The Genetics of Autism

Varun Warrier, *Autism Research Centre, University of Cambridge, Cambridgeshire, UK*

Simon Baron-Cohen, *Autism Research Centre, University of Cambridge, Cambridgeshire, UK and Cambridgeshire and Peterborough NHS Foundation Trust (CPFT), Cambridgeshire, UK*

Autism spectrum conditions (henceforth 'autism') refer to a group of neurodevelopmental conditions involving difficulties in social interaction and communication and unusually repetitive and restricted behaviours and interest. Twin and family studies have established a significant heritability for autism. Autism is polygenic with variations across the allele frequency spectrum contributing to risk. Early linkage and candidate gene association studies were statistically underpowered to identify significant loci. Current genome-wide association studies have identified significant positive genetic correlation between autism and various measures of cognition. The use of genetic microarrays and next-generation DNA sequencing has identified tens of genes and copy number variants associated with autism. In addition, RNA microarray and sequencing studies of postmortem brain samples have identified transcriptionally altered genes and pathways in autism. Multiple lines of evidence converge on altered glial, synaptic and chromatin pathways as contributing to autism risk.

Introduction

Autism spectrum conditions (henceforth autism) refer to a heterogeneous group of neurodevelopmental disorders characterised by difficulties in social interaction and communication alongside unusually repetitive behaviour and unusually narrow interests (Lai *et al*., 2013). It has an estimated prevalence of 1 in 100, although recent reports from the Centers for Disease Control and Prevention (CDC) suggest that it may be higher (1 in 68). The median worldwide prevalence is estimated between 0.62 and 0.70 (Lai *et al*., 2013). There is a marked sex difference: between 3 and

4 times as many males are diagnosed with autism compared to females, which may be due to innate biological factors (e.g. a female protective effect) or due to other social or cultural factors (e.g. females with autism may be better at 'masking' their phenotypes and hence may not be diagnosed with autism, and females are often diagnosed later than males) (Lai *et al*., 2013). In addition to the difficulties in the core diagnostic criteria, individuals with autism often have other comorbid phenotypes. For example, many individuals have atypical language development, sensory hypo or hypersensitivity and difficulties in motor coordination, including dyspraxia. Approximately 38% of all individuals with autism have intellectual disability (ID), as estimated by the CDC. Similarly, there is a reasonably high comorbidity with ADHD, depression and suicidal ideation (Lai *et al*., 2013).

Aside from clinical comorbidities, on average, individuals with autism tend to perform better on measures of 'systemising' drive (Baron-Cohen *et al*., 2003), that is, the drive to analyse and build systems, based on identifying the laws that govern the particular system, in order to predict how that system will work. Systems may be abstract, mechanical, natural, collectible and motoric. They also perform better on tests of attention to detail (Jolliffe and Baron-Cohen, 1997), a prerequisite for systemising. Individuals who are in the science-technology-engineering-maths (STEM) fields, or relatives of these individuals, are more likely to be diagnosed with autism or have higher levels of autistic traits (Ruzich *et al*., 2015; Wheelwright and Baron-Cohen, 2001; Baron-Cohen *et al*., 1997). Autistic individuals also, on average, tend to have difficulties in eye contact (Jones and Klin, 2013), attention to social stimuli (Dawson *et al*., 1998) and interpreting emotions (Baron-Cohen *et al*., 2001), which contribute to persistent difficulties in social interaction and communication. This may be because the social domain is less amenable to systemising, as it does not reduce to a set of rules.

There is considerable evidence that autism is partly genetic. Early twin studies established a prominent role for genetic variants by investigating concordance rate of both the clinical phenotype and associated behavioural and cognitive phenotypes in twins (reviewed in Bourgeron, 2016a; Ronald and Hoekstra, 2011). Recently, with increase in diagnosis rates and the availability of electronic records, it has been possible to establish familial recurrence rates in large population-based cohorts, providing converging evidence for familial recurrence rates (Sandin *et al*., 2014; Sandin *et al*., 2015). Buoyed by the heritability estimates, early molecular genetic studies focused largely on linkage

and candidate gene sequencing and association studies in autism. Candidate gene association studies were conducted in relatively small sample sizes, with systematic inflation of effect sizes (Warrier *et al*., 2015a). Most of the results from these studies have not replicated in studies with larger samples.

However, there were some early successes in candidate gene sequencing studies, particularly in identifying genes for syndromic conditions with comorbid autism such as *FMR1*, *TCS2* and *NF1* (Bourgeron, 2016a). The considerable genetic and phenotypic heterogeneity in autism has made it challenging to identify genes associated with the condition, necessitating investigations in large population cohorts given the small effect sizes and/or rarity of the genetic variants. Recent studies have leveraged large sample sizes available in population databases for autism such as the Simon's Simplex Collection and the Autism Genetic Research Exchange. In this article, we review the different methods used to investigate the genetic architecture of autism and related traits, and recent progress in autism genetics research.

Establishing heritability: twin studies and familial recurrence

Since the first description in 1943 by Kanner (1943), autism was known to be a condition that manifested in early childhood, leading to the hypothesis that the condition is at least partly genetic. Establishing heritability is important, as it provides evidence for a causal role of genes in autism risk, which can then inform molecular genetic studies. Early family studies that were conducted in the 1960s and 1970s did not find evidence for familiality, which was because autism was perceived as an extremely rare condition (in the 1960s and 1970s, prevalence estimates for autism were 2–4 in 10 000). However, deeper examination of family factors provided two clues that autism is likely to be, at least partly, heritable. First, the recurrence rate in siblings was considerably higher than the risk in the general population, and second, there was a family history of delayed speech in about a quarter of the families of autistic individuals surveyed. Despite this, early twin studies in the 1960s and 1970s were inconclusive due to methodological issues and the lack of statistical power.

The first twin study to report evidence for familiality in autism, by Folstein and Rutter in 1977, investigated the concordance of autism in a small sample of 11 monozygotic twins (MZ) and 10 dizygotic twins (DZ) (Folstein and Rutter, 1977). The concordance for autism was 36% in the MZ twins and 0% in DZ twins. Expanding the criteria to include associated cognitive and social impairment or the broad autism phenotype (BAP) showed that 82% of the MZ twins were concordant, whereas only 10% of the DZ twins were concordant. Since then, several studies have investigated the heritability of autism in twin samples in different populations. Heritability estimates have largely been comparable and high across twin studies, regardless of the ascertainment criteria (Ronald and Hoekstra, 2011).

A recent meta-analysis of seven twin studies identified a high twin heritability of 64–91% (Tick *et al*., 2016). In parallel, twin studies of 'autistic traits' have identified modest to high heritabilities between 60% and 90%, although this varies depending on the type of measure used and the age of the participants (Ronald and Hoekstra, 2011). A few studies have also conducted multivariate

coheritability analyses of autism and related traits, suggesting a significant shared genetic influence. The genetic correlation between autism/autistic traits and ADHD/ADHD traits in particular is high reflecting the phenotypic comorbidity (Ronald and Hoekstra, 2011). **See also**: **Twin Studies**

Family recurrence rates have also provided evidence for heritability for autism. Multiple studies from Scandinavian countries have identified similar risk ratio for siblings of individuals with autism (∼10%) (Sandin *et al*., 2014; Grønborg *et al*., 2013; Jokiranta-Olkoniemi *et al*., 2016). Family recurrence rates also offer other clues into the underlying genetic architecture of autism. One interesting observation is that siblings of female probands have higher risk for autism than siblings of male probands – an observation that is called the Carter effect (the effect was originally described in pyloric stenosis (Carter and Evans, 1996), but subsequently used in other conditions). The Carter effect suggests that females have a protective effect, suggesting that a greater mutation burden is required for a clinical diagnosis of autism (this has been confirmed using gene sequencing studies, see the following discussion). If the genetic risk is partly familial, that is not *de novo*, this higher genetic risk can be inherited by siblings, thus increasing the risk for autism. Investigations of twin and multiplex family samples have identified a higher relative risk for autism in siblings of female probands (Werling and Geschwind, 2015; Robinson *et al*., 2013). In contrast, large population studies have failed to find support for the Carter effect (Sandin *et al*., 2014).

Another interesting finding is the identification of autistic traits or the BAP in family members of probands (Wheelwright *et al*., 2010). This is also supported by the identification of higher relative risk for other psychiatric conditions in family members of probands compared to the general population (Frazier *et al*., 2015; Constantino *et al*., 2010; Jokiranta-Olkoniemi *et al*., 2016).

A third interesting finding is that of parental age. A few studies have demonstrated that increased paternal age increases the risk for autism (Sandin *et al*., 2015; Frans *et al*., 2013; McGrath *et al*., 2014). Indeed, a considerable proportion of *de novo* mutations are paternal in origin (Kong *et al*., 2012; Gratten *et al*., 2016). Earlier studies have noted that increased paternal age also increases the risk for *de novo* mutations in the sperm as the number of cell replications increases with age (Kong *et al*., 2012; Gratten *et al*., 2014).

Finally, another hypothesis which has received considerable support is the idea that higher autistic traits or psychiatric liability in individuals is likely to delay fatherhood (McGrath *et al*., 2014; Gratten *et al*., 2014). However, a recent study has shown in addition to increased paternal age, the difference in ages of the parents also contributes to risk for autism, with the risk increasing as the difference in ages increases (Sandin *et al*., 2015). The mechanism underlying the increased risk for increased differences in parental age is unclear.

Early studies: linkage

With evidence of considerable heritability for autism from twin studies, early genetic studies focused on linkage of multiplex autism families to identify loci associated with the condition. Linkage studies investigate the inheritance of regions of

chromosomes in family pedigrees. The first autism linkage study was reported by IMGSAC in 99 families (International Molecular Genetic Study of Autism Consortium, 1998). Early linkage studies were nonparametric and in a relatively small sample size of 100–200 families. These studies used relatively sparse linkage genotyping and yielded limited success. Although several loci have been associated with autism or related traits, only a few of these loci have been consistently associated with the condition (Geschwind and State, 2015a). Some of these loci overlap with observed copy number variation in autism, suggesting that these may indeed reach statistical significance as sample sizes increase. For example, Alarcon and colleagues identified linkage at 7q35 when investigating language-related quantitative traits in autism (Alarcón *et al.*, 2008). Copy number variation in 7q35 has also been implicated in autism (see: https://gene.sfari.org/autdb/CNVSecDis.do?l=7q35), although this is not significant at a genome-wide level (Sanders *et al.*, 2015). Replication and functional analysis in foetal postmortem brain tissues identified *CNTNAP2* as a likely candidate gene associated with language-related phenotypes in autism (Alarcón *et al.*, 2008). However, subsequent sequencing studies have failed to identify a significant association between rare genetic variants in CNTNAP2 and autism (Murdoch *et al.*, 2015; Sanders *et al.*, 2015), although Cntnap2$^-$ mice display language and social deficits (Peñagarikano *et al.*, 2011). **See also**: **Linkage Analysis**

Early studies: syndromic forms of autism and candidate gene associations

Many genes currently associated with autism were first identified through specific syndromic forms of autism. For example, four early genes identified with autism – *FMR1*, *TSC1* and *TSC2* and *MECP2* – are all associated with syndromic forms of autism (fragile X syndrome, tuberous sclerosis and Rett syndrome). Early studies also investigated large chromosomal abnormalities by karyotyping. Because of the low resolution of these studies, it was impossible to identify specific genes associated with the condition. Today, the prevalence of chromosomal abnormalities is estimated to be less than 2% in autism (Bourgeron, 2016a). However, early studies identified genes by sequencing candidate genes in loci with frequent deletions and/or duplications in autism.

Bourgeron and colleagues used this approach to identify three early genes with autism: *SHANK3*, *NLGN3* and *NLGN4X* (Jamain *et al.*, 2003; Durand *et al.*, 2007). *NLGN3* and *NLGN4X* code for postsynaptic, transmembrane proteins called neuroligins that contribute to the formation and maintenance of synapse. Following the observations of *de novo* deletions at Xp22.3, Jamain and colleagues sequenced three neuroligin genes, *NLGN3*, *NLGN4X* and *NLGN4Y*, in individuals with autism and identified mutations in two families (Jamain *et al.*, 2003). This was followed by the sequencing of *SHANK3*, which codes for another postsynaptic protein that binds with neuroligins (Durand *et al.*, 2007). *SHANK3* is in 22q13, microdeletions which were known to contribute to developmental delay and autistic behaviour. Three of the families sequenced carried mutations in SHANK3 providing evidence for the association of *SHANK3* with autism. Subsequent gene sequencing efforts in large cohorts has provided further support for *NLGN3* and *SHANK3* in autism (Sanders *et al.*, 2015).

Candidate gene approaches have also provided several false positives. Several genes have been investigated in autism using a candidate gene association approach (for a list, see: https://gene.sfari.org/autdb/HG_Home.do). These were typically but not always conducted in relatively small sample sizes, investigating a small number of genetic variants. Warrier, Chee and colleagues conducted a meta-analysis of candidate gene association studies in autism where they reviewed the evidence of 552 genes that have been included in association studies in autism (Warrier *et al.*, 2015a). Common genetic variants in only 27 of these genes had been investigated in three or more independent cohorts, suggesting a scarcity of well-replicated genetic associations for autism. None of the variants included in the meta-analysis were significant in a larger genome-wide association cohort.

Genome-wide association studies of autism and related traits

A few genome-wide association studies have also investigated the genetic architecture of autism with limited success. In contrast to candidate gene association studies, genome-wide association studies typically investigate hundreds of thousands of genetic variants across the genomes and then correct for the total number of independent statistical tests performed. Owing to the number of tests performed, sample sizes have to be several orders of magnitude larger than candidate gene association studies to identify significant associations.

The first study, by Wang *et al.* (2009), investigated 780 families initially and a second cohort of 1453 autistic individuals and 7070 controls. Meta-analysis of the two cohorts identified one locus at 5p14.1 that was significant ($P < 5 \times 10^{-8}$). This intergenic locus was located between two cadherin genes (*CDH10* and *CDH9*) that are involved in diverse neural functions and contain a unique calcium-binding domain. They replicated the locus in two smaller, independent cohorts. Interestingly, this region was also implicated in another genetic association study that used data from 438 autistic families (Ma *et al.*, 2009). SNPs in 5p14.1 were nominally significant ($P < 0.05$) although it did not reach genome-wide significance.

Despite these early success, subsequent studies have not been able to replicate association at 5p14.1 at a genome-wide association level, leading to the conclusion that these early studies were statistically underpowered and the effect size inflated due to winner's curse (or regression to the mean, where the effect size that are most likely to cross the threshold of significance are likely to be inflated when the statistical power is limited).

Four further studies have reported significant association results. In 2009, Weiss, Arking and colleagues (Weiss *et al.*, 2009) used data from multiple different cohorts and meta-analysed results from transmission disequilibrium tests and association studies to identify one SNP that was significant at 5p15.2 between genes *SEMA5A* and *TAS2R1*. However, the *P*-value threshold used for significance was not the traditional GWAS threshold of 5×10^{-8}, but a more liberal threshold of 2.5×10^{-7}, identified using permutation and after accounting for LD. Another study by Anney and colleagues (Anney *et al.*, 2010) divided participants into four groups along two axes: one

on ethnicity (primary European ancestry vs all ancestry) and one on diagnosis (strict autism vs inclusive spectrum). They identified an intronic SNP in *MACROD2* that was associated with strict autism below a genome-wide threshold. A further study conducted a cross-ethnic meta-analysis (European ancestry and Chinese ancestry) to identify variants associated with autism. Meta-analysis identified common variants at the 1p13.2 locus associated with autism. Interestingly, 1p13.2 has been previously been linked to autism in linkage studies (Xia *et al.*, 2014). Recently, work from the Psychiatric Genomics Consortium using genetic data on more than 16 000 individuals identified an association at 10q24.32 (rs1409313, $P = 1.05 \times 10^{-8}$) (The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium 2017).

Despite the general lack of replicably associated loci, there is considerable evidence for a role of common genetic variants, *en masse*, identified using different SNP heritability measures. Using data from simplex (only one individual with an autism diagnosis) and multiplex families (at least two individuals with an autism diagnosis in the family), Klei *et al.* (2012) have identified a narrow-sense heritability between 40% and 65% for autism. The heritability was higher for multiplex families (65%) than for simplex families (~40%), consistent with the observation of higher number of *de novo* loss of function (dnlof) mutations in simplex probands than in the general population (Iossifov *et al.*, 2014; Kosmicki *et al.*, 2017; Sanders *et al.*, 2015).

This estimate of narrow-sense heritability was confirmed by another study that suggested that the majority of the genetic risk for autism is attributable to common variants (Gaugler *et al.*, 2014). The same study identified that dnlof mutations contributed to ~3% of the variance but explained a significant proportion of individual liability. Summing up the contribution from different classes of genetic risk, genetic variants explained approximately about 60% of the total variance (Gaugler *et al.*, 2014). The limited success in identifying significant loci despite the considerable SNP heritability may be due to multiple reasons, including the high polygenicity of the condition and the considerable phenotypic heterogeneity.

Other studies have tried to investigate the genetic architecture of specific subtypes of autism. Two studies have investigated the genetic architecture of Asperger syndrome, a subtype of autism where individuals have average or above average intellectual ability and preserved language. Neither of the studies, however, identified genome-wide significant association (Salyakina *et al.*, 2010; Warrier *et al.*, 2015b). A third study conducted family-based association analysis based on IQ and symptom profiles but did not identify significant differences in heritability nor significant associations, possibly owing to the reduced sample size and, consequently, statistical power (Chaste *et al.*, 2015). As there is considerable phenotypic differences between males and females, another study also investigated sex-stratified analysis but did not find evidence for higher genetic risk for females with autism (Mitra *et al.*, 2016).

A few studies have also investigated the genetic architecture of traits related to autism, given the considerable twin heritability of autistic and related social traits. Two studies have investigated the genetic architecture of social communication in children. Using data from a longitudinal cohort (ALSPAC),

St Pourcain and colleagues investigated the SNP heritability of social communication difficulties using the Children's Communication Checklist (CCC) and the Social-Communication Disorders Checklist (SCDC) (St Pourcain *et al.*, 2013, 2014). Both phenotypes were modestly heritable, with an SNP heritability estimate of the 0.18 for the CCC-derived phenotype and SNP heritability estimates ranging from 0.08 to 0.45 for the SCDC across different ages. Work from our laboratory has also identified significant SNP heritabilities for traits related to autism. Measures of empathy (cognitive and self-report) had significant SNP heritabilities of between 0.05 and 0.12 (Warrier *et al.*, 2016; Warrier *et al.*, 2017).

Development in statistical methods has also allowed for the interrogation of SNP coheritabilities (or genetic correlations) between autism and different phenotypes. Work by Robinson, St Pourcain and colleagues identified a significant and replicable genetic correlation between clinically diagnosed autism and the broader autism phenotype measured using the SCDC ($r_g \sim 0.30$) (Robinson *et al.*, 2016). However, this was dependent on the age at which the SCDC was completed by individuals, with the highest genetic correlation in childhood, which declined with age (St Pourcain *et al.*, 2017). Interestingly, there was no significant genetic correlation between autism and different measures of empathy (Warrier *et al.*, 2016; Warrier *et al.*, 2017).

In parallel, genetic correlation analyses have also investigated the shared genetic architecture between autism and nonsocial traits. The most interesting of these is the consistent positive genetic correlation between autism and different measures of cognition including educational attainment, childhood and adult cognition and number of college years (Bulik-Sullivan *et al.*, 2015; Clarke *et al.*, 2015; Sniekers *et al.*, 2017). Select traits that share a phenotypic and genetic correlation with measures of cognition are also positively genetically correlated with autism such as systemising (an interest in rule-based systems) (Warrier *et al.*, 2016).

This is in contrast with several studies that have identified a significant comorbidity and ID (Lai *et al.*, 2013). There is some epidemiological and genetic evidence of different genetic architecture of autism with versus without ID (Robinson *et al.*, 2014), although a comprehensive discussion is outside the scope of this article. A recent study, however, did not identify a difference in polygenic transmission for autism or educational attainment genetic scores between individuals with autism with versus without ID, providing support for a two-hit model (wherein a dnlof mutation in combination with a background of genetic risk predisposes an individual to autism as opposed to a dnlof mutation alone) (Weiner *et al.*, 2017). Interestingly, a recent study has identified that common genetic variants associated with different signatures of positive evolutionary selection in humans, and this may possibly linked to the underlying pleiotropy with different measures of cognition (Polimanti and Gelernter, 2017).

The current genetic correlation results are limited by the sample size and the effect statistical power of the autism GWAS analysis. Work from the Psychiatric Genomics Consortium (forthcoming) using a larger autism GWAS sample has identified several additional significant correlations including with other psychiatric conditions. **See also**: **Genome-Wide Association Studies**

Copy Number Variation in Autism

Copy number variants (CNVs) are submicroscopic genomic deletions or duplications that are larger than 1000 nucleotides (an arbitrary number). These are frequent in the genome and alter gene dosage (Zarrei *et al*., 2015). Several *de novo* and inherited CNVs have been identified in autism. In 2007, Sebat and colleagues published the first investigation of CNVs in autism. Using data from 118 simplex families, 44 multiplex families and 99 control families, they identified a significant excess of *de novo* CNVs in simplex probands (Sebat *et al*., 2007). Since then, several studies have investigated the role of CNVs in autism and replicated the initial results (reviewed in (Chung *et al*., 2014; Geschwind and State, 2015a)). Several well-validated results have emerged. CNVs are found in significantly higher frequency in probands compared to unaffected siblings (approximately 2–3 times more CNVs than siblings) (Sanders *et al*., 2015). Further, in probands, the CNVs tend to affect a larger number of genes, altering gene dosage of multiple genes. Consistent with the Carter effect, female probands carry more *de novo* CNVs than male probands (Sanders *et al*., 2015).

In addition, the number of *de novo* CNVs is significantly associated with lower IQ, a finding that has been replicated in multiple studies (Leppa *et al*., 2016; Levy *et al*., 2011). Overall, *de novo* CNVs are thought to contribute to small but significant proportion of risk in autism, with 5–15% of individuals with autism carrying *de novo* CNVs compared to only 1–2% in the general population (Geschwind and State, 2015a). While several CNVs have been identified, it has been challenging to identify CNVs at genome-wide significance due to the difference in lengths and number of genes affected by different CNVs at the same locus. By investigating *de novo* CNVs in multiple large cohorts, Sanders and colleagues identified six risk loci: 1q21.1, 3q29, 7q11.23, 16p11.2, 15q11.2-13 and 22q11.2 (Sanders *et al*., 2015).

Insights from Next-generation Sequencing Studies

The sequencing of the human genome in 2004, along with the advent of next-generation sequencing methods, allowed for large-scale hypothesis-free interrogation of the genome in autism using whole exome and, more recently, whole genome sequencing studies of large cohorts. These studies have identified a prominent role for dnlof mutations in autism. Although dnlof mutations have large effect sizes in comparison to common variants, their relative rarity in the population in addition to the genetic heterogeneity in the population makes it difficult to identify genes at a genome-wide significant threshold. Considerable advances have been made in identifying high confidence genes in autism using next-generation sequencing in largely simplex families, and there has been convergence on key findings (De Rubeis *et al*., 2014; Iossifov *et al*., 2014; Sanders *et al*., 2015; Samocha *et al*., 2014; Neale *et al*., 2012; O'Roak *et al*., 2012a,b).

Similar to *de novo* CNVs, dnlof mutations are enriched in simplex autism (where one child has a diagnosis of autism and the parents and other siblings do not have an autism diagnosis)

compared to controls. Female probands are likely to harbour more dnlof mutations than male probands, which is in line with the Carter effect. Similar to *de novo* CNVs, dnlof mutations are also associated with lower IQ and more severe autistic phenotypes. It is also clear that the number of dnlof mutations increases with paternal age, likely because spermatogonia undergo more active mitosis to produce sperm cells. Finally, these studies have also identified that *de novo* missense mutations and inherited loss-of-function mutations show smaller effects than dnlof mutations.

Recent efforts have integrated data from multiple sources in order to identify genes that are frequently mutated. Sanders and colleagues (Sanders *et al*., 2015) identified 65 high confidence genes (false discovery rate <0.1), although it is estimated that between 450 and 1000 such genes may be involved in autism (Geschwind and State, 2015a). Two recent studies have expanded and refined this list of genes using different methods. Yuen and colleagues performed whole-genome sequencing on multiplex autism families and identified 18 additional genes (Yuen *et al*., 2015; Yuen *et al*., 2017). In parallel, Kosmicki and colleagues utilised genetic data from a large-scale population resource – the Exome Aggregation Consortium (Lek *et al*., 2016) – to identify which *de novo* variants are not observed in the general population (Kosmicki *et al*., 2017).

Partly due to the families sequenced and partly due to the underlying genetic architecture, many of the genes identified turn not unique to autism. Indeed, several of these genes are also seen in conditions such as ID and schizophrenia (Geschwind and Flint, 2015), a feature that is also shared by CNVs identified in autism and common genetic variation. This shared pleiotropy among autism, ID and schizophrenia, among other conditions, suggests that a combination of different genetic and environmental effects shapes the disease-specific mechanisms. Investigation of transcriptomic signatures of autism and ID has identified distinct biological networks that contribute to ID and autism (Parikshak *et al*., 2013).

The use of large-scale data has also allowed for convergence in identifying pathways, particularly synaptic function, chromatic remodelling and downstream targets of *FMR*1, *MECP2* and *CHD8* (Pinto *et al*., 2014; Bourgeron, 2015). Several of the genes identified are associated with postsynaptic density, and many of the mutations are thought to affect synapse formation and plasticity, both during child development and in adulthood. Functional studies using postmortem brain tissue, and animal models, have identified altered synaptic development and pruning (Zoghbi and Bear, 2012; Tang *et al*., 2014). A few genes identified have also been associated with specific features, leading to subtypes of autism associated with mutations in specific genes.

For example, *CHD8* is the most frequently mutated gene in autism. *CHD8* encodes for a transcriptional repressor and remodels the chromatin by recruiting histone H1. Phenotypically, *CHD8* mutations cause macrocephaly (enlarged head circumference) and increased brain size and persistent gastrointestinal issues, which have been modelled in zebrafish (Bernier *et al*., 2014). These are all clinical signs in subgroups on the autism spectrum. Individuals with *CHD8* mutations also have similar facial dysmorphic features, including widely spaced eyes and a broad nasal tip, alongside cognitive impairments (Bernier *et al*.,

2014). In parallel, sequencing studies have also identified mutations in *CTNNB1*, a gene that encodes a protein (beta-catenin) that closely interacts with CHD8. CHD8 negatively regulates beta-catenin, and mutations in *CTNNB1* cause microcephaly and in some cases autism (Krumm *et al*., 2014). Several other genes identified in autism are associated with specific features, including *DYRK1A* (O'Roak *et al*., 2012a, 2012b) and *ADNP* (Helsmoortel *et al*., 2014). It is important to note that none of these genes have complete penetrance for autism, suggesting a small but significant role for other factors, including background genetic variation and environment, in modulating the effects of the mutation in these genes.

Transcriptional Dysregulation in Autism

As autism is a neurodevelopmental condition, studies have also sought to investigate alterations in gene expression directly in the developing brain. Parikshak *et al*. (2013) and Willsey *et al*. (2013) both used transcriptomic data from developing cortical tissues to identify if genetic risk for autism shows spatiotemporal convergence, using different methods. Willsey and colleagues constructed gene coexpression network using high-confidence autism genes as seed genes and investigated the enrichment for probable autism genes across multiple temporal and spatial windows. They identified enrichment in midfoetal prefrontal and primary motor-somatosensory cortex. Further, by investigating layer-specific gene expression, they were further able to identify enrichment in the cortical innerplate in the midfoetal prefrontal and primary motor-somatosensory cortices.

Parikshak and colleagues used a different approach to investigate convergence of genetic risk in autism in the developing brain. Using whole-genome transcriptome data, they constructed weighted gene coexpression modules agnostic of relationship to candidate genes in autism and followed their expression trajectories across developmental time. They identified three gene coexpression modules that were enriched for candidate genes and transcriptionally dysregulated genes in autism. Interestingly, rare *de novo* variants were enriched in two different coexpression modules, suggesting that transcriptional dysregulation and rare *de novo* variants represent distinct mechanisms of risk in autism. Layer-specific enrichment analyses identified significant enrichment with the inner cortical plate in the developing brain.

A few studies have also investigated gene dysregulation in adult cortical and subcortical tissues, by systematically identifying differentially expressed genes in the autism postmortem brains compared to control postmortem brains (Gupta *et al*., 2014; Voineagu *et al*., 2011; Parikshak *et al*., 2016). These studies have identified several important results. First, cortical gene expression can help to separate the transcriptomes of autistic individuals from population controls. Second, these studies have been able to identify differentially expressed genes (both upregulated and downregulated) in autism cortex compared to control cortex, although analyses of the autism cerebellum in comparison to the control cerebellum have not been forthcoming.

These differences are likely to extend to other cortical and subcortical regions. For example, there is evidence that typical differences in gene expression in the frontal and temporal cortices are altered in autism (Parikshak *et al*., 2016). Third, there is replicable evidence to suggest that differentially downregulated genes are associated with neuronal and synaptic pathways, whereas upregulated genes are associated with glial (microglia and astrocytes in particular) and immune-related pathways.

Integrative transcriptome analyses have also identified similarities and differences across multiple conditions. A meta-analysis of gene-expression microarray data across cortical transcriptional data sets has revealed overlapping neuropathology between autism and psychiatric conditions such as schizophrenia, bipolar disorder and major depression (Gandal *et al*., 2016). The correlation between transcriptional dysregulation between these conditions parallels the genetic correlation identified using GWAS data. This shared pathophysiology was replicated using ribonucleic acid (RNA) sequencing data. Another study provided independent evidence for the shared pathophysiology between autism and schizophrenia, by significant and correlation of the transcriptional dysregulation between the two conditions (Ellis *et al*., 2016).

Conclusions

Autism is an extremely heterogeneous condition. Twin and familial recurrence rates have established significant heritability for the condition and related traits. Rare and common genetic variants, along with copy number variation and transcriptional dysregulation, contribute to risk for the condition. The high genetic and phenotypic heterogeneity makes gene discovery challenging. Interrogating large cohorts have identified some genes and CNVs that contribute to risk for autism, although these represent a small proportion of the genes that are hypothesised to contribute to the condition. Mutations in some genes contribute to specific subtypes in autism with shared clinical and behavioural characteristics.

No common variants have been consistently associated with autism, although it is clear that they contribute, en masse, to a significant proportion of the underlying risk. Bivariate and multivariate analyses have identified considerably pleiotropy with several other conditions, including measures of condition. This pleiotropy is also observed at the level of the cortical transcriptome. There has been considerable effort to develop larger and richer genetic databases of autism, and interrogation of these larger data sets will considerably advance our understanding of the genetics and biology of autism.

Acknowledgements

Glossary

Association study Studies that systematically test for differences in the frequency of variation between cases and controls or for association between allele frequency and a quantitative trait. Candidate gene association studies investigate variations in specific genes. Genome-wide association studies investigate variations across the genome.

Common variation Genetic variation where the minor allele is observed in at least 1% of the population.

Heritability Proportion of the total variance in a condition or trait that can be attributable to genetics.

Rare variation Genetic variation that is observed in less than 1% of the population.

References

Alarcón M, Abrahams BS, Stone JL, *et al.* (2008) Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *American Journal of Human Genetics* **82** (1): 150–159.

Anney R, Klei L, Pinto D, *et al.* (2010) A genome-wide scan for common alleles affecting risk for autism. *Human Molecular Genetics* **19** (20): 4072–4082.

Baron-Cohen S, Wheelwright S, Stott C, *et al.* (1997) Is there a link between engineering and autism? *Autism* **1** (1): 101–109.

Baron-Cohen S, Wheelwright S, Hill J, *et al.* (2001) The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **42** (2): 241–251.

Baron-Cohen S, Richler J, Bisarya D, *et al.* (2003) The systemizing quotient: an investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* **358** (1430): 361–374.

Bernier R, Golzio C, Xiong B, *et al.* (2014) Disruptive CHD8 mutations define a subtype of autism early in development. *Cell* **158** (2): 263–276.

Bourgeron T (2015) From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nature Reviews Neuroscience* **16** (9): 551–563.

Bourgeron T (2016a) Current knowledge on the genetics of autism and propositions for future research. *Comptes Rendus Biologies* **339** (7): 300–307.

Bulik-Sullivan B, Finucane HK, Anttila V, *et al.* (2015) An atlas of genetic correlations across human diseases and traits. *Nature Genetics* **47** (11): 1236–1241.

Carter C and Evans K (1996) Inheritance of congenital pyloric stenosis. *Journal of Medical Genetics* **6** (3): 233–254.

Chaste P, Klei L, Sander SJ, *et al.* (2015) A genome-wide association study of autism using the Simons simplex collection: does reducing phenotypic heterogeneity in autism increase genetic homogeneity? *Biological Psychiatry* **77** (9): 775–784.

Chung BH-Y, Tao VQ and Tso WW-Y (2014) Copy number variation and autism: new insights and clinical implications. *Journal of the Formosan Medical Association* **113** (7): 400–408.

Clarke T-K, Lupton MK, Fernandez-Pujals AM, *et al.* (2015) Common polygenic risk for autism spectrum disorder (ASD) is associated with cognitive ability in the general population. *Molecular Psychiatry* **21** (3): 419–425.

Constantino JN, Zhang Y, Frazier T, *et al.* (2010) Sibling recurrence and the genetic epidemiology of autism. *American Journal of Psychiatry* **167** (11): 1349–1356.

Dawson G, Meltzoff AN, Osterling J, *et al.* (1998) Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders* **28** (6): 479–485.

Durand CM, Betancur C, Boeckers TM, *et al.* (2007) Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nature Genetics* **39** (1): 25–27.

Ellis SE, Panitch R, West AB, *et al.* (2016) Transcriptome analysis of cortical tissue reveals shared sets of downregulated genes in autism and schizophrenia. *Translational Psychiatry* **6** (5): e817.

Folstein S and Rutter M (1977) Infantile autism: a genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry* **18** (4): 297–321.

Frans EM, Sandin S, Reichenberg A, *et al.* (2013) Autism risk across generations: a population-based study of advancing grandpaternal and paternal age. *JAMA Psychiatry* **70** (5): 516–521.

Frazier TW, Youngstrom EA, Hardan AY, *et al.* (2015) Quantitative autism symptom patterns recapitulate differential mechanisms of genetic transmission in single and multiple incidence families. *Molecular Autism* **6** (1): 58.

Gandal MJ, Haney J, Parikshak N, *et al.* (2016) Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *bioRxiv*.

Gaugler T, Klei L, Sanders SJ, *et al.* (2014) Most genetic risk for autism resides with common variation. *Nature Genetics* **46** (8): 881–885.

Geschwind DH and Flint J (2015) Genetics and genomics of psychiatric disease. *Science* **349** (6255): 1489–1494.

Geschwind DH and State MW (2015a) Gene hunting in autism spectrum disorder: on the path to precision medicine. *The Lancet Neurology* **14** (11): 1109–1120.

Gratten J, Wray NR, Keller MC, *et al.* (2014) Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nature Neuroscience* **17** (6): 782–790.

Gratten J, Wray NR, Peyrot WJ, *et al.* (2016) Risk of psychiatric illness from advanced paternal age is not predominantly from de novo mutations. *Nature Genetics* **48** (7): 718–724.

Grønborg TK, Schendel DE and Parner ET (2013) Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study. *JAMA Pediatrics* **167** (10): 947–953.

Gupta S, Ellis SE, Ashar FN, *et al.* (2014) Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. *Nature Communications* **5**: 5748.

Helsmoortel C, Vulto-van Silfhout AT, Coe BP, *et al.* (2014) A SWI/SNF-related autism syndrome caused by de novo mutations in ADNP. *Nature Genetics* **46** (4): 380–384.

International Molecular Genetic Study of Autism Consortium (1998) A full genome screen for autism with evidence for linkage to a region on chromosome 7q. International Molecular Genetic Study of Autism Consortium. *Human Molecular Genetics* **7** (3): 571–578.

Iossifov I, O'Roak BJ, Sanders SJ, *et al.* (2014) The contribution of de novo coding mutations to autism spectrum disorder. *Nature* **515** (7526): 216–221.

Jamain S, Quach H, Betancur C, *et al.* (2003) Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nature Genetics* **34** (1): 27–29.

Jokiranta-Olkoniemi E, Cheslack-Postava K, Sucksdorff D, *et al.* (2016) Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism spectrum disorders. *JAMA Psychiatry* **73** (6): 622.

Jolliffe T and Baron-Cohen S (1997) Are people with autism and Asperger syndrome faster than normal on the embedded figures test? *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **38** (5): 527–534.

Jones W and Klin A (2013) Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. *Nature* **504** (7480): 427–431.

Kanner L (1943) Autistic disturbances of affective contact. *Nervous Child: Journal of Psychopathology, Psychotherapy, Mental Hygiene, and Guidance of the Child* **2**: 217–250.

Klei L, Sanders SJ, Murtha MT, *et al.* (2012) Common genetic variants, acting additively, are a major source of risk for autism. *Molecular Autism* **3** (1): 9.

Kong A, Frigge ML, Masson G, *et al.* (2012) Rate of de novo mutations and the importance of father's age to disease risk. *Nature* **488** (7412): 471–475.

Kosmicki JA, Samocha KE, Howrigan DP, *et al.* (2017) Refining the role of de novo protein-truncating variants in neurodevelopmental disorders by using population reference samples. *Nature Genetics* **49** (4): 504–510.

Krumm N, O'Roak BJ, Shendure J, *et al.* (2014) A de novo convergence of autism genetics and molecular neuroscience. *Trends in Neurosciences* **37** (2): 95–105.

Lai M-C, Lombardo MV and Baron-Cohen S (2013) Autism. *Lancet* **383** (9920): 896–910.

Lek M, Karczewski KJ, Minikel EV, *et al.* (2016) Analysis of protein-coding genetic variation in 60,706 humans. *Nature* **536** (7616): 285–291.

Leppa VM, Kravitz SN, Martin CL, *et al.* (2016) Rare inherited and de novo CNVs reveal complex contributions to ASD risk in multiplex families. *The American Journal of Human Genetics* **99** (3): 540–554.

Levy D, Ronemus M, Yamrom B, *et al.* (2011) Rare de novo and transmitted copy-number variation in autistic spectrum disorders. *Neuron* **70** (5): 886–897.

Ma D, Salyakina D, Jaworski JM, *et al.* (2009) A genome-wide association study of autism reveals a common novel risk locus at 5p14.1. *Annals of Human Genetics* **73** (3): 263–273.

McGrath JJ, Petersen L, Agerbo E, *et al.* (2014) A comprehensive assessment of parental age and psychiatric disorders. *JAMA Psychiatry* **71** (3): 301–309.

Mitra I, Tsang K, Ladd-Acosta C, *et al.* (2016) Pleiotropic mechanisms indicated for sex differences in Autism. *PLOS Genetics* **12** (11): e1006425.

Murdoch JD, Gupta AR, Sanders SJ, *et al.* (2015) No evidence for association of autism with rare heterozygous point mutations in contactin-associated protein-like 2 (CNTNAP2), or in other contactin-associated proteins or contactins. *PLoS Genetics* **11** (1): e1004852.

Neale BM, Kou Y, Liu L, *et al.* (2012) Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature* **485** (7397): 242–245.

O'Roak BJ, Vives L, Fu W, *et al.* (2012a) Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. *Science* **338** (6114): 1619–1622.

O'Roak BJ, Vives L, Girirajan S, *et al.* (2012b) Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature* **485** (7397): 246–250.

Parikshak NN, Luo R, Zhang A, *et al.* (2013) Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. *Cell* **155** (5): 1008–1021.

Parikshak NN, Swarup V, Belgard TG, *et al.* (2016) Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. *Nature* **540**: 423–427.

Peñagarikano O, Abrahams BS, Herman EI, *et al.* (2011) Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell* **147** (1): 235–246.

Pinto D, Delaby E, Merico D, *et al.* (2014) Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *American Journal of Human Genetics* **94** (5): 677–694.

Polimanti R and Gelernter J (2017) Widespread signatures of positive selection in common risk alleles associated to autism spectrum disorder. *PLoS Genetics* **13** (2): e1006618.

Robinson EB, Lichtenstein P, Anckarsater H, *et al.* (2013) Examining and interpreting the female protective effect against autistic behavior. *Proceedings of the National Academy of Sciences* **110** (13): 5258–5262.

Robinson EB, Samocha KE, Kosmicki JA, *et al.* (2014) Autism spectrum disorder severity reflects the average contribution of de novo and familial influences. *Proceedings of the National Academy of Sciences* **111**: 15161–15165.

Robinson E, St Pourcain B, Anttila V, *et al.* (2016) Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. *Nature Genetics* **48** (5): 552–555.

Ronald A and Hoekstra RA (2011) Autism spectrum disorders and autistic traits: a decade of new twin studies. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **156** (3): 255–274.

De Rubeis S, He X, Goldberg AP, *et al.* (2014) Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature* **515** (7526): 209–215.

Ruzich E, Allison C, Chakrabarti B, *et al.* (2015) Sex and STEM occupation predict autism-spectrum quotient (AQ) scores in half a million people. *PLoS One* **10** (10): e0141229.

Salyakina D, Ma DQ, Jaworski JM, *et al.* (2010) Variants in several genomic regions associated with asperger disorder. *Autism Research: Official Journal of the International Society for Autism Research* **3** (6): 303–310.

Samocha KE, Robinson EB, Sanders SJ, *et al.* (2014) A framework for the interpretation of de novo mutation in human disease. *Nature Genetics* **46** (9): 944–950.

Sanders SJ, He X, Willsey AJ, *et al.* (2015) Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron* **87**: 1215–1233.

Sandin S, Lichtenstein P, Kuja-Halkola R, *et al.* (2014) The familial risk of autism. *The Journal of the American Medical Association* **311** (17): 1770–1777.

Sandin S, Schendel D, Magnusson P, *et al.* (2015) Autism risk associated with parental age and with increasing difference in age between the parents. *Molecular Psychiatry* **21** (5): 693–700.

Sebat J, Lakshmi B, Malhotra D, *et al.* (2007) Strong association of de novo copy number mutations with autism. *Science (New York, N.Y.)* **316** (5823): 445–449.

Sniekers S, Stringer S, Watanabe K, *et al.* (2017) Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nature Genetics* **49**: 1107–1112.

St Pourcain B, Whitehouse AJO, Ang WQ, *et al.* (2013) Common variation contributes to the genetic architecture of social communication traits. *Molecular Autism* **4** (1): 34.

St Pourcain B, Skuse DH, Mandy WP, *et al.* (2014) Variability in the common genetic architecture of social-communication spectrum phenotypes during childhood and adolescence. *Molecular Autism* **5** (1): 18.

St Pourcain B, Robinson EB, Anttila V, *et al.* (2017) ASD and schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. *Molecular Psychiatry*. [Epub ahead of print].

Tang G, Gudsnuk K, Kuo SH, *et al.* (2014) Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. *Neuron* **83** (5): 1131–1143.

The Autism Spectrum Disorders Working Group of the Psychiatric Genomics Consortium (2017) Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Molecular Autism* **8** (1): 21.

Tick B, Bolton P, Happé F, *et al.* (2016) Heritability of autism spectrum disorders: a meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **57** (5): 585–595.

Voineagu I, Wang X, Johnston P, *et al.* (2011) Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* **474** (7351): 380–384.

Wang K, Zhang H, Ma D, *et al.* (2009) Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature* **459** (7246): 528–533.

Warrier V, Chee V, Smith P, *et al.* (2015a) A comprehensive meta-analysis of common genetic variants in autism spectrum conditions. *Molecular Autism* **6** (1): 49.

Warrier V, Chakrabarti B, Murphy L, *et al.* (2015b) A pooled genome-wide association study of Asperger syndrome. *PLoS One* **10** (7): e0131202.

Warrier V, Toro R, Chakrabarti B, *et al.* (2016) Genome-wide analyses of empathy and systemizing: heritability and correlates with sex, education, and psychiatric risk. *Cold Spring Harbor Labs Journals*.

Warrier V, Grasby K, Uzefovsky F, *et al.* (2017) Genome-wide meta-analysis of cognitive empathy: heritability, and correlates with sex, neuropsychiatric conditions and brain anatomy. *Molecular Psychiatry*. [Epub ahead of print].

Weiner DJ, Wigdor EM, Ripke S, *et al.* (2017) Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. *Nature Genetics* **49**: 978–985.

Weiss LA, Arking DE, Daly MJ, *et al.* (2009) A genome-wide linkage and association scan reveals novel loci for autism. *Nature* **461** (7265): 802–808.

Werling DM and Geschwind DH (2015) Recurrence rates provide evidence for sex-differential, familial genetic liability for autism spectrum disorders in multiplex families and twins. *Molecular Autism* **6** (1): 27.

Wheelwright S and Baron-Cohen S (2001) The link between autism and skills such as engineering, maths, physics and computing: a reply to Jarrold and Routh, Autism, 1998, 2(3): 281–289. *Autism* **5** (2): 223–227.

Wheelwright S, Auyeung B, Allison C, *et al.* (2010) Defining the broader, medium and narrow autism phenotype among parents using the autism spectrum quotient (AQ). *Molecular Autism* **1**: 10.

Willsey AJ, Sanders SJ, Li M, *et al.* (2013) Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. *Cell* **155** (5): 997–1007.

Xia K, Guo H, Hu Z, *et al.* (2014) Common genetic variants on 1p13.2 associate with risk of autism. *Molecular Psychiatry* **19** (11): 1212–1219.

Yuen RKC, Thiruvahindrapuram B, Merico D, *et al.* (2015) Whole-genome sequencing of quartet families with autism spectrum disorder. *Nature Medicine* **21** (2): 185–191.

Yuen RK, Merico D, Bookman M, *et al.* (2017) Whole genome sequencing resource identifies 18 new candidate genes for autism spectrum disorder. *Nature Neuroscience* **20**: 602–611.

Zarrei M, MacDonald JR, Merico D, *et al.* (2015) A copy number variation map of the human genome. *Nature Reviews Genetics* **16** (3): 172–183.

Zoghbi HY and Bear MF (2012) Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. *Cold Spring Harbor Perspectives in Biology* **4** (3). pii: a009886.

Further Reading

Bourgeron T (2016b) Current knowledge on the genetics of autism and propositions for future research. *Comptes Rendus Biologies* **339** (7): 300–307.

Geschwind DH and State MW (2015b) Gene hunting in autism spectrum disorder: on the path to precision medicine. *The Lancet Neurology* **14** (11): 1109–1120.

Lai M-C, Lombardo MV and Baron-Cohen S (2013b) Autism. *Lancet* **383** (9920): 896–910.