



The National
Autistic Society

Information sheet

The genetics of autism spectrum disorders: a briefing

Autism is a complex neurodevelopmental disorder, marked by multiple symptoms that include atypicalities in:

1. social interactions (ie people with autism would often find it difficult to understand others' mental states and emotions, and respond accordingly)
2. verbal and non-verbal communication
3. repetitive behaviour (ie people with autism might repeat certain words or actions over and over, usually in a rigid rule-governed manner).

There is a wide variability in the degree to which these symptoms manifest themselves, leading to the use of the term 'autism spectrum disorders' (ASD). While 'autism', as originally described by Leo Kanner in 1943, represents an extreme end of the spectrum, often marked by severe impairments in one or more of these three domains described above, other manifestations of these symptoms are sometimes associated with diagnostic labels such as 'Asperger syndrome', 'atypical autism' or 'pervasive developmental disorder – not otherwise specified (PDD-NOS)'. All of these are sometimes referred to as ASD, or 'autism spectrum conditions' (ASC).

Early twin studies showed that Kanner's autism was highly heritable (see Box 1), suggesting that there is a considerable genetic component to this condition. This represented a major shift in the then dominant models, which speculated autism to be largely a product of one's environment and upbringing. The genetic component was further supported by a series of later findings that ASD runs in families (Silverman et al., 2002). Additionally, it was found that autistic traits (which are distributed normatively in the general population, and are not indicative of a clinical diagnosis by themselves) are highly heritable (Ronald, Happé and Plomin, 2005). This study suggested that if a particular twin had a very low score on a specific autistic trait (e.g. social behaviour as measured by a questionnaire), then the chance that the other monozygotic (MZ) twin would also have a very low score was very high, and vice versa for high scores. All of these studies provide support for the premise that there is a strong genetic element in the development of ASD and autistic traits. An increasingly popular view among mental health researchers is that complex conditions such as autism are best conceptualised within a dimensional framework, ie as extremes of traits that are distributed normatively within the general population.

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Box 1: Heritability

A key way to determine if a particular condition has a genetic basis, is to explore the similarities and differences among identical twins (monozygotic, ie from the same fertilized egg) and non-identical/fraternal twins (dizygotic, i.e. from two different fertilised eggs). A measure of genetic contribution that is calculated by comparing the proportion of monozygotic (MZ) twins that share a particular condition, with that of dizygotic (DZ) twins that share the condition. Statistically, heritability refers to the proportion of the variance in a particular phenotype that is explained by purely genetic effects and is estimated after accounting for phenotypic variance due to shared and non-shared environments. A condition with a high heritability (usually greater than 50%) is believed to have a strong genetic basis, while one with a low heritability is associated with low/moderate genetic basis.

Recent studies, however, have highlighted an important difference in the types of families that have members with ASD. There are some families where only one member has a diagnosis of ASD, and no one in the extended family has a diagnosis. Such 'one-off' incidences of autism are referred to as 'simplex' autism. Recent research suggests that some of these might be due to 'de novo' changes in DNA sequence (eg a rare sequence variant or a copy number variation, see Box 2), ie a one-off change that happens during the formation of gametes. It is believed that these rare variants can account for nearly 10% of all people diagnosed with ASD (Sebat et al., 2007). On the other hand, there is a multitude of families, where more than one member of the extended family has a diagnosis, or several members have very high levels of autistic traits – even though they might have never received a formal clinical diagnosis. Such families are referred to as 'multiplex' families. It is believed that there are specific genetic variations, passed down through generations (see Box 2), that might underlie the increased incidence of ASD in these families.

Another increasingly important distinction in the genetics of autism is that between 'syndromic' and 'non-syndromic' (or idiopathic) autism. 'Non-syndromic autism' is a term used to describe cases where autism is the primary diagnosis – and not secondary to an existing condition caused by a well-known genetic variant, such as Rett syndrome, Fragile X syndrome, tuberous sclerosis, and the Smith-Lemli-Opitz syndrome. While we are far from developing a diagnostic genetic test for ASD, it is possible to check for a number of these known variants using standardised techniques. This has led to the suggestion that some of these conditions could potentially be included in a checklist of genetic testing of people with ASD (Lintas and Persico, 2009).

Terminology

(Adapted from official Medline definitions, available at www.ncbi.nlm.nih.gov/sites/entrez)

Genes: Specific sequences of nucleotides (eg A/T/C/G) along a molecule of DNA which represent functional units of heredity.

Genome: The genetic complement of an organism, including all of its genes, as represented in its DNA.

Chromosome: In the context of human cells, a chromosome is a structure that consists of or contains DNA which carries the genetic information essential to the cell. Human cells have 23 pairs of chromosomes, 22 of which are nearly identical to each other (autosomes). The 23rd pair consists of sex chromosomes, and are non-identical for males (who have X and Y chromosomes), but nearly identical for females (who have two X chromosomes).

Phenotype: The outward appearance of the individual. It is the product of interactions between genes, and between the genotype and the environment. In humans, a phenotype could constitute a wide variety of observables, from, say, a bodily feature (eg brain structure) to a measurable behaviour.

Genotype: The genetic constitution of the individual; the characterisation of the genes.

Box 2: Genetic variations: polymorphisms, rare variants, CNVs

The human genome is made up of 23 pairs of chromosomes, each of which consists of double stranded DNA. Each DNA strand is a long sequence of four 'bases' – coded A, T, C, and G, and we have about 6 billion of these (~3 billion for each set of chromosomes). Interestingly, about 99% of this enormous sequence of DNA is nearly identical between different humans. There are a number of types of genetic variation between individuals that account for the remaining 1% - which underlies some of our variability as a species.

Among these, Single Nucleotide Polymorphisms (SNPs, pronounced 'snips') account for a large part. These are small variations in the DNA sequence that occur when a single base is altered. For example, in a sequence ATTTCG, if an A gets replaced by a C, this would constitute a SNP. For it to be (officially) considered a SNP, at least 1% of the population under study should have this replaced base, ie the 'C' in our example (a base is also referred to as an 'allele' in this context). However, if the instances of the replaced allele are much lower than 1%, it would be classified as a 'rare variant'. In the past, several such 'rare variants' would be termed 'mutations', especially if they were strongly linked to a particular clinical condition. Increasingly it is clear that such distinctions between mutations and polymorphisms are not well-warranted. Accordingly, a recent recommendation from the Human Genome Variation Society (see www.hgvs.org/mutnomen/recs.html) suggests the use of the term 'sequence variant' to denote such single-nucleotide changes in the genome.

Another major class of genetic variability arises from structural differences in the genome, ie differences that arise when identical chunks of DNA (usually longer than 1,000 base pairs) are replicated several times across a chromosome. These structural changes may manifest themselves in various ways, including duplications, deletions and inversions (when a large chunk of DNA is present in a certain chromosome, but exactly in the reverse order). An umbrella term used to describe these changes is Copy Number Variations (CNVs). Until recently, laboratory techniques used to spot sequence variations were not ideally suited for spotting such large-scale duplications/deletions across a chromosome. Current techniques such as oligonucleotide microarrays have made it possible to test a sizeable number of these variations in the human genome, and it is believed that they may be as frequent as 1 in every 800 base pairs, making them even more frequent than SNPs (Sebat et al., 2007).

Common strategies of studying the genetics of ASD

In light of the body of evidence on the genetic element in ASD and autistic traits, it is imperative to focus on the strategies through which the underlying genetic architecture can be studied. 'Guided missiles' represent experiments where there is a clear hypothesis about the role of a particular region of the chromosome (eg in linkage studies, see Box 3) or specific candidate genes (eg in candidate gene association studies, see Box 3). The hypotheses are generally based on prior experiments in other populations and/or on existing literature on the role of specific genes studied in other species. 'Carpet bombs', on the other hand, represent studies where experimenters study the whole genome all at once, looking for genes/chromosomal regions that are associated with ASD or related phenotypes. These are often referred to as 'genome-wide' linkage or association studies, as the case may be, and requires much larger sample sizes.

Box 3: Linkage and association

Linkage studies rely on the basic principle of meiosis – the process that DNA within a cell undergoes during formation of the gametes (spermatozoa/ova). Bits of DNA that are close-by on a chromosome tend to be inherited together, while bits of DNA that are far apart are more likely to get mixed between chromosomes, ie equivalent bits of DNA from the maternal and paternal chromosomes might get interchanged (this process is called 'recombination'). In a typical linkage study, DNA from several generations of a multiplex family (called a 'pedigree' in this context) is tested for specific markers that are passed on only to members with a phenotype of interest (in our case, this could be a diagnosis of ASD). Linkage studies can focus on bits of specific chromosomes (eg Chromosome 7q, 17q), or on the whole genome. These studies identify genomic regions (which may/may not contain known genes) that are sometimes thousands of base pairs long.

On the other hand, association studies tend to focus on sequence variants within specific genes, usually in a population of unrelated individuals, and look for differences in distribution of the particular variant between people with and without ASD. These sequence variants can be SNPs, or longer bits of DNA, including CNVs. The assumption in these studies is that if there is a higher frequency of a particular sequence variant within a sample of people with ASD, when compared to a matched (ideally in ethnicity) group of people with no clinical diagnosis, then the gene under study might be related to ASD. Recent advances in microarray technology have led to the rise of genome-wide association (GWA) studies, which can test for the presence of a large number of such sequence variants from nearly all known human genes in one experiment.

The score so far

Over twenty years of autism genetics research has implicated nearly every chromosome, and generated many candidate genes (see Figure 1; For a beautifully accessible recent review, see Abrahams and Geschwind, 2008).

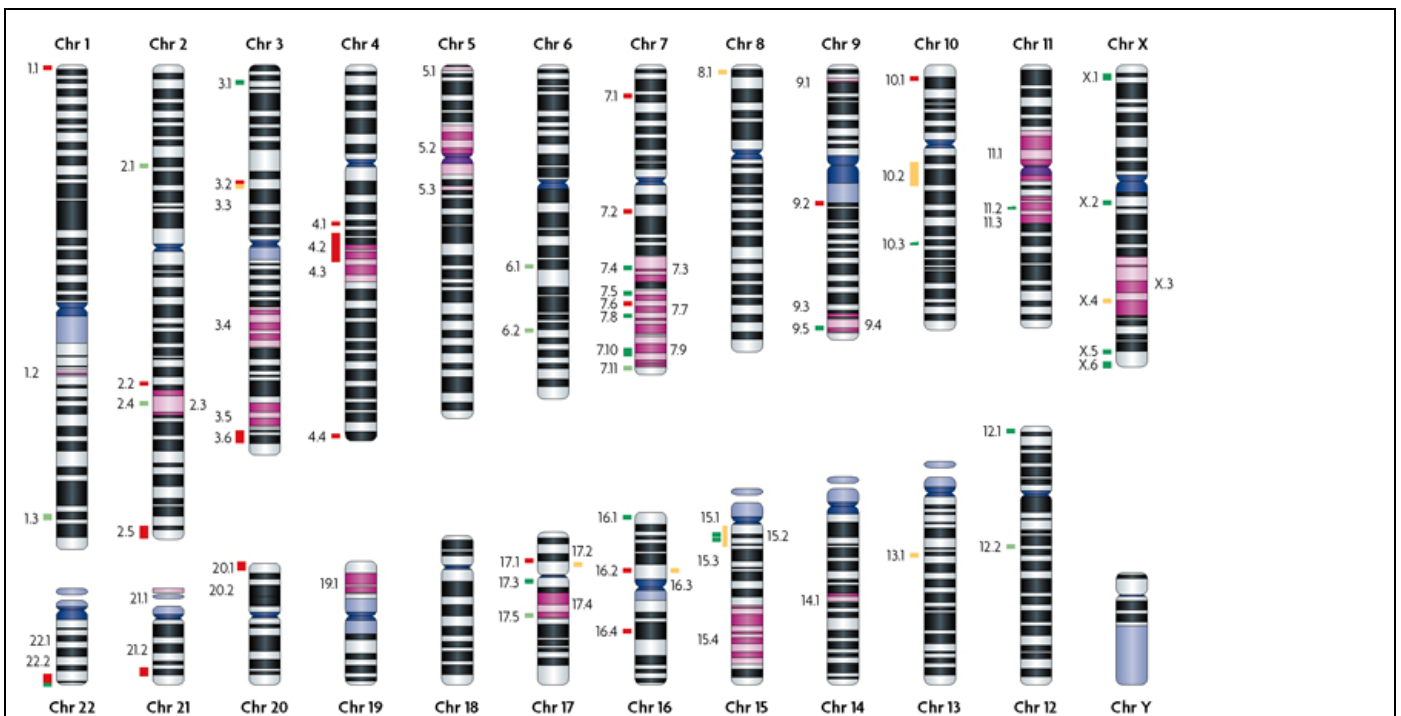


Figure 1:

A schematic summary of association and linkage studies of ASD, organised by chromosome. Purple bands indicate a chromosomal region that shows a linkage with ASD. Red and yellow bars (parallel to the chromosome) correspond to losses/gains in copy number, respectively, that are observed in people with ASD when compared to matched controls. Green bars correspond to genes that are observed to modulate the risk for ASD (either through a rare syndrome or genetic association): light green and dark green bars represent locations of candidate genes.

Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Genetics (Abrahams and Geschwind, 2008: 9, 341-355), copyright (2008).

While still preliminary, there are clearly emerging functional themes within the genes and chromosomal regions that have been associated, that point to the underlying neurobiology. One such theme is that of neural development. ASD is a developmental psychopathology, and it is not surprising that a large amount of converging evidence suggests a role for genes involved in neural growth, patterning, formation and stabilisation of synapses (eg *NLGN4X*, *NRXN1*, *CNTNAP2*, *EN2*, *PTEN*). Altered glutamatergic and calcium signalling are among the suggested mechanisms through which these genes manifest their effects. Neuroimaging studies of adults with ASD have shown some evidence of altered connectivity, suggesting a degree of atypical wiring. It is logical to expect that this class of genes might play a defining role in developing such atypical patterns of neural connectivity.

Another line of work suggests a role of genes that are known to influence social behaviour in animals. One of the best known examples of this is the oxytocin-vasopressin system, known for its role in maternal behaviour as well as mate-loyalty in rodents. Recent studies using oxytocin administration on humans have also shown some evidence that it results in increased trust among strangers in a laboratory situation (Baumgartner, Heinrichs, Vonlanthen, Fischbacher and Fehr, 2008). In view of the atypicalities of social behaviour seen in ASD, an increasing number of studies have focussed on such genes known to be involved in social behaviour. The oxytocin receptor gene, *OXTR*, is one of the few candidate genes that have been shown to be associated with ASD in multiple studies.

A third, emerging, line of evidence suggests that the extent of exposure to testosterone in the womb ('prenatal testosterone') is related to the development of autistic-like traits in the general population (Baron-Cohen, Knickmeyer and Belmonte, 2005). A primary clue for this line of investigation has been that ASD is associated with a strong sex difference, affecting nearly seven times as many males when compared to females. Two recent studies (Chakrabarti et al., 2009; Hu et al., 2009) have found evidence that genes related to sex hormone function are associated with ASD and/or autistic traits in the general population.

For a more detailed discussion of some of these candidate genes, and the accompanying evidence of their relation to ASD, see (Abrahams and Geschwind, 2008). For a continuously updated database of candidate genes that have been associated to autism, along with evidences of replication/non-replication across different studies, see <http://gene.sfari.org/>

Several of these initial studies have been limited by low sample sizes, which makes it difficult to generalise the findings to encompass all of ASD. Together, the inherent heterogeneity within ASD and the possibility that the role played by individual genes is likely to be small, underscore the need for much larger sample sizes, especially so for genome-wide studies. Efforts in this direction are already underway with consortia such as Autism Genome Project Consortium (AGPC), which pool genetic material from a large number of laboratories across the world.

Beyond genes

Association and linkage studies of ASD, while being informative, are only the first steps toward understanding the biology of autism. A number of stages occur between the DNA sequence (the level at which we study the sequence variants) and the complex range of phenotypes that are seen in ASD. A highly simplified schematic representation of these stages is as follows:

DNA → mRNA → Protein → Interaction between proteins and with DNA → Physiology/Behaviour

Gene 'expression' refers to the processes by which a given gene is 'switched on', ie the DNA sequence gives rise to mRNA and subsequently, to a specific protein, in the cell. The expression of a gene is often dependent on the sequence variants discussed (see Box 2), and an underlying assumption is that a 'functional' variant (eg a SNP) is one that is associated with differences in expression levels of the gene. It is also at this stage where environment plays a very significant role. The expression of a gene can be measured in terms of the abundance of the resulting mRNA/protein. In contrast to the plethora of genetic association studies of ASD, there are surprisingly few studies that examine differences in gene expression. One reason for this is that many of the genes of interest express themselves primarily in the brain. Since it is currently almost impossible to measure mRNA abundance in a living human brain, such research relies primarily on a handful of brains from people with ASD that have been kindly donated for postmortem research. This enterprise too is fraught with problems, as some of the genes of interest do not express themselves throughout the entire lifespan of an individual. Fortunately, however, expression levels between blood and brain are positively correlated for a number of these genes. There is a slow and promising increase in such studies, that look at gene expression levels in blood of people with and without ASD. As with association studies, there are two streams of such research: those that focus on expression of specific candidate genes ('guided missiles', eg oxytocin receptor OXTR gene, the RELN gene (Fatemi et al., 2005) and those that study the expression of all genes in the human genome using genome-wide expression microarrays ('carpet bombs', eg Hu et al., 2009).

A key direction for future autism genetics research is to parse out how the environment influences the functioning of the genetic framework that is being uncovered by the range of linkage and association studies. In addition to focussing on the genes within functional pathways such as neural development, social behaviour and sex steroid hormonal functioning, this research would also focus on genes underlying symptoms commonly observed in ASD (eg gastrointestinal symptoms). Research into these areas is only just beginning, and holds promising clues for a clearer understanding of the biology of autism.

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