The complex enigma of autism

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Autism isolates individuals in society, denying them access to the complex world of social interaction. Mark Greener reviews some of the recent research into the genetic, molecular and neuroanatomical basis of ASD's diverse clinical presentation.

Despite intensive research, savants' place as cultural icons and a proliferation of theories, autism remains, arguably, the most enigmatic neurological disease. Dustin Hoffman's Rain Man, the MMR vaccine controversy and the link between 'geek culture' and Asperger's syndrome dominate public perception of autism spectrum disorder (ASD). But behind popular culture's tropes, autism is often devastating.

In one study, for example, 83% of people with autism could not live independently. Their problems did not arise from learning disabilities (all had IQs over 70), but rather from profound issues with social communication.[1] In the modern world, psychologist Bruce Hood notes, 'we need to be expert socializers' able to recognise what other people are thinking, what they want, and whether and how to cooperate. Yet 'social skills that may seem trivially easy for many of us turn out to be some of the most complex calculations our brains can perform'.[2]

In ASDs, these complex calculations often turn out wrong. People with autism show markedly impaired verbal and non-verbal communication and social interactions. They also exhibit abnormal (eg highly restricted, repetitive and stereotyped) behaviour, interests and activities.[1,3,4] Recent research into genes, molecules and neuronal networks are transforming our understanding of the basis of autistic behaviours and cognition. However, the studies also suggest that ASD is more complex than almost anyone imagined.

Diverse explanations for a diverse disease

Autism is not a simple, single disease, with a straightforward universal explanation. As Geschwind and Levitt noted, 'autism has many etiologies and should be considered not as a single disorder but, rather, as "the autisms" '.[4]

Certainly, people with ASD vary widely. Some are aloof. Some seek interactions with other people, but are 'socially odd'.[4] Perhaps 0.05% of people with autism are savants, able to, for example, calculate eight-digit prime numbers almost instantly, state the day of the week for any date in 80 000 years or create photorealistic cityscapes.[5,6] These rare, fascinating savants inevitably attract much of the media's attention. But behind the headlines, approximately half of ASD patients live with profound intellectual disabilities. These patients generally show the most challenging behaviours and are the most difficult to manage.[1]

Psychologists devised numerous theories to explain ASD's diversity. Early researchers blamed emotionally detached 'refrigerator mothers' – a now discredited idea.[5] But none of the more recent ideas – such as impaired theory of mind, empathising-systemising and mirror neurons – gained universal acceptance.[3,5] Theory of mind, for example, describes our ability to empathise with and imagine other people's thoughts and feelings. These insights allow us to understand and predict another person's behaviour.[3] The empathising-systemising theory suggests that while people with autism have 'delays and deficits' in empathy, they may have preserved or superior 'systemising' skills. A strong systemiser sees each system as unique, which limits their ability to generalise.[3] Each theory – there are many more – has critics and they do not really characterise the underlying abnormalities.

The 'broken mirror neuron system' attempted to trace the neuroanatomical source of poor social cognition in ASD.[7] Italian researchers discovered mirror neurones when recording activity in the premotor cortex of macaque monkeys. Certain neurons fired when the monkeys reached for a raisin. The same neurons fired when a researcher reached for the raisin.[2] In other words, the mirror neuron system is active when the person performs an action and when they observe someone else performing the same action.[7] Some researchers suggest that the mirror neuron system is central to human empathy, culture and basic social skills, from imitation, to crying at weddings, to feeling other people's pain.[2,5]

Mirror neurons attracted a lot of attention in ASD and beyond. However, a review of 25 papers concluded that 'overall, there is little evidence for a global dysfunction of the mirror system in autism'.[7] Indeed, people with autism do not seem to experience

problems with imitation itself. Their difficulties lie in knowing when and how much to imitate, which is a much more subtle social skill.[5] Furthermore, researchers do not know whether mirror neurons are present at birth or arise because we watch other people.[2]

From genotype to phenotype

No single theory currently accounts for autism's complexity. Indeed, recent studies suggest that autism is even more complex and complicated than the clinical variation might suggest. For example, we have realised for decades that ASD runs in families. Concordance rates, for example, are 47–96% in monozygotic twins for ASD and 0–36% in dizygotic twins for autism and wider ASD phenotypes.[8] Genetic studies link 'hundreds of susceptibility loci' to ASD.[9] Broadly, however, 2.6% of ASD cases seem to arise from rare *de novo* mutations, 3% from rare inherited variants, and 49% from common inherited variants. However, twin studies suggest that environment accounts for between 10% and 55% of the risk.[8]

Some genetic changes associated with ASD – such as those affecting an area of the short arm of chromosome 16 (16p11.2), which contains 29 genes – are relatively well characterised. Deletions of 16p11.2 occur in 0.1% to 0.7% of ASD patients and 16p11.2 duplications in 0.1% to 0.5% – a rate 10 times higher than in the general population. Copy number variations in 16p11.2 seem to be associated with several problems, including intellectual disabilities, delayed development, speech problems, schizophrenia and seizures.[8]

However, the largest autism genome study, recently published in *Nature Medicine*, reveals that the disorder's genetics are even more complex than previously thought. Researchers sequenced 340 whole genomes from members of 85 families, each with two children with ASD. Among the children, 69.4% carried different ASD-related mutations to their siblings. Siblings with different mutations tended to show greater clinical variability than those sharing a variant. Forty-two per cent of families expressed genes known to increase ASD risk.[9]

Previously, researchers assumed that siblings with ASD inherited the same susceptibility genes. 'We knew that there were many differences in autism, but our recent findings firmly nail that down,' says study author Stephen Scherer, who directs the Centre for Applied Genomics at Toronto's Hospital for Sick Children. 'We believe that each child with autism is like a snowflake – unique from the other'.

Against this background, correlating genotypes and phenotypes might help hone diagnostic and prognostic accuracy, and personalise treatment. So, a team lead by Dennis Vitkup, associate professor of systems biology and biomedical informatics at Columbia University, recently investigated the links between mutations and autism traits by analysing 991 unique genes from 624 loci.[10]

Not surprisingly, patients with 'more damaging' mutations tended to show worse intellectual, social and behavioural outcomes. For example, autism patients with low verbal or nonverbal IQs usually had damaging mutations in genes that are strongly expressed in the brain. Those with higher IQs expressed mutations that only partially compromise the gene's normal function.[10]

The studies also help explain differences in ASD between the sexes. At least four males have diagnosed ASD for every diagnosed female. But the ratio falls to about to 2:1 for people with ASD who also show profound intellectual disability.[11] The Columbia researchers found that mutated genes in females tended to be more active than those mutated in males. In girls, very damaging mutations linked to ASD are almost twice as active as typical genes in normal brains.[10]

Recent studies confirm that females with ASD tend to show more developed social and emotional skills than males, which may 'camouflage other diagnostic features'. Further research should explore the underlying causes for the sex differences to develop diagnostic criteria and treatments appropriate for each sex.[11]

'These [genetic] patterns are consistent with the idea that there are mechanisms that protect females,' Dr Vitkup says. 'Most often, only when a mutation hits a highly active gene do we see symptoms in females. Given that the inherent differences in gene activity in male and female brains are typically on the order of a few percent, these findings are quite remarkable.'

The researchers, based on animal models, suggest that ASD-related mutations usually simultaneously affect several brain areas. 'The idea that eventually all autism mutations would converge onto a single type of neuron or single brain area isn't what we see in the data,' Dr Vitkup said. Nevertheless, certain neurons seem especially strongly affected, including cortical and striatal neurons that form a circuit controlling repetitive motions and behaviours.[10]

'Idiosyncratic' synchronisation

Identifying such circuits, and determining interactions between genes and environment that create the aberrant pathways, is essential to understanding autism. But,

again, recent neuroanatomical studies underscore autism's complexity. For example, some previous studies reported that ASD patients showed poor synchronization between parts of the brain that normally work together. However, other studies found over-synchronisation. Now new research suggests that people with autism display unique synchronisation patterns.

Functional magnetic resonance images while participants were at rest, the time when patterns emerge spontaneously, revealed several differences in brain activity between healthy volunteers and people with ASD. For instance, regions that in controls showed high connectivity between the brain's hemispheres (such as the sensory-motor and occipital cortices) while those with ASD tended to have *reduced* connectivity. In contrast, regions that typically showed low levels of connectivity between the hemispheres (eg frontal and temporal cortices) in controls tended to have *increased* connectivity in people with ASD. In addition, healthy brains showed 'substantially similar connectivity profiles'. Those with ASD were much more unique. The researchers dubbed synchronisation patterns in controls and ASD patients 'conformist' and 'idiosyncratic' respectively.[12]

Differences in the way individuals interact and communicate may determine whether they show conformist and idiosyncratic patterns. 'From a young age, the average, typical person's brain networks get moulded by intensive interaction with people and the mutual environmental factors,' said study author Avital Hahamy from Carnegie Mellon University, Pittsburgh. 'Such shared experiences could tend to make the synchronization patterns in the control group's resting brains more similar to each other. It is possible that in ASD, as interactions with the environment are disrupted, each one develops a more uniquely individualistic brain organisation pattern.' Hahamy's explanation is only 'tentative'. Additional research needs characterise the factors that may lead to idiosyncratic synchronisation and the ways in which differences in connectivity and synchronisation translate into ASD's myriad cognitions and behaviours.

Spitting out a diagnosis

Such advances offer new approaches to diagnosis. In a recent pilot study, for example, researchers studied proteins in saliva from six children diagnosed with autism, aged 8 to 16 years, and six neurotypical children in a similar age range. Levels of nine proteins were significantly higher in saliva of autism patients. Three were present at lower levels or absent in people with ASD.[13]

Many of the 'biomarker' proteins in the saliva contribute to immunological responses and inflammation.[13] Several other strands of evidence suggest that infections and inflammation may also contribute to ASD. For example, maternal infections during pregnancy seem to increase ASD risk.[8] In the pilot study, salivary levels of lactotransferrin (also called lactoferrin) were 30% higher in ASD patients than controls. Lactotransferrin is involved in gastrointestinal immune responses. Gastrointestinal symptoms are common in people with ASD and correspond with severity. Similarly, levels of prolactin-inducible protein, which seems to contribute to innate and adaptive immunity, were 59% higher in ASD patients. Further studies need to confirm the findings and ascertain whether ASD subtypes have different biomarker signatures.[13]

As these examples show - which barely scratch the surface of the literature - researchers are gaining unprecedented insights into the genetic, molecular and neuroanatomical basis of ASD's diverse clinical presentation. However, recent research underscores ASD's essential complexity and the link between genotype and clinical phenotype is often far from clear. As psychologist Christian Jarrett remarks, 'the simple term "autism" conceals a world of complexity'.[5]

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