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# Autism genetics: opportunities and challenges for clinical translation

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**Abstract**

Genetic studies have revealed the involvement of hundreds of gene variants in autism. Their risk effects are highly variable, and they are frequently related to other conditions besides autism. However, many different variants converge on common biological pathways. These findings indicate that aetiological heterogeneity, variable penetrance and genetic pleiotropy are pervasive characteristics of autism genetics. Although this advancing insight should improve clinical care, at present there is a substantial discrepancy between research knowledge and its clinical application. In this Review, we discuss the current challenges and opportunities for the translation of autism genetics knowledge into clinical practice.

## Introduction

Tremendous progress has been made in identifying the genetic variants that have an impact on the development of autism spectrum disorders (ASDs), providing a window into the biology of this group of conditions1,2 . Variants associated with ASDs have been found in hundreds of different genes, are mostly rare and cover the entire spectrum of mutations, from alterations of individual base pairs (single-nucleotide variants (SNVs)) to the loss or gain of a thousand to millions of base pairs (copy number variants (CNVs)). In addition to inherited variants, numerous studies have shown that in individuals with an ASD the rate of de novo genetic variants — that is, variants that are detected for the first time in the proband and are not present in the parental genome — is increased. For instance, in probands, de novo CNVs occur four times as frequently as in their unaffected siblings, and de novo loss-of-function mutations are twice as common3 . It is estimated that rare genetic variants, both de novo and inherited, are causal in 10–30% of people with ASDs3–5. This represents an

enormous step forwards compared with 15 years ago, when a specific genetic contribution could be detected in only 2–3% of individuals with an ASD. For some of these rare genetic variants, strong causal effects on ASD risk have been known for a long time, such as mutations in TSC1 and TSC2 leading to tuberous sclerosis complex6 or those in fragile X mental retardation 1 (FMR1; also known as FMRP) leading to fragile X syndrome7 . These examples illustrate another key point: some consider ASDs to be medical disorders with possible consequences beyond their purely behaviourally defined phenotypes. Genetic findings from the past decade indicate that ASDs can indeed exist in the context of a fast-growing list of specific, individually rare but collectively common genetic disorders with clinical manifestations outside the central nervous system (CNS). Common genetic variation also contributes to the risk of ASDs8–10. The risk increase conferred by a single common variant is very modest (the relative risk is only approximately 1.1–1.2). However, when considered cumulatively, the contribution of common inherited variants towards the aetiology of ASDs is estimated to be between 15%8 and 50%9,10. Nevertheless, unlike the findings in schizophrenia11, no common risk loci have been identified to date for ASDs. The identification of common variants of small effect requires the study of even larger cohorts than those that have been included in genome-wide association studies (GWAS) to date (Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium, unpublished observations). Indeed, despite the considerable evidence to support a major role of common genetic variation in ASDs9 , it has been rare and de novo variants, which can typically confer a much higher risk in an individual than a common variant, that has led to the discovery of novel ASD risk genes. These rare genetic causes of autism are starting to highlight possibilities for the development of specific targeted therapies with the aim of modulating clinical outcomes and improving people's quality of life12. The translational potential of these findings is one of the most challenging and exciting areas in our field. In this Review, we provide a brief overview of the current state-of-the-art of autism genetics, discuss the clinical importance of those genetic findings and outline what is required for a more effective translation of this research knowledge into medical practice. We focus on rare variants of large effect, as they currently have the most potential to inform clinical care. We argue that, contrary to what is generally assumed, the existing genetic findings are already able to inform our current clinical practice for some people and their families. Moreover, we make the case for how these new insights could lead to a new wave of translational studies.

## Increasing insight into ASD genetics

### *New technologies*

Since individual chromosomes became physically identifiable in the 1970s, karyotyping has been used to delineate various clinical conditions with observable morphological hallmarks. This operator-dependent technique allows the identification of large deletions and duplications of genetic material (usually larger than 5Mb in size), as well as translocations. Subsequent technical improvements over the following decades increased the resolution of the technique to enable the detection of smaller genetic imbalances. In addition, the use of labelled DNA probes hybridized to genomic targets (fluorescence in situ hybridization (FISH)) greatly improved sensitivity for the detection of small aberrations at predetermined chromosomal regions. The combination of observations obtained from karyotyping and FISH provided a first glimpse of the genetic heterogeneity of ASDs13. The next crucial breakthrough was the development of chromosome microarray (CMA) technology, which includes array comparative genomic hybridization (aCGH) and singlenucleotide polymorphism (SNP) genotyping. CMA allows for testing simultaneously across the genome, unlike the specific targeted nature of FISH, and can detect aberrations at a much higher level of detail. CMA testing has been shown to be superior to and more cost effective than karyotyping14,15. Therefore, the American College of Medical Genetics and Genomics, the International Standard Cytogenomic Array Consortium (now known as ClinGen), the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry all revised their guidelines to recommend CMA as part of the first-line evaluation for children with a developmental disability or an ASD14,16–18. The identification of SNVs has also greatly advanced in recent years such that whole-genome sequencing (WGS) and whole-exome sequencing (WES) have become viable alternatives to selective genotyping. Generally, most of the approximately 20,000 variants identified in the

exome sequence of any individual19 are inherited and correspond to normal variation in the general population (that is, they are SNPs). Approximately 75 de novo SNVs arise per genome per generation, the vast majority of which occur in non-coding sequence. It is estimated that on average each newborn carries one or two de novo SNVs affecting coding regions20–22. Although coding variants are likely to have the most potential for inducing phenotypic variation, possible functional effects of non-coding variants on processes such as gene regulation and 3D chromatin folding are becoming increasingly appreciated23. In addition to confirming a diagnosis when a genetic disorder is suspected, sequencing is increasingly used to identify a specific genetic cause in patients with unexplained developmental disorders24. The emerging use of WES and WGS has already led to the identification of many novel rare variants with a large effect size (including small insertions or deletions), and along with the previously identified CNVs, such novel variants have important implications for risk prediction, diagnosis and treatment of ASDs and other neuropsychiatric disorders25. These current technologies also have limitations. The exact resolution of CMA depends on the platform used, and regardless of the platform and unlike karyotyping, CMA cannot detect truly balanced translocations or inversions. When using WES or WGS, identifying CNVs is challenging. The standard protocols and quality control measures for sequencing-based genetic tests are still evolving, and the detection of events varies with the read lengths of the method used. In addition to these technical issues, it can sometimes be difficult to establish or exclude the clinical relevance of each variant identified by CMA and sequencing results despite the use of considerable bioinformatics resources. As a consequence, the proportion of variants of unknown significance (VUS) identified through genome-wide testing is high relative to targeted genetic testing, which poses formidable challenges for clinical interpretation and practice. In addition, genome-wide approaches can identify incidental findings that are clinically relevant: that is, genetic variants of clinical significance that are not directly related to the phenotype under study. A recent study reported incidental 'medically actionable' findings in 4.6% of consecutive patients referred to a clinical laboratory for WES26. The majority of these patients were children with neurological or developmental disorders. One strategy to reduce the likelihood of both VUS and incidental findings is the use of predesigned gene testing panels. However, this should be weighed against the limitation inherent to restricting the test scope to a limited set of a priori defined, clinically relevant candidate genes. The use of WES and WGS is more advanced in cancer genetics than in other health care settings27. For ASDs, sequencing shows promise, but a better understanding of the clinical implications of many genetic variants is required before we can gauge the potential of sequencing to improve the clinical care of people with an ASD.

***ASD risk variants converge in biological mechanisms.***

As of December 2016, more than 800 genes have been included in the AutDB, a database of genes implicated in ASDs28. The strength of the evidence supporting each of these observations varies greatly. One challenge resides in the fact that the mere occurrence of a rare CNV or SNV affecting a gene does not inevitably equate to causation. To gain insights into the potential genetic mechanisms driving risk for ASDs, different types of affected families have been studied, including those with consanguinity, those with a single affected person (a simplex family) and those with multiple people with an ASD, sometimes across many generations. Using WES in families enriched for ASDs owing to consanguinity, specific mutations were identified in AMT, MECP2, NLGN4X, PAH, PEX7, POMGNT1, SYNE1 and VPS13B24; of these genes, MECP2, NLGN4X and SYNE1 have previously been associated with ASDs. The increased access to CMA and WES technologies has now also opened the way to the discovery of rare and private mutations in larger clinical cohorts. A recent study of 2,147 individuals with an ASD, by the Autism Genome Project (AGP), reported that 4.6% (n=99) carried a de novo rare CNV29. Studies of the Simons Simplex Collection show that the rate of de novo rare CNVs increases to more than 10% when restricting to simplex cases5 . Similarly, the study of 1,532 families with multiple affected individuals from the Autism Genetic Resource Exchange (AGRE) showed that both rare de novo and inherited CNVs contribute to the development of ASDs. Although the rate of de novo CNVs identified in the AGRE study was lower than that of the simplex families (as expected, considering the study design), there was a higher burden of large, rare CNVs, including inherited variants, in individuals with an ASD when compared with their unaffected siblings30. Interestingly, in more than two-thirds of the families in which a known high-risk ASD-associated CNV was identified, the CNV was not shared by all affected siblings, highlighting the intrafamilial

genetic heterogeneity of ASDs30. Recurrent inherited and de novo CNVs have been shown to affect regions of the genome that are important in known genomic disorders (for example, 1q21 duplication and 15q11–q13 duplication syndromes) as well as to occur in known genes that are implicated in ASDs or intellectual disability (for example, NRXN1, SHANK3 and PTEN). When data from the AGP were combined with those from the Simons Simplex Collection, 12 such loci (false discovery rate (FDR) < 0.1) associated with ASDs were identified, including 1q21, 2p16 (NRXN1), 3q29, 7q11.23, 15q11–q13, 15q12, 15q13 (in 3 nonoverlapping microregions), 16p11, 16q23 and 22q11 (REF. 5). When data from small single-gene de novo CNVs and WES were incorporated, a further 65 genes were identified (FDR<0.1)5.

One of the strongest discoveries propelled by WES has been the role of chromodomain helicase DNAbinding 8 (CHD8) in ASDs. CHD8 is a transcriptional repressor that binds to β-catenin and negatively regulates WNT signalling. Interestingly, the CHD8 binding targets are strongly enriched for other ASD risk genes, suggesting that the disruption of these genes is working through a common biological process31. In addition to WES, targeted resequencing approaches have further implicated CHD8 in children with an ASD or 'developmental delay' (that is, disordered development). In a recent study of 3,730 children with ASD or developmental delay, a total of 15 independent CHD8 truncating mutations were observed compared with the absence of observed truncating events in 8,792 controls, including 2,289 unaffected siblings32. As CHD8 mutations were observed in less than 0.5% of cases and many of the other genes discovered are likely to be altered in even smaller proportions of patients, a more appropriate strategy may be to focus on aberrant processes, beyond specific genes. Therefore, to better understand the pathophysiology of ASDs, it is pertinent to ask whether identified genes are involved in common processes, or are active within discrete cells types or at specific developmental stages. Gene set enrichment approaches indicate that the known genes and loci involved in ASD risk converge into distinct biological processes: disruptions to synaptic functioning, chromatin remodelling, WNT signalling, transcriptional regulation, interactions with FMR1 and, more broadly, MAPK signalling29,33–37. Moreover, the relationship of ASD-implicated genes with gene co-expression networks further points towards the importance of WNT signalling and synaptic functioning38, early transcriptional regulation and synaptic development39, cell adhesion and chromatin remodelling40, and midfetal deep (layer 5 or 6) cortical projection neurons41. Many of these approaches use weighted gene co-expression network analysis (WGCNA), which is a method to identify highly interconnected groups (known as modules) of genes from gene expression data. The genes in these expression modules offer insight into the biological processes underlying ASDs and the extent to which these processes may be inter-related (reviewed elsewhere in detail in relation to neurodevelopmental disorders42). In addition to ASD-implicated genes being used to identify risk modules, these data can be further leveraged to predict a broad family of 'associated' genes that are 'guilty by association' or, more specifically in this context, 'guilty by co-expression'. Applying machine-learning approaches, information from 594 'ASD-associated' genes can be modelled to predict a role in ASDs for 2,500 genes clustered within nine brain-specific functional modules, including synaptic functioning, chromatin remodelling and MAPK signalling, alongside genes involved in processes including ion transport and cell signalling43.

***Emerging complexity of genotype–phenotype architecture.***

Estimates of the penetrance and expressivity of well-established risk variants for ASDs vary widely, reflecting the fact that little clinically relevant information is known about many variants. Both penetrance and expressivity are highly relevant for a given genetic variant because they allow us to know the frequency at which people with a given genetic variant show a phenotype on a population level (penetrance), and the severity of its clinical manifestation in a given individual (expressivity). Penetrance estimates for ASDs vary from 5% to 8% for mutations in the dystrophin gene (DMD; associated with Duchenne muscular dystrophy) and the neurofibromin gene (NF1; associated with neurofibromatosis type 1), to approximately 80% for mutations in the synaptic scaffold gene SHANK3 (associated with Phelan–McDermid syndrome) or the calcium ion channel gene CACNA1C (associated with Timothy syndrome)1 . In addition, penetrance can be influenced by gender, as discussed below. An alternative approach to the concept of penetrance has gained increasing traction in recent years. This approach is applicable to proband–parent trios in a family with a de novo variant: it characterizes an

individual proband on continuous traits (for example, IQ and social abilities), compares the proband with his or her parents and estimates how far these traits deviate from what would be expected for the proband given the family's context44. This provides an estimate of the neuropsychiatric effect of the genetic variant studied and gives a clearer understanding of its expression, independent of whether formal criteria are met for a specific diagnosis such as intellectual disability or an ASD45,46. This strategy is likely to enable a more accurate investigation of additional modifiers, which may include both genetic and environmental factors. Mechanisms of action for genetic modifiers include various types of compound heterozygosity, in which two different loss-of-function variants occur at the same locus47,48; the influence of gender (females have a higher resilience to ASD-linked mutational load49); oligogenic heterozygosity, in which mutations in more than one risk gene occur in the same individual (this occurs at a higher rate in autistic individuals than in unaffected individuals)50; and possibly the cumulative effect of common variants on the remainder of the genome. In addition to variable penetrance, it is also increasingly clear that many established ASD risk variants are associated with other phenotypes, including intellectual disability, epilepsy, schizophrenia and attention deficit hyperactivity disorder (ADHD), as well as various somatic phenotypes, even within the same individual. Aetiological heterogeneity, variable penetrance and a broad phenotypic pleiotropy are thus now recognized as pervasive characteristics of ASD genetics. These phenomena affect our ability to interpret and reliably use genetic findings in clinical practice51 as well as the way we conceptualize ASDs themselves.

## Genetic knowledge in clinical practice

### *ASDs as part of broader medical (genetic) conditions.*

Early in the 1990s, Gillberg proposed that additional somatic conditions were identified in many individuals with autism52. Since then, numerous studies have shown increased rates of a range of somatic phenotypes in individuals with an ASD, including gastrointestinal53, immunological54 and sleep55 abnormalities. Findings from genetic studies confirm these early clinical observations (TABLES 1,2). For example, in addition to an ASD, the 1q21.1 duplication can also lead, amongst others, to intellectual disability, epilepsy and schizophrenia56,57,133. Phenotypic pleiotropy is not restricted to CNVs57,58, but is also associated with many SNVs that lead to ASDs. For instance, in addition to increasing the risk for an ASD59, SNVs in SCN2A are associated with higher rates of intellectual disability60, schizophrenia61, epilepsy62 and episodic ataxia62. Importantly, pleiotropy may extend beyond CNS-related phenotypes. For example, the 3q29 deletion is also associated with increased rates of gastrointestinal problems and heart defects63. Although it will be challenging, identifying the full range of phenotypes that are affected by a genetic variant will be crucial because it presents a valuable opportunity to enhance the clinical management of coexisting conditions for individuals with an ASD. Potential clinical interventions relate to specific body systems (BOX 1). First, genetics can lead to active surveillance and early intervention for conditions before they develop in individuals who are at risk because of a known risk association with a genetic abnormality. Second, the knowledge of the genetic cause may indicate the involvement of a specific biological mechanism. In some cases, this can enable targeted pharmacological interventions with already available compounds. In other cases, it can guide the choice of medication based on known somatic comorbidities, either those currently present or those for which people are at risk. Finally, as genetic disorders may be associated with specific cognitive and behavioural profiles64, genetic information can direct the avenues of behavioural treatment. A recent study of CMA results of 1,780 subjects over a 3-year period showed that 55% of 187 genetic findings prompted changes in clinical management. The vast majority of those management decisions involved referral to additional specialty services65. Risk variants for ASDs may also exert pleiotropic effects on the risk of other psychiatric disorders66 and on cognitive ability in the general population67. Substantial challenges remain, especially in the context of VUS and incidental findings, but genetic information can have a direct immediate impact in current clinical management and can afford clinical practitioners the opportunity to improve the health, quality of life and lifespan of some people with an ASD; this is especially important in the context of recent studies showing premature mortality in individuals with an ASD, in part due to coexisting conditions68,69. These findings highlight how, in many circumstances, an ASD is part of a broader medical condition. In the clinical context, this perspective would automatically prompt careful

clinical assessments of other organ systems (for example, gastrointestinal, cardiovascular and endocrine) that currently receive limited clinical attention70. In this regard, a distinction is often made between 'syndromic' versus 'non-syndromic' autism, in which syndromic refers to the presence of somatic symptoms in addition to autism, mostly in association with a known genetic cause (for example, a TSC1 mutation). However, the emerging picture of genetic risk variants for ASDs indicates that high rates of diverse somatic symptoms are the rule rather than the exception for variants reported in ASDs (TABLES 1,2). In addition, it is likely that ASDs associated with many of the rare genetic variants are currently considered non-syndromic because too few people with those variants have been observed to enable the recognition of somatic comorbidity patterns. Instead of the syndromic versus non-syndromic dichotomy, a more valid approach would be to cluster patients according to whether or not additional phenotypes are observed and whether a genetic contribution or cause has been identified. These observations of broad medical consequences associated with ASDs are likely to affect our research strategies, as the observed high rate of psychiatric, cognitive and somatic comorbidity in ASDs could indicate shared genetic aetiologies between these different phenotypes. Conversely, genetically defined subgroups within the autism spectrum seem to be more phenotypically homogeneous than the unstratified ASD population64,71–73. A molecular taxonomy, based on specific genetic variants and their associated phenotypic profile, may provide a useful new perspective. Similar taxonomies have proved valuable in clinical neurology, for instance for the classification of the spinocerebellar ataxias and prion diseases74,75. These concepts may eventually have long-term consequences on the classifications described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). Although these classifications, which are currently based on distinguishable behavioural phenotypes, are very helpful for standardizing observed phenotypes and facilitating communication among health care professionals, they lack a direct relationship with putative biological causes76,77.

***Gain of knowledge for the family.***

For many caregivers, knowing the cause of the ASD in their child is frequently important in itself, regardless of any potential benefits regarding treatment options78. In keeping with other conditions diagnosed in childhood, many parents question whether they have caused their child's ASD through their activities or the environment. In a study of 50 parents receiving genetic test results, almost two thirds reported that the result had been helpful for the child and family79. Such knowledge prevents extended searches for answers that may be unproductive, expensive and disruptive of the treatment relationship. In particular, for patients with de novo CNVs, the exposed attributable risk (essentially a measure of the causality of the variant) has been estimated to be greater than 80%80. In addition, finding a specific genetic cause of an ASD in a family can give them an opportunity to connect with other families with that same genetic profile, providing a strong source of understanding, support and networking.

***Genetic counselling.***

Many families of children with an ASD are actively making reproductive decisions regarding future pregnancies or have questions about the development of a sibling (these decisions should be seen in the context of variable views about genetic testing for ASDs (BOX 2)). The background rate of ASDs within the general population is approximately 1%. In the absence of specific genetic test results, only general recurrence rate (also known as recurrence risk) estimates can be made; the recurrence rate with one previously affected sibling is around 10–15%81. If there are two affected siblings in the family, the estimated rates predicted by a theoretical model are around 50% and 12% in subsequent newborn boys and girls, respectively3 . The recurrence rate varies as a function of the gender of the previously affected sibling, with higher recurrence rates in the case of a female affected sibling 82. This difference in recurrence rate has been attributed to the Carter effect; that is, a higher quantitative burden of genetic susceptibility in females versus males (females need to have more ASD-associated variants to be affected than do males) predicts a higher likelihood of an ASD in the relatives of a female affected proband compared with relatives of a male affected proband83,84. However, in a recent large prospective study, striking differences were found in development between males and females generally85, suggesting that these differences observed in males and females with an ASD reflect typically occurring sex

differences seen in children without an ASD. Access to genetic counselling may be particularly relevant to unaffected female family members given the overall lower penetrance of risk variants in females49. As ASDs are more common in males, the same genetic factors do not always result in ASDs in females (the 'female protective effect'). Findings from genetic assessment can provide more specific genetic counselling information in a substantial minority of cases (FIG. 1). The information for parents of children with an inherited variant may have immediate relevance, as it may allow the clinician to be more precise about recurrence rate. For example, when an inherited 22q11.2 duplication is identified in a proband with an ASD, the chance that the next-born child from the same parents will also carry a 22q11.2 duplication is 50%. In addition, the determination of family members who carry the same variant may also affect family planning decisions. Although counselling in the context of a known inherited variant leads to quantifiable risk, accurately predicting recurrence rates in the context of an identified de novo variant is more challenging when the penetrance of the identified variant is low or unknown, when genetic background plays an important modifying part or when a seemingly de novo variant results from parental germline mosaicism22. Questions about recurrence and inheritance delineate a rapidly expanding area in which findings from genetics research are clearly affecting clinical practice. Large-scale longitudinal studies involving clinical genetics services are needed to provide additional information that can be used in counselling.

### *Genetic-testing recommendations and current implementation in clinical practice.*

At present, the multiple guidelines proposing genetic testing of all individuals with an ASD14,18 are not implemented consistently in clinical practice, even within well-funded health care systems. Although in clinical settings genetic testing of children with an ASD has increased in the past 15 years86,87 , a recent study in Texas, USA, found that more than 80% of parents of children with an ASD reported never having received any information regarding the possibilities of genetic testing in their child88. A common policy for services is to select people with an ASD for testing only when there is also somatic comorbidity, intellectual disability and/or dysmorphism — the strategy that had been adopted for karyotyping previously. Such an approach is likely to lead to the identification of only a small proportion of the clinically useful variants related to ASDs. The consequences are twofold: first, potentially relevant information will not be identified for some children and their families; second, the essential worldwide accumulation of genotype–phenotype information is slowed down.

There may be several reasons why clinical implementation is lagging despite strong recommendations for genetic testing in individuals with an ASD, even in countries with substantial clinical genetic testing capacity. First, the medical and specialty training of many clinicians includes only sparse exposure to genetics, often lagging behind cutting-edge research. Consequently, health care professionals may consider that they do not have the knowledge needed to explain genetic results. If this is the case, in a disorder with a complex inheritance pattern such as an ASD, clinicians may be reluctant to propose genetic testing. Second, clinicians may feel that the currently available clinical rationale and justification for genetic testing in individuals with an ASD is insufficient. This notion underscores the need to disseminate to clinicians the data showing that genetic results can already improve recurrence rate quantification and reproductive decision-making. More translational research is needed to elucidate how these genetic results can improve quality of life, therapeutic options and clinical management for people with an ASD. Third, it is likely that genetic testing is often unavailable owing to a scarcity of resources, especially in low-income countries89. Even in developed countries, there are financial barriers to testing for some people with an ASD. In the United States, testing is often, but not universally, covered by American third-party payers. Insurance status (private, Medicaid or Medicare, or none) affects the likelihood of utilization of genetic services90. In Canada and Europe, these tests are generally undertaken as part of universally available health care, free at the point of delivery, although national guidance may not support testing of all children (for example, in the United Kingdom91).

## **Bridging the gap between research and the clinic**

### *The potential of new therapeutic strategies.*

Arguably, the most important goal of genetic studies in ASDs may be to provide much needed clues about the underlying neurobiology of these disorders. With increasing insight into the genetic aetiologies of ASDs, the potential clinical use of genetic stratifiers may come within reach92. The fundamental premise is that stratifying individuals with an ASD into subgroups based on shared genetic aetiology, reflecting a shared underlying biological mechanism, may display clinically relevant differences between the subgroups with regard to treatment response and risk of side effects; this is the concept of 'personalized' or 'precision' medicine75. Over the past few years, an increasing number of studies have confirmed the potential clinical value of this approach. These early findings require replication, but they highlight, among other insights, the fact that specific genetic variants in people with an ASD can moderate the clinical response of the patients to treatment with methylphenidate93, or their risk of weight gain with risperidone94–96. At present, two central characteristics of the available pharmacological strategies limit their efficacy in people with an ASD. First, although medications are successfully used to treat some of the frequently coexisting conditions (for example, hyperactivity anxiety and sleep difficulties), none of the available medications directly targets the core domains of ASDs (note that some in the autism community would not want this: see BOX 2 for relevant community perspectives). Second, none of the currently available medications was developed with a clear a priori defined ASD-linked molecular target97. Converging biological insights derived from genetic studies are beginning to reveal potential targets for the development of pharmacological compounds12,98. These novel insights give a strong impetus to the development of medication strategies for ASDs, which historically have always been under-represented in pharmacological trials in comparison with other mental disorders99. Currently, more than 30 compounds are being studied in clinical trials for their treatment potential in ASDs; this number excludes existing compounds that are frequently used in the treatment of ASDs, such as atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs) and stimulants. In fact, in addition to the clear increase in the number of registered medication trials for ASDs over the past 15 years, the proportion of studies examining the therapeutic effects of novel compounds on ASDs has dramatically increased from 44% between 2001 and 2003 to 81% in the studies initiated between January 2013 and December 2015 (FIG. 2). Interestingly, the proportion of studies in which genetic findings have contributed to the rationale for the novel compound under study (albeit often partly and not exclusively) has increased over the same time period (from 25% to 59%, respectively; FIG. 2). These studies often constitute the first step towards the development of new therapeutic avenues that may need additional refinement, as is exemplified by the recent negative results of clinical trials with agonists targeting metabotropic glutamate receptor 2 (mGluR2) and mGluR3 for schizophrenia (for example, REF. 100). This is to be expected, however, given the biological complexity of psychiatric illnesses and does not refute the potential of initiating genetically informed clinical trials. Two well-established examples of such novel compounds in ASDs — that is, compounds for which the study rationale is at least partly based on genetic findings — are the mechanistic target of rapamycin (mTOR) inhibitors (for which the biological rationale is derived from studies of TSC1, TSC2, PTEN and NF1) and mGluR antagonists (on the basis of studies of FMR1), which have been extensively discussed elsewhere12. Other examples of novel compounds for which selection for clinical trials is at least partly informed by genetic studies include glutathione, memantine and riluzole. Glutathione is a peptide that plays a part in intracellular detoxification and maintenance of redox balance. Its involvement in ASDs arises from studies linking glutathione metabolism genes and this disorder101. Memantine is an NMDA receptor antagonist, whereas riluzole is thought to inhibit glutamate release and enhance its reuptake pre-synaptically. The target of both memantine and riluzole is thus glutamatergic neurotransmission, which has been deemed relevant for ASDs through the association of variants in several glutamate receptor and glutamate transporter genes, as well as through the evidence of glutamatergic deficits in genetic disorders related to ASDs (including fragile X syndrome, tuberous sclerosis complex and the 22q13 deletion that causes hemizygous loss of SHANK3 as a form of Phelan–McDermid syndrome)102.

***Education of health care professionals about genetics.***

The number of people for whom testing is performed is steadily increasing. Expert and non-expert health professionals are increasingly confronted with inheritance questions from patients and their families103. Clinicians are being called upon more often to have informed discussions with individuals and families about

genetic results. If genetic testing were available for all individuals with an ASD, the number of potentially important genetic findings would outstrip the capacity for reliable and valid interpretation and counselling. In the coming years, expanding the role and size of the genetic counselling workforce to accommodate testing across health services will be essential, but even this will not be sufficient to fill the demand104, as frontline professionals in mental health care will also need to acquire the relevant genetic knowledge and skills. Several educational strategies can be used in parallel in order to achieve a better baseline knowledge about ASD genetics among providers of mental health care. First, clinical genetic reasoning should be added to basic genetic principles in medical and specialist training. Second, teaching modules with this focus should be made available for continuing medical education programmes for specialist and family clinicians. The likely result of this will be a better availability of advice to families, accepting that novel identified variants and complex cases will remain within the domain of clinical geneticists.

***Collaborative genotype–phenotype databases.***

CMA and sequencing can identify a high number of genetic variants in any given individual, thereby spawning an entirely novel challenge: how to distinguish the variants of no significance from those that are potentially relevant to the phenotype under examination. Given the rarity of some genetic variants and the complexity of some of the associated phenotypes, this obstacle can be overcome only if such observations are collected collaboratively, on a global scale, and preferably including the possibility of longitudinal data collection. An important aspect of such global initiatives would be the inclusion of developing countries in these programmes, at the level of both data collection and knowledge accessibility. Some recent initiatives are listed in Further information at the end of this article. However, large, longitudinal studies tend to be unpopular with funding agencies owing to the time taken to gather definitive results. An increasing amount of detailed patient-related data is being collected over time in electronic health records (EHRs), and integrating these data with genomic data is central to personalized and precision medicine initiatives105,106. With large enough samples, this will allow the identification of genetic contributions to specific phenotypes and the delineation of clinical syndromes at a low cost. However, ASDs are often not well captured in EHRs, with confirmation rates between 33%107 and 43%108. Using broader criteria, validation rates increased to 74% and 81%, respectively. Large consortia of ASD clinics and centres will be required to generate data sets based on an agreed set of diagnostic criteria109. Considering the lifetime costs associated with ASDs110, one could ask whether governments and funders can afford not to do more to understand ASDs and develop effective treatments to reduce comorbidity and early mortality. To date, there have been limited systematic collaborative longitudinal efforts to capture detailed information from clinical ASD genetic testing. Considering the annual worldwide number of CMAs undertaken clinically in individuals with an ASD, this is a missed opportunity, as such efforts would probably lead to a much better understanding of known and new causal variants. Although databases such as DECIPHER and ClinGen111 are of great utility, autism-specific initiatives are now required to provide rich information from clinical services about very large numbers of people, at minimal cost to research funding agencies. Initiatives relating to specific CNVs have shown the utility of this method112,113, but a broader approach, possibly funded per person reported, is needed to collect detailed genetic and phenotypic information about a wide range of rare variants, while also contributing to gene discovery.

## Conclusions

The recent progress in our knowledge derived from genetic studies of ASDs is such that, at present, the question is not so much when these findings will start to influence our clinical practice but rather how we can optimally use the knowledge we already have and what is required to use its full clinical potential in the future. TABLE 3 provides an overview of strategies discussed in this Review that are likely to help bridge the gap between current research insights and clinical needs in the realm of autism genetics. Already, in our daily practice, genetic knowledge can have a relevant clinical impact; in up to one-third of individuals with an ASD, a genetic aetiology can be identified, which in some instances leads to the identification of treatable somatic comorbidities. In addition, knowing the causative genetic variant or variants can provide decisive information for genetic counselling. Guidelines of major European and American health associations concur on the

importance of genetic testing in ASDs. However, despite the steady increase of the number of genetic tests performed, no policy regarding genetic testing in ASDs is uniformly implemented across countries. In addition to variability in financial resources, it is likely that clinicians' reluctance to consider genetic testing is also a relevant variable. The only way to overcome the latter would be to invest in the education of clinicians working in the ASD field regarding their relevant knowledge of genetic principles. The identification of risk genes for ASDs has also led, for the first time, to rapidly emerging insights into the neurobiology underlying autism pathophysiology. The impact on pharmaceutical research can no longer be considered speculative, given the evident increase in clinical trials using novel compounds and/or using genetic information for treatment stratification. Finally, evolving genetic insights are bound to gradually alter the scientific and clinical conceptualization of ASDs from exclusively behaviourally defined disorders towards broader medical conditions with the possibility — or even likelihood — of comorbidity of other CNS-related and CNS-unrelated somatic phenotypes. Accordingly, a careful broad assessment of such phenotypes may be more useful than the dichotomy between syndromic and non-syndromic ASDs. Clinicians need to shift from a narrow focus on the behavioural deficits that are characteristic of ASDs to a broader view that encompasses not only psychiatric but also somatic comorbidity. From a classification standpoint, it may be necessary to evolve towards a taxonomy using genetic aetiology as the ordering principle. The high-resolution methods that are currently available to investigate the human genome appear to have outpaced our ability to adequately handle the results in a clinical setting. To resolve this, we urgently require longitudinal research protocols that can be implemented in multiple large clinical academic sites simultaneously, with appropriate consent for data sharing. An integrated approach to autism genetics and phenotyping, and improved clinical understanding and management is needed, requiring unprecedented international cooperation between autism researchers, the autism community and research funders.

## Box#1: How can genetic information lead to actionable clinical interventions?

### *Opportunities for active surveillance of ASD comorbidities*

Genetic findings could have an impact on the clinical management of individuals with an autism spectrum disorder (ASD). Arguably, the first area of impact of recent genetic findings is the identification of treatable somatic comorbidities. The examples discussed here (and see the figure) represent a non-exhaustive list of comorbidities observed in individuals harbouring ASD-related genetic variants. Screening of individuals with an ASD can lead to the identification of a causal variant associated with additional phenotypes, for example, the 22q11.2 deletion114. This should prompt referral to the relevant specialties to screen for additional medical comorbidities, such as cardiovascular or velopharyngeal abnormalities, immune deficiency and calcium metabolism problems in individuals with the 22q11.2 deletion115. In addition, active surveillance of neurodevelopment is warranted, particularly regarding early signs of psychotic disorders, as 25% of individuals with 22q11.2 deletion syndrome will eventually develop a psychotic disorder in late adolescence or early adulthood115. Similarly, the detection of a paternal 15q11–q13 deletion (Prader–Willi syndrome) warrants endocrine evaluation along with neuropsychiatric screening116. Such implications are not limited to CNVs. For instance, a deleterious PTEN variant in someone with an ASD and macrocephaly has implications for cancer screening for the individual and their family117, whereas a mutation in the gene encoding activity-dependent neuroprotector homeobox protein (ADNP)118 in an individual with an ASD warrants screening for heart defects, vision impairment, epilepsy and immune status118.

### *Genetics can inform choice of pharmacotherapy*

Currently, there is a growing list of genetic disorders for which emerging evidence indicates that genetically based management decisions would potentially affect neuropsychiatric status. For example, a detailed case report suggests that people with severe aggressive behaviour and deletions of 15q13.3 from breakpoint 4 (BP4) to BP5, which include cholinergic receptor nicotinic α7 (CHRNA7), appear to benefit significantly from galantamine treatment119. Galantamine is both an allosteric modulator of the CHRNα7 protein and an acetylcholinesterase inhibitor. Additional examples include dietary treatment for phenylketonuria and

S-adenosyl methionine treatment for Lesch–Nyhan syndrome120,121. Genetic information can also be relevant with regard to potential drug side effects. For instance, a person with an ASD and comorbid psychotic disorder and mood symptoms may require mood-stabilizing and antipsychotic medication. A 17q12 deletion would not only explain the psychiatric diagnosis in this individual (it has previously been associated with ASDs and schizophrenia122), but would also lead to clinically actionable recommendations, as this copy number variant (CNV) is also associated with renal cysts and subsequent renal failure, and maturity-onset diabetes of the young type 5 (MODY5)122. Given the nephrotoxicity of lithium and the association of olanzapine with weight gain and metabolic syndrome, the genetic results would highlight the need to choose a different medication regimen for this patient.

***Choosing the right behavioural interventions***

Genetic findings in ASDs can also help to direct behavioural intervention strategies. For instance, people with SHANK3 deletions tend to have more advanced receptive communication skills than expressive (verbal) language ability123. This implies that they may benefit from assistive communication strategies that may not have been an intervention focus had the genetic cause of their ASD not been known.

<INSERT FIGURE - Somatic pleiotropy of ASD-related genetic variants - ABOUT HERE>

**Box#2 - Insight into perspectives in the autism community**

Advances in autism spectrum disorder (ASD) genetics and the translation of those advances into clinical settings should be seen in the context of community views regarding the opportunities and challenges involved. This is particularly relevant because some parents, individuals with an ASD and professionals consider the autism spectrum to be a 'difference' between people rather than a disorder. In that context, some people would prefer that the term risk is not used when discussing genetic factors and recurrence within families, as risk implies a negative connotation. Similarly, some people are concerned that genetic testing may lead to terminations of pregnancy or lead to interventions that are specifically designed to change the core features of ASDs. There may be less concern about the utility of genetic findings in the treatment of health or mental health conditions. These views are in keeping with the findings from UK research priority-setting exercises (see Further information), which suggest that many within the community would like more focus on research about diagnosis, intervention and services124–126, rather than biological understanding. The emphasis may therefore be too heavily on parent reproductive decisions, whereas efforts to examine the utility of genetic information to improve the health and quality of life of people with an ASD are receiving little discussion. It is important to understand and respect the perspectives from all those involved in the debate about genetics research and the resulting translational opportunities. This process has already started: some initiatives have focused on identifying the differing views of parents about clinical genetic testing. A US-based survey among 397 parents of children with an ASD demonstrated that 86% of parents agreed or somewhat agreed with the statement "I am interested in finding out if genetic factors are a cause of my child's ASD" (REF. 90). A UK-based survey of 380 parents regarding theoretical opinions about clinical genetic testing found that most parents favoured the availability of testing that might lead to knowledge about the cause of their child's ASD127. Some parents were keen on testing for the following reasons, as shown by these quotes: "To find out if there was a high risk of ASD for future children" and "To prepare ourselves for what difficulties may lay ahead, and to seek early intervention". Importantly, some British parents disagreed with testing or would not have testing, stating that it would not alter their reproductive decisions127. Some parental responses were: "The outcome [of genetic testing] wouldn't change my wish to have another child. My daughter who has ASD is wonderful" and "Autistic kids may take quite a bit of extra hard work, but they are also amazing in the way they see the world around them, the world would be boring if we all got perfection." The British survey also found that improved parental education of ASD genetics is important. Half of parents in the UK study said that having a child with an ASD had affected their reproductive decision-making, but there was evidence that they overestimated the chance of recurrence, as three-quarters of parents estimated that their risk of having another child with an ASD was above 10–15%, and one-third of parents considered that the risk was greater than 50%. This is in line with the

US study showing that the median recurrence rate estimate by parents of children with an ASD was 50%90. In addition, there may be concerns about ambiguous interpretation of results and psychological burdens related to genetic testing. To families, it may not be clear to what extent genetic testing can improve the health outcome of individuals, as evinced by statements from British parents, such as “The test may not give a definite answer” or “How accurate would the information be?” These findings are in keeping with clinical experience, which shows that some parents turn down the opportunity for CMA testing despite the knowledge that this may lead to new information about recurrence rates for any future pregnancies. Further quantitative and qualitative research is needed to give insights into views about clinical genetic testing from the parents and siblings of individuals with an ASD, from people on the autism spectrum who have one or more children with an ASD, and from all adults with an ASD.

## Key Definitions

***DECIPHER (Database of Genomic Variation and Phenotype in Humans Using Ensembl Resources).***

An interactive web-based database that incorporates a suite of tools designed to aid in the interpretation of genomic variation.

***Exposed attributable risk***

The difference in the rate of an outcome in an exposed and an unexposed population, expressed as a fraction of the exposed population. In genetics, the exposure is the genotype.

***Gene set enrichment approaches***

Analytical strategies to investigate whether there is enrichment in association signals attributed to a predetermined group of genes.

***Incidental findings***

Genetic discoveries that have an effect on the individuals in which they occur but are not directly relatable to the disease under investigation. An example would be the discovery of a genetic alteration with relevance to familial cancer while interrogating the genome for mutations associated with an autism spectrum disorder.

***Machine-learning approaches***

Research strategies in which a predictive model is trained using data. Examples of machine-learning approaches include neural nets, support vector machines and decision trees.

***Penetrance***

The proportion of individuals with a particular genetic variant who display a particular phenotype. Expressivity The extent to which an individual exhibits a given trait or phenotype

***Pleiotropy***

The association of two or more independent phenotypes with one gene, or variation in that one gene

***Private mutations***

Rare or unique mutations in the DNA sequence that are restricted to an individual, family or population.

***Somatic phenotypes***

Variations in or symptoms of the body (soma) or bodily functions. Somatic phenotypes can be distinguished from psychiatric phenotypes, which refer to variation in or symptoms of behaviour, cognition, perception and feelings.

***Taxonomy***

Classification based on a priori defined shared characteristics. The current classification of psychiatric disorders (as used in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD)) is based mainly on observed symptoms and disease course.

***Truncating mutations***

Variations in the genetic code that alter the transcripts in such a way that the resultant proteins are shortened and incomplete, or not formed.

***Variants of unknown significance (VUS)***

Genetic variants for which a phenotypic effect is unknown.

***Weighted gene co-expression network analysis (WGCNA)***

An analytical approach that clusters genes into modules according to the strength of the correlations between their expression values.

**Figure Legends**

***Figure 1- The potential contribution of genetic assessment.***

On the left side of the figure are the recurrence rate estimates for offspring in three different scenarios in the absence of any specific genetic information. On the right side of the figure are the same families but with genetic findings. Estimates of recurrence rates of ASDs are evolving with the collection of samples from large numbers of families (simplex, multiplex and multigenerational), and figures given are based on the currently available knowledge. a | A mother is affected with an autism spectrum disorder (ASD) and intellectual disability (ID). Without genetic testing, the risk of an ASD in the offspring can only be roughly estimated, as at present, few data are available to provide evidence-based estimates. Offspring risk is likely to be higher than the population risk of ~1% and is probably close to the sibling risk estimate (10–15%). After genetic assessment, a highly penetrant variant is identified in the mother. Note that for many genetic variants, accurate penetrance rates are still evolving with ongoing studies. For instance, with genetic knowledge in this scenario, the recurrence rate in male offspring may vary between 50% (assuming 100% penetrance) and, for example, 4% (in the case of a genetic variant with 8% penetrance). b | Unaffected parents have a daughter with an ASD. For an individual with a full sibling with an ASD, the recurrence rate (sibling risk) is estimated to be 10–15%. The risk for female siblings may be lower than for male siblings, although this is not a consistent finding82,128. After genetic assessment, a de novo variant is identified in the affected child, and the recurrence rate for the siblings can now be estimated as the population risk of ~1%. To be more precise, the recurrence rate may be somewhat higher than ~1% owing to the impact of residual risk, although probably not by much. This scenario assumes that the de novo variant occurred in a parental germ cell or the resulting zygote; if the variant occurred earlier during parental germline development it may still be present in mosaic form in the germ line of one of the parents, which will increase the recurrence risk for future offspring depending on the proportion of germ cells harbouring the variant. c | Unaffected parents have a son with an ASD. The recurrence rate for siblings is estimated to equate to standard sibling risk (10–15%). After genetic assessment, an inherited highly penetrant variant is identified in this child, transmitted by his unaffected carrier mother (this variant exhibits incomplete penetrance in females and 100% penetrance in males). The recurrence estimates are therefore 50% in male offspring (50%×the 100% penetrance in male offspring) and ~10–50% in female offspring (50%×the<100% penetrance rate in female offspring). Note that these examples are necessarily somewhat simplified and therefore do not entirely do justice to the complexity of the genetic counselling. For example, the phenomenon of assortative mating may further influence the recurrence rate (such as in the scenario depicted in part a). In addition, the female protective effect and parental age are reported to be factors of influence, but accurate estimates of their impact on recurrence rates are not well established and are likely to vary as a function of the specific causative variant involved. For instance, the penetrance of an ASD in carriers of SHANK3 deletions appears to be equal in males and females.

***Figure 2 - Medication trials for people with an autism spectrum disorder.***

This graph summarizes numbers and types of medication trial for people with an autism spectrum disorder (ASD) during the period 2001–2015; data are from ClinicalTrials.gov. In red are the trials examining existing drugs that are typically used in the treatment of psychiatric disorders, including selective serotonin reuptake inhibitors (SSRIs), stimulants and antipsychotics. In blue are the novel trials involving compounds or existing drugs that are not typically used in psychiatric disorders, such as oxytocin and antibiotics. Within each bar, the numerator provides the number of trials of novel compounds for which genetic studies have contributed to the rationale for the choice of the compound under study; the denominator reflects the total number of trials of novel compounds in that time period. The x axis depicts 3-year time periods, starting in January 2001. For additional information on the individual trials, including ClinicalTrials.gov identifiers, see Supplementary information S1 (table).

**Table Legends**

***Table 1 - Recurrent structural abnormalities consistently reported in association with ASDs.***

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; Del, deletion; Dup, duplication; ID, intellectual disability; OCD, obsessive–compulsive disorder. *Estimates of penetrance (the rate of ASD in carriers of each variant) are preliminary and may be influenced by ascertainment. In particular, the individuals undergoing genetic testing are likely to be enriched for people with an ASD, which will inflate penetrance estimates. Robust estimation of penetrance will require an assessment of ASD and genetic-variant frequencies in wider, unselected populations. ‡ The reported phenotypic spectrum for associated neuropsychiatric and somatic phenotypes is likely to be incomplete owing to novelty of the association and/or a paucity of broad clinical observations in people with a deleterious genetic variant (that is, mutation carriers).

***Table 2 - Genes associated with ASDs by sequencing studies***

Genes with strong evidence for ASD association (from REF. 1), as indicated by single-nucleotide variants (SNVs) identified by sequencing studies. The table provides an overview of the estimated penetrance for ASDs of each gene affected by mutation, as well as other associated neuropsychiatric phenotypes (neuropsychiatric pleiotropy) and associated somatic abnormalities (somatic pleiotropy). ADHD, attention deficit hyperactivity disorder; ADNP, activity-dependent neuroprotector homeobox protein; ANK2, ankyrin 2; ARID1B, AT-rich interactive domain-containing 1B; ASD, autism spectrum disorder; CHD8, chromodomain helicase DNA-binding 8; DYRK1A, dual specificity tyrosine-phosphorylation-regulated kinase 1A; GRIN2B, glutamate ionotropic receptor NMDA type subunit 2B; ID, intellectual disability; KATNAL2, katanin p60 subunit A-like 2; POGZ, pogo transposable element with ZNF domain; SCN2A, sodium voltage-gated channel α-subunit 2; SYNGAP1, synaptic RAS GTPase-activating 1; TBR1, T-box brain 1. *Preliminary assessment may be influenced by ascertainment. In particular, the individuals undergoing genetic testing are likely to be enriched for people with an ASD, which will inflate the penetrance estimates. Robust estimations of penetrance will require an assessment of ASDs and genetic-variant frequencies in wider, unselected populations. ‡ The reported phenotypic spectrum is likely to be incomplete owing to the novelty of the association and/or a paucity of broad clinical observations in people with a deleterious genetic variant (that is, mutation carriers).

***Table 3 - Strategies to bridge the gap between research knowledge and clinical need***

ASD, autism spectrum disorder; CNS, central nervous system

## Tables

### *Table 1*

| | ASD penetrance* (rate of ASD in carriers) | Neuropsychiatric pleiotropy‡ (associated neuropsychiatric phenotypes) | Somatic Pleiotropy‡ (associated somatic phenotypes) |
|---|---|---|---|
| Del1q21.1 | 8%[129] | ID[130], ADHD[129], Schizophrenia[131] | Microcephaly[129], Heart defect[132], Eye abnormalities[129], Short stature[129], Epilepsy[129] |
| Dup1q21.1 | 36%[133] | ID[133], ADHD[129,133], Schizophrenia[133], Speech delay[134] | Epilepsy[133,134], Macrocephaly[133], Heart defect[133] |
| Del2q23.1 | 100%[135] | ID[135], ADHD[135], Language Disorder[136], Motor delay[136] | Epilepsy[135,136], Obesity[136], Brachycephaly[136], Microcephaly[136], Short stature[136] |
| Del2q37 | 25-42%[137,138] | ID[139], ADHD[138] | Epilepsy[137], Short stature[139], Obesity[139], Heart defect[137] |
| Del3q29 | 27%[63,140] | ID[63], Speech delay[63], language disorder[63], Anxiety disorder[63], Schizophrenia[63], Bipolar disorder[63] | Gastrointestinal problems[63], Heart defect[63], Feeding problems[63], recurrent ear infections[63], abnormal dentition[63] |
| Del5q14.3 | 43%[141,142] | ID[141], Absent Speech[141] | Epilepsy[141,142], Capillary Malformation[141,142] |
| Dup7q11.23 | 41%[143] | ID[143], ADHD[144,145], Anxiety Disorder[145,146], Oppositional Defiant Disorders[145], Speech delay[134,145] | Epilepsy[143], Macrocephaly[145], Brachycephaly[147] Dilatation of ascending Aorta[145,147], Patent Ductus Arteriosus[147], Chronic obstipation[147], Kidney abnormalities[147] |
| Del8p23 | | ID[148], ADHD[138] | Heart defect[148], congenital diaphragmatic hernia[148] |
| Dup15q11-q13 | 69%[149] | ID[150], ADHD[151] | Epilepsy[134,152], defect[134], Muscle hypotonia[153], Short stature[153] |
| Del15q11.2 | 32%[154,155] | ID[154,155], ADHD[154,155], Schizophrenia[156], OCD[156], Speech delay[155] | Epilepsy[154,155], Ataxia[156], defect[156] |
| Dup15q11.2 | 43%[155] | ID[154], ADHD[155], Speech delay[155] | Epilepsy[154,155], Ataxia[155], Hypotonia[155] |
| Dup15q13.2–q13.3 | 80%[157] | ID[134], Speech delay[134] | Epilepsy[134], Urogenital anomalies[134], Recurrent infections[134] |
| Del15q13.2–q13.3 | 60%[157] | ID[157], ADHD[157] | |
| Del16p11.2 | 15%[158] | ID[158] | Epilepsy[158], Hypotonia[159], Sacral dimples[159], Speech articulation problems[159] |
| Dup16p11.2 | | Schizophrenia, Bipolar disorder[160] | Epilepsy[159], Hypotonia[159], Tremor[159], Ataxia[159], Sacral dimples[159], Speech articulation problems[159] |
| Dup16p13.11 | 25%[161] | ADHD[161], Speech delay | Epilepsy[134] |
| Del17p11.2 | Unknown | | Epilepsy[134] |
| Del17q12 | | Schizophrenia[122] | Macrocephaly[122], Renal anomalies[122] |
| Del22q11.2 | 30%[106] | Schizophrenia, ADHD, speech delay[115], anxiety disorders[115] | (amongst others:) Heart defect[115], Palate abnormalities[115], hypocalcaemia[115], Feeding difficulties[115], Recurrent infections[115] |
| Dup22q11.2 | 18%[162] | ID[162], ADHD[162] | Heart defect[163], Hearing loss[163], Urogenital anomalies[163], Palate abnormalities[163] |
| Del22q13.3 | >50%[123] | ID[123], Language disorder[123] | Epilepsy[123], Heart defect[123], Renal anomalies[123], Strabismus[123] |

## *Table 2*

| | Chromosome location | Estimated percentage of individuals with ASD in whom this variant is identified | ASD Penetrance1 (rate of ASD in carriers) | Neuropsychiatric Pleiotropy[2] (associated neuropsychiatric phenotypes) | Somatic Pleiotropy[2] (associated somatic phenotypes) |
|---|---|---|---|---|---|
| ***KATNAL2*** [37] | 18q21.1 | 0.08% | Unknown | Unknown | Unknown |
| ***POGZ*** [37] | 1q21.3 | 0.08% | Incomplete[164] | ID[164,165], Speech delay[164], language delay[164], Schizophrenia[61] | Microcephaly[164]<br>Obesity[164]<br>Impaired vision[164] |
| ***TBR1*** [37,166] | 2q24.2 | 0.08% | Unknown | ID[167] | Unknown |
| ***ADNP*** [37] | 20q13.13 | 0.10% | Complete[118] | ID[118,165], ADHD[118] | Recurrent Infections[118], Short stature[118], Heart defect[118], Hypotonia[118], Hypermetropia[118], Epilepsy[118], Hyperlaxity[118] |
| ***SYNGAP1*** [37] | 6p21.32 | 0.10% | Unknown | ID[168,169] | Epilepsy[168] |
| ***GRIN2B*** [37,166] | 12p13.1 | 0.13% | Unknown | ID[170] | Epilepsy[170] |
| ***ANK2*** [37] | 4q25-q26 | 0.13% | Unknown | None reported | Heart arrhythmia[171] |
| ***ARID1B*** [37] | 6q25.3 | 0.13% | Incomplete[172] | ID[172], Speech impairment[172,173] | Short stature[174], Hypertrichosis[173], cryptorchidism[173], Epilepsy[173], Vision impairment[173] |
| ***SCN2A*** [37] | 2q24.3 | 0.13% | Incomplete[59] | ID[60], Schizophrenia[61] | Epilepsy[62], Episodic Ataxia[62] |
| ***DYRK1A*** [37,166] | 21q22.13 | 0.13% | Incomplete[175] | ID[175,176] , Speech impairment[175,176], ADHD[175], Anxiety[175] | Microcephaly[175,176], Epilepsy[175,176], Vision impairment[175], Short Stature[175], Gastrointestinal symptoms / feeding difficulties[175,176] |
| ***CHD8*** [37,166] | 14q11.2 | 0.21% | Incomplete[32] | ID[32,177], Schizophrenia[177], Speech delay[177], Sleep problems[32] | Macrocephaly[32,177], Gastrointestinal symptoms[32] |

## *Table 3*

| State-of-the-art research knowledge of ASD genetics | Clinical need | Required to bridge the gap | Helpful strategies |
|---|---|---|---|
| Numerous rare *de novo* and inherited genetic variants can increase ASD risk in an individual. | The ability to inform the affected individual and family about the contribution of the identified genetic variant. | - Sufficient confidence in determining causality between the variant and ASD risk | - Reliable and comprehensive collection of genotype–phenotype data into accessible databases on a global scale.<br>- Strive for uniform implementation of genetic testing guidelines.<br>- Educate healthcare professionals about clinical genetic reasoning. |
| Genetic variants display variable penetrance. | The ability to inform the affected individual and family about recurrence risk. | - Identification of factors (genetic and environmental) driving variable penetrance. | - Evaluate phenotypes as continuous traits in the familial context. |
| Genetic variants are often associated with other phenotypes within or outside of the CNS (pleiotropy). | The ability to inform the affected individual and family for other associated phenotypes, and screen or treat if appropriate. | - Identification of all other phenotypes associated with the genetic variant.<br>'- Identification of factors (genetic and environmental) driving pleiotropy. | - Stimulate broad phenotyping (including assessment of non-CNS related phenotypes) in genetic studies.<br>- View ASD as a medical disorder.<br>- Abandon dichotomy of syndromic versus non-syndromic classification. |
| Genetic risk variants converge on shared biological mechanisms. | Effective treatment strategies. | - Personalized medicine. | - Use genetic information to select individuals for specific treatment trials.<br>- Use biological insights to develop new molecular compounds. |
| Different opinions about genetic testing exist in the autism community. | A balanced and respectful view of possible ethical concerns related to genetic testing. | - Improve insight into autism community perspectives. | - Encourage studies investigating different perspectives, using quantitative and qualitative methods.<br>- Increase participation of the autism community in research agenda. |

## Figures

***Figure 1***

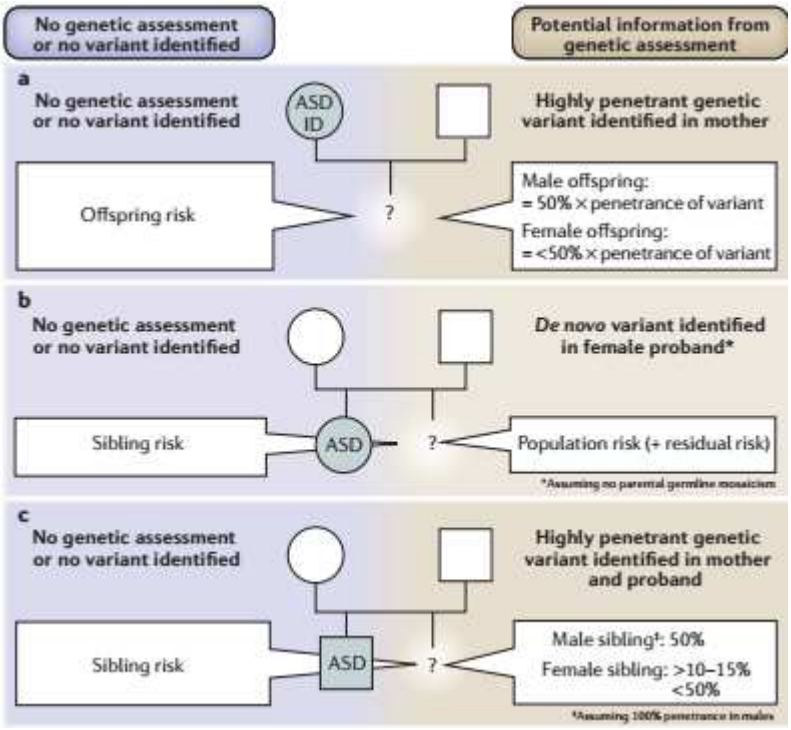
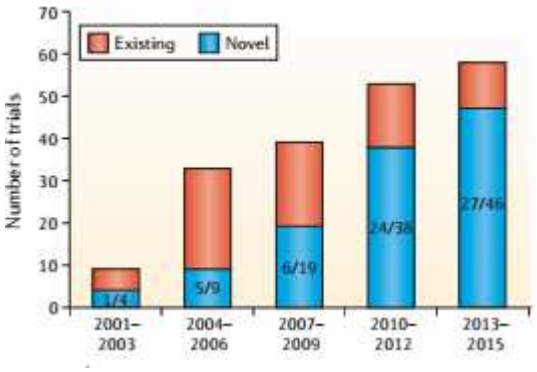
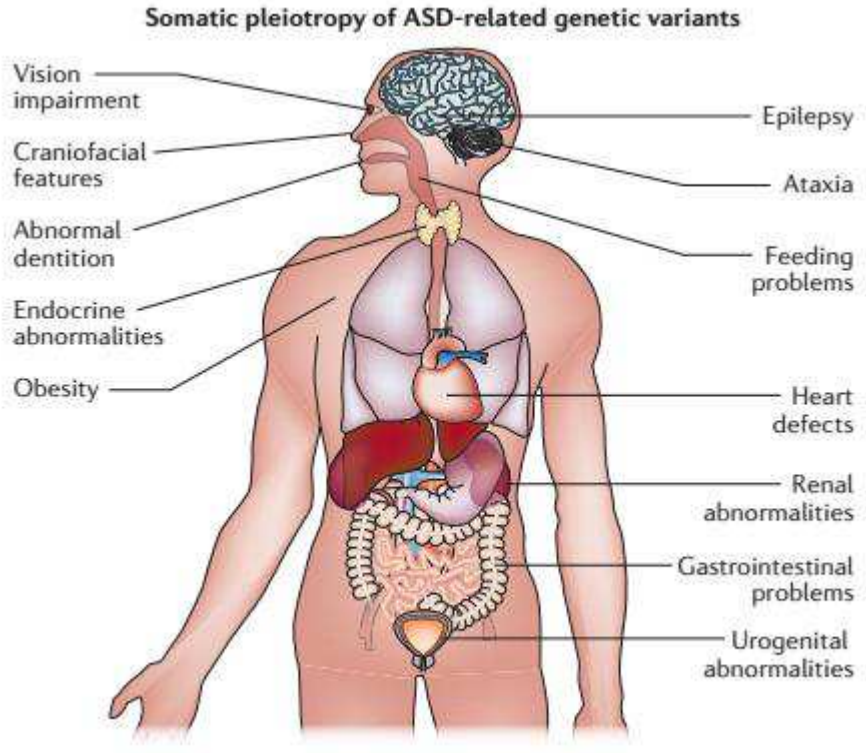



***Figure 2***




***Box1 Figure***

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