 16p11.2 deletion/duplication, ~29 genes), depending on the CNV. Importantly, some genes located in CNV regions associated with ASD have been independently identified as having common variants that are also associated with ASD diagnosis [14,18,19]. The Simon's Foundation Autism Research Initiative (SFARI) Gene database provides a valuable, extensive database that rationalises the contribution of risk genes and CNVs for ASD (https://gene.sfari.org).

Genetic rodent models relevant to ASD

Due to their small effect size, genetic rodent models based on risk SNPs in common gene variants, such as those identified as being associated with ASD by GWAS, have not yet been prioritised. To ensure translatability, preclinical rodent models with high construct validity are required. In the context of risk SNPs in common gene variants, such genetic models would optimally be based on multiple risk gene polymorphisms, which is technically challenging. Future preclinical work in ASD will no doubt benefit from the development of SNP-based, polygenic risk gene models with high construct validity. Instead, preclinical rodent models for ASD based on single risk genes and CNVs with high penetrance have been prioritised, in part due to the technical capability of generating these models but also due to the predicted pronounced impact of these genetic changes in terms of neurobiology and translational phenotypes (Figure 1). One potential limitation of this approach is that the observations made may not be more broadly translational to the general ASD population, due to the relative rarity of these mutations. However, the hope is that key aetiological mechanisms can be identified and prioritised for drug development by integrating observations across multiple CNV and risk gene models. In addition, these models offer the advantage that they have high construct validity for individuals who harbour the specific genetic mutation, aligning with a personalised-medicine focus for drug development and the opportunity to develop new interventions for individuals harbouring these mutations. In addition, many CNVs affect multiple genes (e.g. 16p11.2 deletion/duplication) and so align with the polygenic risk basis of ASD, which potentially confers a higher overall construct validity and generalisability to these models in comparison with those based on single risk gene mutations.

Risk mechanism insights from CNV models

Utilising rodent models based on risk CNVs has been fundamental in improving our understanding of the key biological mechanisms implicated in the neurobiology of ASD. Often, surprising and unexpected alterations in neurobiology emerge from these CNVs, particularly at the systems-level, due to their complex effects on neurodevelopmental processes and trajectories. This highlights the essential utility of risk CNV rodent models, and other risk gene models, in addressing the challenges of understanding ASD aetiology and in the drug development process for these disorders. Here we review a range of recent insights gained from three rodent models based on CNV deletions associated with an increased risk of developing ASD, with a focus on the impact at

Table 1. Single risk genes and CNVs that substantially increase the risk of ASD diagnosis. Part 1 of 2

Monogenic disorder/CNV syndrome	Gene(s) involved[a]	ASD odd's ratio (OR)/ hazard ratio (HR)/% population	Key biological mechanisms and phenotypic outcomes
Fragile X	Fragile X messenger ribonucleoprotein 1 (*FMR1*)	-	Transcriptional regulation including the regulation synaptic mRNAs (Darnell et al., 2011, PMID: 21784246) [77]
Rett's syndrome	Methyl-CpG binding protein 2 (*MECP2*)	-	Regulation of neuronal transcriptional programmes (Tillotson and Bird, 2020, PMID: 31629770) [78]
2p16.3 deletion	Neurexin-1 (*NRXN1*)	~14.9 OR (Matsunami et al., 2013, PMID: 23341896 [34]; Wang et al., 2017, PMID: 29045040 [35]; Yuen et al., 2017, PMID: 28263302 [79])	Synaptic protein which binds to post-synaptic partners to regulate synaptic maturation and function, including glutamate synapse function (Gomez et al., 2021, PMID: 33420412 [36]; Sudhof, 2017, PMID: 29100073 [37])
16p11.2 deletion/ duplication	~29 genes including Mitogen-activated protein kinase 3 (*MAPK3*), *Thousand and one amino-acid kinase 2 (TAOK2)*, *Major Vault Protein (MVP)*	Deletion = ~38.7 OR Duplication = ~20.7 OR (Walsh and Bracken, 2011, PMID: 21289514 [80])	*MAPK3*: Extracellular signal regulated kinases essential for cell proliferation, differentiation, and cell cycle progression (Boutros, Chevet & Metrakos, 2008, PMID: 18922965 [81]) *TAOK2*: Activates the p38 kinase cascades through activation of MEK kinases (Chen et al., 1999, PMID: 1047253 [82]). Regulates the cytoskeleton and dendrite formation (de Anda et al., 2012, PMID: 22683681 [83]; Nourbakhsh et al., 2021, PMID: 34879262 [84]). Loss induces ASD-relevant phenotypes in mice (Richter et al., 2019, PMID: 29467497 [85]). *MVP:* neuronal function incompletely understood, regulates ERK signalling. Regulates brain morphology and modified anxiety-like behaviour in mice (Kretz et al., 2023, PMID: 37968726 [86]). *KCTD13*: Regulates neuronal development (Kizner et al., 2020, PMID: 31402430 [87]) and excitatory neurotransmission (Gu et al., 2023, PMID: 37142655 [88]).
15q13.3 deletion/ duplication	~6 genes including Cholinergic receptor nicotinic alpha 7 subunit (*CHRNA7*), OTT-domain containing protein 7A (*OTUD7A*), Transient receptor potential cation channel subfamily M member 1 (*TRPM1*)	Deletion: ~10% affected individuals have an ASD diagnosis (Lowther et al., 2015, PMID: 25077648 [89]; Breakpoint BP4-BP5).	*CHRNA7*: Nicotinic acetylcholine receptor subunit, modulates glutamatergic (Stone, 2021, PMID: 34111447 [90]) and GABAergic (Lin et al., 2014, PMID: 24983521 [91]) transmission. *OTUD7A*: putative deubiquitinating enzyme that localises to dendritic spines.

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Table 1. Single risk genes and CNVs that substantially increase the risk of ASD diagnosis. Part 2 of 2

Monogenic disorder/CNV syndrome	Gene(s) involved[a]	ASD odd's ratio (OR)/ hazard ratio (HR)/% population	Key biological mechanisms and phenotypic outcomes
			Regulates glutamatergic synapse development (Kozlova et al., 2022, PMID: 35931052 [92]) and deletion induces ASD-relevant behavioural phenotypes in mice (Yin et al., 2018, PMID: 29395075 [93]). *TRPM1*: divalent cation (Ca^{2+}, Mg^{2+}, Zn^{2+}) permeable channel, potentially interacts with glutamate mGluR6 in neurons (Shen et al., 2012, PMID: 22586107 [94]) and deletion induces ASD-relevant phenotypes in mice (Hori et al., 2021, PMID: 33785025 [95]).
22q11.2 deletion/ duplication	~90 genes (~40 protein coding expressed in brain) including T-Box transcription factor 1 *(TBX1)*, *DiGeorge syndrome critical region 8 (DGCR8)*, *Proline dehydrogenase (PRODH)*	~2.95 HR (Olsen et al., 2018, PMID: 29886042 [96])	*TBX1*: encodes transcription factors regulating developmental processes (Papaioannou et al., 2014, PMID: 25294936 [97]). Heterozygous deletion impairs myelination, reduces postnatal progenitor cells in hippocampus and impairs cognitive flexibility (Hiramoto et al., 2022, PMID : 34737458 [98]). *DGCR8*: Regulates microRNA biogenesis (Burger and Gullerova, 2015, PMID: 26016561 [99]). Influences brain development and heterozygous deletion impacts on GABAergic signalling and neuronal network plasticity (Amin et al., 2017, PMID: 29146941 [100]). *PRODH*: Regulates proline metabolism. Prodh deficient mice show altered glutamate and GABA function (Paterlini et al., 2005, PMID: 16234811 [101]) and Prodh depletion impacts on neuronal morphology (Yao et al., 2024, PMID: 37815900 [102]).

A selection of genes and CNVs associated with an increased risk of developing ASD, with a focus on those with a large number of cases that have currently been relatively well characterised in rodent models.[a]A few select genes of interest shown for polygenic CNVs only. A more extensive list of risk genes and CNVs is available at http://gene.sfari.org.

the systems-level, including the impact on cognition, behaviour, brain network connectivity and neurotransmitter system function.

16p11.2 deletion

One of the first and most common CNVs associated with ASD is located at 16p11.2, with both deletions and duplications conferring increased ASD risk [19–21]. Interestingly, there is evidence for clinical heterogeneity between 16p11.2 deletion and duplication carriers, with duplication carriers more likely to be diagnosed with

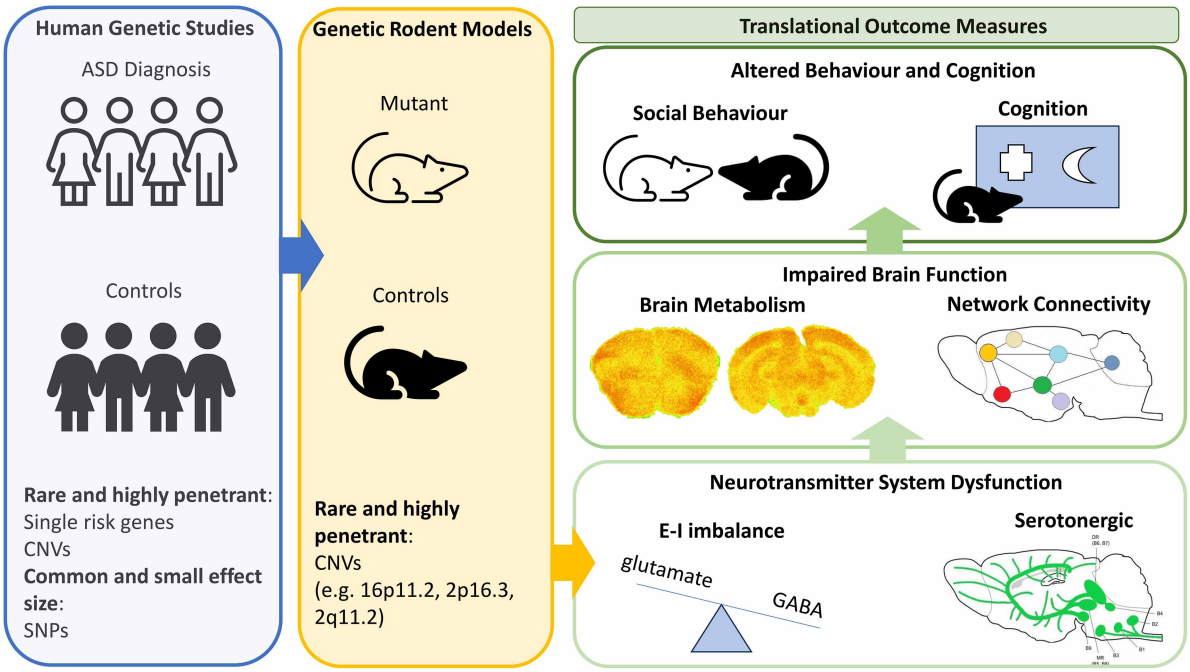

Figure 1. Translational rodent models based on genetic risk factors for ASD provide new mechanistic insight into the aetiological basis of the disorder.

Risk genes identified in human genetic studies have identified common variants of small effect (such as SNPs) and rare highly penetrant risk genes and CNVs. Rodent models based on risk CNVs identified in human studies have shown these risk genes impair neurotransmitter system function, particularly in terms of E-I (glutamate-GABA) balance, and potentially in serotonin system function. This neurotransmitter system dysfunction contributes to abnormal brain metabolism/function and brain network connectivity, which underscores abnormal behaviour and cognition, including deficits in social and executive function.

attention deficit hyperactivity disorder (ADHD) and psychotic symptoms than individuals carrying a 16p11.2 deletion [22]. This suggests that there is uncharacterised, mechanistic heterogeneity between deletion and duplication at this locus, that results in differential risk for ADHD and psychotic psychopathology, and potentially to ASD symptomatology, which is yet to be studied in detail. In addition to ASD, 16p11.2 CNVs are associated with intellectual disability and epilepsy [23,24], which may result from disturbed excitation-inhibition (E-I) neurotransmitter balance in the brain, as discussed below.

Mouse models with a 16p11.2 deletion analogous to human carriers, which results in haploinsufficiency of ~29 genes (including *Taok2*, *Mapk3* and *Mvp*, Table 1) show ASD-relevant behavioural phenotypes including hyperactivity and repetitive circling behaviours [25]. Interestingly, enhanced cognitive abilities have also been shown in 16p11.2 deletion mice in terms of visual attentional processing [26], suggesting that the model reflects both key behavioural deficits and some of the enhanced cognitive abilities reported in individuals with ASD, such as increased visual search ability [27]. In terms of brain network connectivity, there is evidence for the widespread functional brain network dysconnectivity in 16p11.2 deletion mice, that includes abnormal prefrontal cortex (PFC) connectivity, which parallels that seen in human individuals with 16p11.2 deletion and those with ASD [26,28]. In addition, there is evidence for widespread E-I neurotransmitter system imbalance in 16p11.2 deletion mice [26,29,30] with some behavioural (activity and social) deficits corrected by the E-I neurotransmission modulator N-acetyl cysteine [31]. Moreover, there is also emerging evidence for serotonergic dysfunction as a consequence of 16p11.2 deletion, with the hyperactivity and social deficits in these animals corrected by the 5-$HT_{1B/1D/1F}$ receptor agonist eletriptane [31], sociability deficits reversed by MDMA and the 5-HT_{1B} agonist CP-94,253 [32], and performance in the forced swim test rescued by the 5-HT_{2A} receptor antagonist volinanserin (MDL 100 907) [33]. Despite these pharmacological observations, the cellular and molecular basis of serotonin (5-hydroxytryptamine, 5-HT) system dysfunction in this model has not yet been characterised. This would certainly be of interest, to further understand its role in ASD symptom risk.

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2p16.3 deletion

2p16.3 deletions, involving heterozygous deletion of the *NRXN1* gene, substantially increase the risk of developing ASD [20,34,35]. The vast majority of 2p16.3 deletions identified impact on the longer NRXN1α isoform, while leaving the shorter NRXN1β isoform intact, resulting in heterozygous NRXN1α deletion. NRXN1α is a presynaptic protein that interacts with a diverse range of post-synaptic binding partners to regulate synaptic maturation and efficacy [36,37].

Mouse models based on decreased NRXN1α expression have identified a range of behavioural phenotypes relevant to ASD, and to human individuals with the 2p16.3 deletion. This includes delayed development, abnormal communication (ultrasonic vocalisations) and impaired memory and executive cognition [38–40]. In addition, *Nrxn1α* heterozygous (Hz) deletion in mice induces deficits in brain metabolism and network connectivity that have translational relevance to the alterations seen in individuals with ASD, including reduced PFC metabolism and abnormal PFC connectivity [40,41]. Evidence from *Nrxn1α* Hz mice also supports disturbed balance in terms of excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmitter system function in the brain [40], and the regulation of E-I balance by Nrxn1α is supported in other mouse models [42,43]. Altered E-I balance in *Nrxn1α* Hz mice parallels the disturbed E-I balance reported in individuals with ASD, and data from cultured human cortical neurons from ASD patients with *NRNX1* heterozygous deletion supports neuron hyperexcitability and abnormal glutamatergic function [44]. Emerging data from *Nrxn1α* Hz mice also support potentially dysfunctional serotonergic signalling [40], which may parallel dysfunctional serotonin activity in individuals with ASD [45]. More work is needed to define the nature of serotonin system dysfunction that results from *Nrxn1α* heterozygosity and whether serotonergic drugs can correct some of the behavioural phenotypes observed. This could include testing some of the serotonergic drugs that have previously been found to be beneficial in 16p11.2 deletion mice.

22q11.2 deletions

Genetic deletions at 22q11.2, resulting in DiGeorge (velocardiofacial) syndrome, have been relatively well characterised and are associated with increased risk of developing ASD, and a range of other brain disorders, including schizophrenia [46,47]. The typical ∼3.0 Mb 22q11.2 deletion region contains ∼90 genes, including 46 protein coding genes with confirmed expression in the human brain [48].

Mouse models that either partially or fully replicate the ∼3.0 Mb deletion seen in most patients, have been generated [49]. These mouse models demonstrate a range of behavioural phenotypes and cognitive deficits which parallel those seen in individuals with ASD, including impaired social memory and circadian rhythms [49–51]. In terms of brain network connectivity, abnormal PFC connectivity has been reported in 2q11.2 mouse models [52,53] and is also found in humans with the 22q11.2 deletion [54]. Studies in both humans with the deletion and 2p11.2 deletion mouse models also support disturbed E-I neurotransmitter system balance because of the deletion, with alterations in both glutamate and GABAergic neurotransmission supported [55–57], although effects on glutamate are not always found in patients [58]. While several studies have characterised the impact of 22q11.2 deletion on dopaminergic function in the brain, given that the dopamine degrading enzyme Catechol-*O*-methyltransferase is coded for in the 22q11.2 region and its independent association with schizophrenia (reviewed in [59]), very few studies have characterised the impact on serotoninergic function. However, lower urine serotonin levels have been reported in individuals with 2q11.2 deletion, which were found to positively correlate with IQ [60] and recent evidence supports a potential positive effect of long-term selective serotonin reuptake inhibitor (SSRI) treatment on cognition in children and adolescents with the deletion [61]. Thus, further study on the impact of the 2q11.2 deletion on serotonin neurotransmitter system function is certainly warranted.

Summary: integrating observations across multiple risk gene models to identify risk mechanism and drug target prioritisation

Observations across the CNV models outlined above support a role for altered synaptic function, E-I balance and potential serotoninergic dysfunction as key alterations underlying ASD symptomatology. While E-I imbalance has been relatively well characterised, further work on the potential role of disturbed serotonin system function in these CNV models is needed. While E-I balance is more studied, important gaps in our

understanding of how E-I balance is altered across these models remain, particular in terms of (i) the brain regions most affected, (ii) the molecular aspects of glutamate and GABA neurotransmitter system function most impacted, (iii) the relationship of these changes to functional outcomes, and (iv) the conserved nature of these specific changes across the different models. More systematic, granular, and integrated work across these models is required to further elucidate the conserved changes in E-I function and their relationship to behavioural and cognitive outcomes. This seems particularly important given evidence supporting the potential efficacy of drugs targeting E-I balance for some ASD symptoms [62,63].

The emerging data supporting serotonergic dysfunction across these models is also of particular interest given the diverse data supporting serotonergic dysfunction in people with ASD and in other ASD-relevant animal models. Observations in humans with an ASD diagnosis include reduced serotonin-reuptake transporter (SERT) availability, lower expression of the 5-HT degrading enzyme mono-amine oxidase A (MAOA) and complex, subtype-dependent alterations in 5-HT receptor expression (reviewed in [45]). In addition, data supporting the ability of drugs targeting the serotonergic system to relieve some ASD symptoms, particularly SSRIs that block SERT [64,65], also implicate dysfunction of this neurotransmitter system in ASD, although positive effects are not always found [66] and the evidence for some ASD symptom domains is very limited. The serotonin system, a monoamine, modulatory neurotransmitter system, originates from cells located in the raphé nuclei of the brainstem with extensive projections to the forebrain and brainstem in both humans and rodents (Figure 1) [67,68]. Thus, the serotonin system innervates and modulates activity in a range of brain regions known to be dysfunctional in ASD, including the PFC and hippocampus [69,70]. The serotonin system utilises a diverse range of receptors, ordered into seven families (5-HT_{1-7}), in its signalling, with some acting primarily as post-synaptic effectors (e.g. 5-HT_2) and others with functions as both post-synaptic effectors and autoreceptors (e.g. 5-HT_{1A}) that modulate serotonin release [71]. A range of receptor agonists and antagonists, with variable selectivity, are available to target these receptors, supporting the tractability of the serotonin system as a therapeutic target in ASD (https://www.guidetopharmacology.org [72]). The serotonin system also regulates a wide range of behavioural and cognitive processes relevant to ASD symptomatology, including vulnerability to social stress [73], repetitive/compulsive behaviours [74] and the regulation of executive function [75], further supporting the potential of targeting the serotonin system to relieve these symptoms in ASD. Given the emerging data supporting serotonin system dysfunction in the CNV models considered in this review, further work is required to understand the changes present and the specific molecular aspects of serotonin system signalling that are of putative therapeutic value in these models and ASD.

Converging evidence across multiple CNV models also supports the PFC as an important locus of brain network dysfunction, paralleling PFC dysfunctional connectivity in ASD [76]. This PFC dysfunction likely contributes to the higher-order cognitive, emotional, motor and interoceptive processing alterations experienced by individuals with ASD. Thus, pharmacological interventions that aim to restore PFC function and connectivity to alleviate these symptoms are of particular interest. The above consideration of the available literature highlights the utility of combining observations made across multiple genetic models relevant to ASD in identifying key aetiological mechanisms and prioritising these for drug validation. This integration is particularly important given that penetrance for any given CNV is incomplete and the prevalence of ASD symptom heterogeneity in both individuals harbouring these CNVs and those with an ASD diagnosis. While conserved changes across models may be insightful in terms of prioritising targets for the drug development process, divergences between models are also of interest. There is considerable heterogeneity in symptomatology across individuals with an ASD diagnosis, that likely results in part from underlying genetic risk and the resultant changes in neurobiology. This is very poorly understood. Thus, identifying mechanisms that diverge across mouse models may be useful in informing the neurobiological basis of symptom heterogeneity in ASD.

Future directions

Insight into the risk genes that underly ASD has provided valuable new information into the aetiological mechanisms that underlie the condition and have identified novel targets for drug development aimed at improving symptoms. However, several challenges remain, including the generalisability of observations made in models based on rare single risk genes and CNVs. While integrating information from multiple models to identify conserved mechanisms may overcome these challenges, particularly in the context of prioritising the focus of future drug development for ASD, developing new genetic rodent models with high construct validity and broad generalisability, based on multiple risk gene variants of small effect, will also be important. Integrating existing and new genetic models with established environmental risk factor manipulations will also

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be useful, providing new insight into mechanisms that regulate genetic penetrance. In addition, future work systematically characterising the diversity of biological mechanisms underlying symptom heterogeneity in ASD, and the relevance of different risk factor models to these, is required.

Perspectives

- Understanding the biological mechanisms underlying the risk of developing ASD is an essential step in developing novel therapeutics. Human genetic studies and rodent models based on rare but highly penetrant genetic risk factors have been fundamental in improving our understanding of the mechanistic basis of ASD.
- Integrating information from multiple rodent transgenic risk models, including CNV models, has identified key aetiological mechanisms in ASD risk. Observations made in CNV models support altered synaptic function, E-I neurotransmitter balance and abnormal brain network connectivity as key ASD risk mechanisms.
- Emerging evidence from CNV models also supports serotonergic dysfunction in ASD, but this remains underexplored. To date, polygenic common gene variant, environmental and modifiable risk factor preclinical models have been relatively under-utilised. Future studies using these models will likely provide valuable new insight into the mechanistic basis of ASD and will be useful in the drug development and validation process.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CNV, copy number variant; E-I, excitation-inhibition; GWAS, Genome Wide Association Studies; PFC, prefrontal cortex; MAOM, monoamine oxidase a; SERT, serotonin-reuptake transporter; SSRI, selective serotonin reuptake inhibitor.

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