The genetics of autism spectrum conditions

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Autism spectrum conditions (ASC) are a set of neurodevelopmental conditions marked by difficulties in social interaction, communication alongside repetitive behaviour/unusually narrow interests/resistance to change. Thus, people with ASC tend to have excellent attention to detail and find unexpected change aversive, adhering to rigid rule-governed routines, whilst finding friendships and socializing challenging. There is wide variability in the degree to which these 'symptoms' are manifest. 'Classic autism' as originally described by Leo Kanner in 1943, is one subgroup on the autistic spectrum, another being 'Asperger syndrome'. The difference between these two subroups is that in classic autism the individual may have additional learning difficulties (below average IQ) and invariably has a history of language delay (not speaking by 2 years old). In Asperger Syndrome, the individual has language and IQ in the average range, or even above.

Early twin studies showed that autism was highly heritable, suggesting a genetic component to these conditions. The genetic component was supported by a series of later findings that ASC runs in families (Silverman et al., 2002). Additionally, autistic traits (which are distributed normatively in the general population, and by themselves are not-indicative of a clinical diagnosis) are highly heritable (Ronald, Happé, & Plomin, 2005). The modern view is that ASC is best conceptualised within a dimensional framework, i.e. as extremes of traits that are distributed normatively within the general population.

There are some families where only one member has a diagnosis of ASC, and no one in the extended family has a diagnosis. These families are referred to as 'simplex' families. On the other hand, in other families more than one member of the extended family has a diagnosis, or several members have high levels of autistic traits – even though they might have never received a formal clinical diagnosis. Such families are referred to as 'multiplex' families. Another increasingly important distinction in the genetics of autism is 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. Some of these conditions could potentially be included in a checklist of genetic testing of people with ASD (Lintas & Persico, 2009).

It is important to consider the strategies through which the underlying genetic architecture of ASC can be studied. 'Guided missiles' represent experiments where there is a clear hypothesis about the role of a particular region of the chromosome (e.g. in linkage studies) or specific candidate genes. 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 ASC or related phenotypes. These are often-referred to as 'genome-wide' linkage or association studies and require much larger sample sizes. Over twenty years of autism genetics research has implicated nearly every chromosome, and generated many candidate genes (see Figure 1). For an accessible review, see Abrahams and Geschwind (2008).

While still preliminary, there are clearly emerging functional themes that point to the underlying neurobiology. One such theme is that of neural development. ASC is a developmental set of conditions, and it is not surprising that a large amount of converging evidence suggests a role for genes involved in neural growth, patterning, formation and stabilization of synapses (e.g. NLGN4X, NRXN1, CNTNAP2, EN2, PTEN). Altered glutamatergic and calcium signalling are among the suggested mechanisms through which these genes manifest their effects. Neuroimaging studies have shown some evidence of altered neural connectivity. It is therefore 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 in humans suggest that it results in increased trust among strangers in a laboratory situation (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). In view of the difficulties in social behaviour in ASC, an increasing number of studies have focussed on such genes. The oxytocin receptor gene, OXTR, is one of the few candidate genes that have been shown to be associated with ASC 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, & Belmonte, 2005). A primary clue for this has been that ASC is associated with a strong sex difference affecting many more males 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 ASC and/or autistic traits in the general population.

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

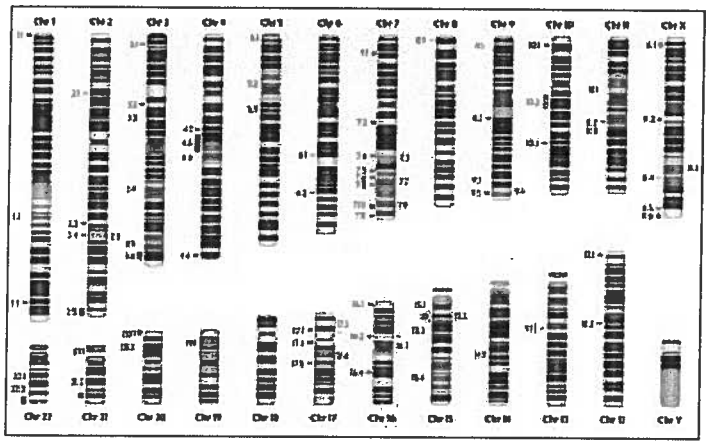

Figure 1: A schematic summary of association and linkage studies of ASC organised by chromosome.

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

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sample sizes, which makes it difficult to generalize the findings to encompass all of ASC. Efforts to combat the issue of sample size are underway with consortia such as Autism Genome Project Consortium (AGPC), which pool genetic material from a large number of laboratories across the world.

Association and linkage studies of ASC, while 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 seen in ASC. 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', i.e. 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, and an underlying assumption is that a 'functional' variant (e.g. 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. 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 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 donated for post-mortem research. This is fraught with problems, as some of the genes of interest do not express themselves across the lifespan of an individual but only at key points in development. Therefore, by the time researchers receive a brain at post-mortem, the 'window' for measuring expression levels may have been missed.

Expression levels between blood and brain are positively correlated for a number of these genes that makes this kind of research more feasible. As with association studies, there are two streams of such research: those that focus on expression of specific candidate genes ('guided missiles', e.g. 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 micoarrays ('carpet bombs', e.g. Hu et al., 2009).

A key direction for future autism genetics research will be to study 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 focusing on the genes within functional pathways such as neural development, social behaviour and sex steroid hormones, this research also needs to focus on genes underlying associated symptoms commonly observed in ASC (e.g. gastrointestinal symptoms). Research into these areas is only just beginning, and holds promising clues for a clearer understanding of the biology of ASC.

Some Key References

Abrahams, B. S., & Geschwind, D. H. (2008). Advances in autism genetics: on the threshold of a new neurobiology. Nature reviews. Genetics, 9(5), 341-55.

Baron-Cohen, S., Knickmeyer, R., & Belmonte, M. (2005). Sex differences in the brain: implications for explaining autism. Science, 310(5749), 819-823.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron, 58(4),639-650.

Chakrabarti, B., Dudbridge, F., Kent, L., Wheelwright, S., Hill-Cawthorne, G., Allison, C., et al. (2009). Genes related to sex steroids, neural growth, and social-emotional behavior are associated with autistic traits, empathy, and Asperger syndrome. Autism Research, 2(3), 157-177.

Fatemi, S. H., Snow, A. V., Stary, J. M., Araghi-Niknam, M., Reutiman, T. J., Lee, S., et al. (2005). Reelin signaling is impaired in autism. Biological Psychiatry, 57(7), 777-87.

Hu, V. W., Nguyen, A., Kim, K. S., Steinberg, M. E., Sarachana, T., Scully, M. a., et al. (2009). Gene expression profiling of lymphoblasts from autistic and nonaffected sib pairs: altered pathways in neuronal development and steroid biosynthesis. PloS One, 4(6), e5775.

Lintas, C., & Persico, a. M. (2009). Autistic phenotypes and genetic testing: state-of-the-art for the clinical geneticist. Journal of Medical Genetics, 46(1), 1-8.

Ronald, A., Happé, F., & Plomin, R. (2005). The genetic relationship between individual differences in social and nonsocial behaviours characteristic of autism. Developmental Science, 8(5), 444-58.

Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., et al. (2007). Strong association of de novo copy number mutations with autism. Science, 316(5823), 445-9.

Silverman, J. M., Smith, C. J., Schmeidler, J., Hollander, E., Lawlor, B. A., Fitzgerald, M., et al. (2002). Symptom domains in autism and related conditions: evidence for familiality. American Journal of Medical Genetics, 114, 64-73.

Parts of this article appeared in Chakrabarti, B, (2009), published on the National Autistic Society website.