Genetics of Autism Spectrum Disorder: research to clinical practice

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Abstract

Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder causing significant lifetime morbidity. Recent advances in molecular genetics research highlighted the contribution of genetic risk factors to increasing genetic susceptibility to ASD. This review outlines the evidence supporting the role of genetic risk factors based on clinical genetic studies that have highlighted relatively strong heritability for ASD. Also discussed are the converging findings from molecular genetic studies showing evidence for the role of rare genetic risk factors, such as copy number variants (CNV) and rare sequence variants, in causing autism in a small proportion of individuals with ASD. Strong evidence for the contribution of common genetic variation to increased risk of ASD will likely require much larger samples as has been demonstrated in other complex genetic disorders. Application of bioinformatic approaches to data emerging from ASD molecular genetics studies is increasingly informing on the biology of the condition, and will ultimately lead to improved diagnostics and therapeutics.

Introduction

Autism spectrum disorder (ASD) is among the commonest neurodevelopmental disorders of childhood, affecting around 1% of the population (1). It is characterised by social communication deficits, repetitive behaviours and other associated behavioural features. There are often other comorbid medical and mental health disorders. ASD occurs across a spectrum of intellectual disability from profoundly intellectually disabled to average and superior intelligence. Independent of intellectual ability, ASD is frequently associated with significantly impaired functioning and engagement in society persisting across the life span and leading to significant disability. ASD is increasingly viewed as a collection of syndromes of varying severities as reflected in recent revisions of the Diagnostic and Statistical Manual 5th Edition (DSM-5) (2).

Although clearly neurodevelopmental in origin, the underlying neurobiology of ASD has, until recently, remained elusive. Genetic factors have long been considered to play a role in the condition and this is supported by early clinical genetics studies investigating recurrence rates in twins and first-degree family members. Greater understanding of the underlying genetic risks for ASD is now rapidly providing insight into the neurobiology; ultimately the goal will be to provide improved diagnostics and the development of better therapeutics. Genetic risk factors are likely to act in tandem with other biological and environmental risk factors but these have not been as extensively investigated. Recent advances in genetic technologies enabled large-scale genome-wide approaches that have been successful in identifying an increasing proportion of the underlying genetic risks and, to a lesser extent, have identified pathogenic mutations that are likely to be causative. Additionally, research data are providing greater insights into the underlying molecular pathways that may be implicated in ASD. These advances have genuine value to clinical care, with genetic testing rapidly becoming a standard of care (3) and a larger number of molecular targets emerging for new drug development.

Heritability of ASD

The first twin study of ASD in the 1970s demonstrated increased recurrence rates of autism in identical twins compared to non-identical twins (4). Identical twins are theoretically 100% genetically identical

compared to non-identical twins, who share approximately 50% of their genes. Further studies have strongly supported the role of genetic risk factors in ASD, with heritability for autism estimated to be in excess of 90% (5-8), (6). High heritabilities, ranging from 70-80%, have also been reported for core autism, broader ASD traits and for autism severity (9, 10). More recently, a large twin study (n=192) showed lower concordance rates and estimated genetic heritability of 37% for autism, with shared environmental factors contributing 55% of risk, indicating a greater role for environmental factors in ASD than previously (11). Other approaches to estimate heritability have utilised genomic data in unrelated individuals rather than classical twin and family studies. Klei et al. calculated the heritability from common genetic variation (SNPs) in ASD to be as high as 60% (12). Taken together with the classical twin designs, the evidence strongly supports a role of genetic factors in ASD, albeit that these factors are likely to act in tandem with other less extensively studied biological and environmental risk factors.

Common genetic variation and risk for ASD

Genome-wide association studies (GWAS) examine associations between common SNP variations across the entire genome with a given trait, e.g. ASD. Genome-wide significant associations have been reported at loci on chromosomes 5 and 20, e.g. SEMA5A, TAS2R1 and MACROD2 (13-15). However, despite sample sizes in excess of 1000 families, robust replication of these loci has not been achieved. Common SNP variants explain phenotypic variation in ASD in part. However, given a highly polygenic model of many hundreds of genes, they are underpowered to detect the risk of a small effect.

Notwithstanding relatively high heritability, ASD is not inherited in a Mendelian manner; multiple genes are implicated, many more than previously suggested, with hundreds of genes likely to play a role (16, 17). It has been estimated that much larger studies, in excess of 10000 individuals, will be required to achieve replicable results (17), a strategy that has proven successful in GWAS of schizophrenia (18).

Chromosomal rearrangements and Copy number variants (CNV)

ASD has long been associated with the presence of chromosomal rearrangements; inversions, deletions, duplications and translocations of chromosomal material have been reported on almost every chromosome (19). The commonest described rearrangement is maternally derived trisomy of Chromosome 15q11-13 (Chr15q11-q13 microduplication syndrome) (20), i.e. the inheritance of two maternal copies of this part of the chromosome with one paternal copy is associated with ASD, developmental delay and a risk of seizures. The region in question, which is also implicated in two other neurodevelopmental disorders, Prader-Willi Syndrome and Angelman Syndrome, harbours a number of neurodevelopmental genes which could contribute to all three phenotypes. Additionally, micro-rearrangements have been described in this region in other neurodevelopmental phenotypes such as schizophrenia, and dyslexia (21).

Chromosomal rearrangements are typically visible using a microscope but previously undetected submicroscopic rearrangements are now increasingly identified in ASD using high-resolution microarray technologies. Copy number variants (CNV) are structural variants in the genome leading to abnormal copies of sections of DNA that may impact a gene, partly or wholly, or a number of genes within a region. Non-pathogenic CNV occur as a form of genetic variation. However, large-scale studies in ASD have identified an excess of large or de novo CNV in genes that impact on neurodevelopment, or genes previously associated with intellectual disability or ASD (22, 23). Further examination of the genes impacted by rare and de novo CNV converge on plausible biological processes such as synaptic plasticity, neuronal cell signalling and mechanisms controlling gene expression such as chromatin remodelling (24, 25).

Up to 10% of ASD cases may carry pathogenic CNV. Specific pathogenic CNV are rare, generally with frequencies less than 1%. However in ASD, CNV at 16p11.2 and the loci which contain the genes SHANK2, NRXN1, and PTCHD1 occur more frequently (26). These findings have led to clinical genetics laboratories using CNV microarray to screen for CNV in ASD patients. This is arguably one of the most

prominent translations from ASD genetics research to the clinical setting, with information regarding ASD genetic risk becoming available to a significant minority of families. It is important to note that there is extensive clinical and genetic heterogeneity associated with CNV. CNV may vary in size, type (deletion or duplication) and impact on genes (i.e. the region and amount of coding DNA that is disrupted). Moreover, associated clinical outcomes may vary widely from mild to very severe and the same CNV may be found in different neurodevelopmental disorders, such as schizophrenia and epilepsy. Consequently the clinical predictive value of CNV remains limited.

Single Nucleotide Variants (SNV)

Early sequencing efforts in ASD were focused on identifying disrupting sequence mutations in candidate genes. The detection of mutations in Neuroligin genes (NLGN3 and NLGN4) (27) and SHANK3 (28) provided evidence for the role of glutamate function and glutamatergic synapses as putative pathways in ASD. Significant advancement in sequencing technologies has enabled researchers to extend analyses to all genes in the genome at a relatively low cost to rapidly identify single nucleotide variants (SNV) that are potentially mutagenic. In autism, these "next-generation" sequencing studies have provided evidence supporting rare and de novo SNV as potential risk factors in individuals with ASD. As with CNV, SNV also are associated with variable penetrance, further supporting a polygenic risk model for ASD and the influence of stochastic factors.

Sanders et al. identified an excess of highly disruptive de novo mutations (particularly nonsense or splice site mutations) in brain-expressed genes in individuals with ASD compared with unaffected siblings (Odds Ratio, OR=5.65) (29). Mutations of major effect were detected in two individuals in SCN2A, a gene encoding a sodium gated channel receptor. Further studies also identified an excess of missense and nonsense mutations in affected individuals within genes that appeared functionally connected and related to previously identified ASD loci (30, 31). Some highlighted the role of genes that are targets of the FMRP protein, which is disrupted in Fragile X syndrome, a condition that frequently presents with comorbid ASD symptoms. From these data it has been estimated that around 1% of autism cases harbour a disruptive mutation in one of six genes; CHD8, DYRK1A, GRIN2B, PTEN, TBL1XR1 and TBR1. Some studies suggest that the risk of de novo disrupting mutations increases with paternal age (29), possibly due to paternal germline mutations. The application of systems biology based analytic techniques (see below) has demonstrated functional convergence on a number of molecular pathways, including neuronal and synaptic functioning, transcriptional pathways, relevant cell signalling pathways and chromatin remodelling.

Using systems biology approaches to identify molecular pathways and interactions

Bioinformatics-based analytic approaches, typically referred to as network or pathway analyses, explore the relationship between associated genes identified in the studies described above. These methods examine whether identified genes are related through their function, expression profile or biological role.

Using GWAS enrichment, Wang et al., following association in a region flanked by the cadherin genes CHD9 and CDH10, identified association enrichment for a group of 25 cadherin-related genes in ASD ($P = 0.02$) which was strengthened with the inclusion of eight additional neurexin family genes ($P = 0.004$) (13). Using a more systematic approach applied to their AGP GWAS study, Anney et al. examined enrichment across gene set described in the gene otology database. They found enrichment for genes in biologically plausible processes such as the F-box protein family (FBXO31 and FBXO6) that are implicated in protein degradation, synapse formation and circadian rhythm as well as gene sets related to the MAPK signalling cascade (32).

Analyses of gene expression data have highlighted down-regulation in genes related to the synapse, neurotransmitter transport and neuron projection, with up-regulated genes enriched for immune and cell adhesion categories (33).

Pinto and colleagues identified a number of gene-sets showing enrichment for rare genic CNVs in ASD (23). Network mapping of the data highlighted two major clusters: genes related to cell proliferation, motility and cell projection, and those involved in GTPase/RAS signalling. RAS signalling is of interest, as alongside MAPK signalling it is impaired in RASopathies, developmental syndromes such as Noonan syndrome, Costello Syndrome and Neurofibromatosis type 1 (34). Overlaps were also identified between these networks and gene-lists previously implicated in ASD and intellectual disability and a larger interconnected network of genes related GO-terms pertaining to CNS development and cell adhesion clusters. In a separate dataset, Gilman et al. applied NETBAG (NETwork-Based Analysis of Genetic associations) to identify biological networks of genes affected by rare de novo CNVs in ASD. They identified enrichment in gene sets related to synapse formation, learning and memory, axonogenesis and cell adhesion (35).

Using data from exome sequencing, Iossifov et al. identified an excess of gene-disrupting mutations in FMRP targets in children with ASD, lending further support to the role of synaptic plasticity mechanisms in ASD (31). Further analysis of whole exome sequencing data identified that 39% of the most damaging de novo mutations impacted on the β-catenin (cadherin-associated-protein)/ chromatin network (36). Separately, two significant extended protein-protein interaction networks were identified: the first centred on the SMARCC2 gene, implicated in chromatin unzipping and regulation of gene expression; the second contained genes related to cell adhesion and was centred around FN1 (30). Transcription regulation and chromatin remodelling was also implicated in a combined analysis of the genes disrupted by de novo CNV in all four published whole-exome sequencing studies in ASD using both pathway and network approaches (37). Network analysis showed enrichment in neuronal genes, including genes implicated in clathrin dependent endocytosis fundamental to synaptic vesicle protein internalization (38).

These analyses have been further informed by resources such as the Brain Span project (http://www.brainspan.org/static/home) providing an atlas of the transcriptome over the course of development. This has permitted more refined analyses of the temporo-spatial expression of genes impacted by loss of function mutations in ASD as shown by recent studies, demonstrating convergence on glutamatergic projection neurons in human midfetal prefrontal and primary motor-somatosensory cortex (39, 40).

Conclusion

Rapid advances in recent years have identified pathogenic mutations in a significant minority of individuals with ASD. ASD is associated with marked genetic complexity and up to 400 genes may be implicated. Many individuals with ASD may carry rare or even private mutations that have extremely low recurrence rates in the population. Notwithstanding the complexity, identifiable genetic aetiologies can now be determined for 15-20% of individuals with ASD, providing information on genetic recurrence risks that can be utilised in the clinic. Given variable penetrance and observations in other neurodevelopmental disorders, however, the predictive validity of SNV and CNV is low. CNV and SNV at specific loci have, however, been associated with comorbidities and thus their identification may aid in other health promotion strategies, e.g. tumour screening in the presence of PTEN mutations, since PTEN acts as a tumour suppressor, or dietary advice in association with 16p11.2 deletions, associated with the development of obesity.

While the evidence is complex, with many genes and loci being implicated, it is somewhat reassuring that there is functional convergence on a smaller number of molecular pathways. Increasingly there is support for the role of pathways involved in neural development, synaptic development and plasticity, downstream cell signalling and control of gene expression such as transcription and chromatin remodelling. Overlaps of these pathways with other neurodevelopmental disorders indicate that these processes are not specific to ASD per se. However, advances in treatments for related disorders such as Fragile-X syndrome, Rett Syndrome and Tuberous Sclerosis provide hope that greater understanding of these pathways may also provide new therapeutics for many of the disabling characteristics of ASD.

While improving diagnostics and therapeutics for ASD is a fundamental goal of genetics research,

elucidation of other risk factors, especially environmental factors, will be necessary to understand the development of the condition fully. It will further be necessary to relate the myriad risk factors with clinical characteristics and comorbid features such as anxiety, aggression and self-injury in order to develop treatments that are targeted and effective.

Glossary of terms

Term	Description
Heritability	Refers to the relative contribution of genetic and non-genetic factors to the variance of a trait in the population. Traditionally calculated based on recurrence rates within twin or family studies.
Concordance	Recurrence of genetic trait or condition, typically used in context of twin studies to describe within twin pair recurrence rates
Penetrance	The proportion of individuals with a disease causing mutation displaying the associated trait or clinical symptoms
Copy Number Variant (CNV)	Structural variation in the genome leading to either gain or loss of sections of DNA. CNV contributes to up to 12% of normal genetic variation but may also be pathogenic when associated with loss or gain of gene function
Single Nucleotide Polymorphism (SNP)	A form of genetic variation referring to single base change in DNA sequence. SNPs may be synonymous (no change in gene function) or non-synonymous (effect changes in gene function). Genetic variation may be used to identify common genetic susceptibility to disease
Single Nucleotide Variant (SNV)	SNV is the term used to describe SNPs of low frequency and that have not been described previously in the population.
Exome	The coding component of the genome, comprised of the exons which are transcribed into RNA
De novo	Used to refer to CNV or SNV arising in an individual and does not appear to be present in either parent. Rarely mutations in the germline of either parent can arise that are not detectable in parental DNA leading to recurrence of a de novo mutation in offspring.
Whole exome sequencing	Targeted sequencing of the coding regions of the genome which is faster and more cost-effective than whole genome sequencing. The objective of WES is to identify functional SNV disrupting the gene product
Genomewide Association Studies (GWAS)	A whole genome strategy seeking to identify association between common genetic variation, i.e. SNPs and a trait (e.g. ASD). The strategy is focused on the identification of common genetic variation conferring relatively modest risk for the trait. GWAS data also inform the identification of molecular pathways.

GP Comment.

What have I learned from this paper?

1. The heritability of autism is high. Early twin studies in the 1970s evidenced the importance of genetic influences on autism by showing that if one twin of the pair had autism then the chances of the other twin having this condition were much higher if the twins were monozygotic (identical) than if they were dizygotic.

2. No single gene accounts for the heritability of ASD; probably at least 400 genes are implicated.

3. A genetic aetiology can be identified in 13 - 20% of individuals with ASD; for this minority of people additional information can be given in the clinic with regard to recurrence risks in the family.

4. Although there has been a tremendous amount of genetic research in autism, there are still many unanswered questions. The research has perhaps revealed the complexity of the genetics, rather than providing specific answers that can be used for the majority of cases in the clinic or in the GP surgery.

5. Genetic and environmental factors interact to determine whether an individual is likely to have ASD. More research is needed to understand the myriad of risk factors which may result in ASD and thereby improve diagnostics, develop effective treatments and most importantly assist in prevention of this disabling condition.

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