Can genetics find a 'cure' for autism?

August 10 2015, by Adrian Harwood

Credit: ready made from Pexels

We live in an age of genetics. Major genetic success stories such as breakthroughs in treating cystic fibrosis and breast cancer inspire hope that it can one day provide a cure for all ills. So when we hear that mental disorders are at least partially genetically determined, we may wonder what progress is being made.

A paper in the journal *Cell* into the psychiatric condition autism shows not only the condition's daunting genetic complexity, but also how we may combine different genetic approaches to pinpoint a potential cure. The study of an autistic child with a rare genetic mutation of a specific gene, UBE3A, has indicated a possible treatment.

Autism, or more correctly Autism Spectrum Disorder (ASD), affects around one in 100 individuals and is usually first seen during early childhood. Symptoms are diverse, but include difficulties with communication and social interaction, and repetitive behaviour or movements. ASD is associated with high intellectual and artistic ability in some individuals, but around half of patients have learning difficulties of varying severity. The disorder is currently incurable.

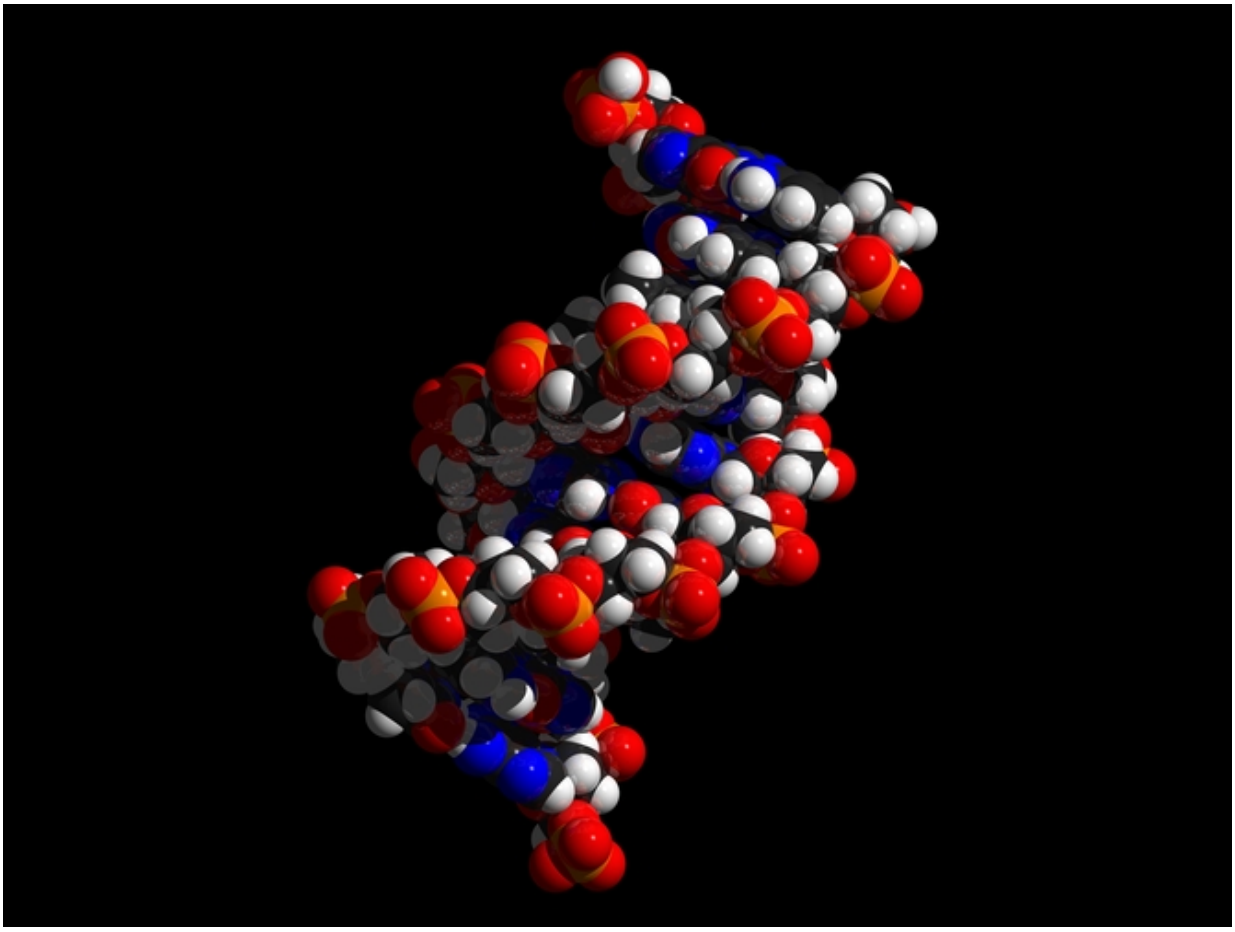
Big changes, big effects

Evidence indicates that genetics present a significant risk of developing ASD. Genes, written as DNA stored on chromosomes, contain a blueprint for proteins that control how cells work, and there is evidence that brain cells of children with ASD operate differently to those without.

But, unsurprisingly given the diversity of its symptoms, there is no evidence for a single genetic mutation. In fact, current evidence suggests that hundreds of genes may be involved, with each one having only a small effect. Only when many detrimental mutations occur at the same time is there a significant risk.

As most genes are identified by Genome-Wide Association Studies (GWAS), which averages the genomes of hundreds of thousands of patients and compares them to the general population, it's not possible to link a specific DNA change to a particular individual. We can see the smoke, but not the gun.

Identifying the culprit



A DNA double-helix model. Credit: Ude

So can genetic studies of ASD risk ever lead to a discovery of a treatment? Occasionally geneticists find rare individuals where a large loss or gain of a chromosome segment either reduces or increases the numbers of genes. These very rare chromosome abnormalities tend to have strong effects, making it easier to determine which genes contribute significantly to a disorder.

But things are not always that simple. A missing part of chromosome 15 causes Angelman Syndrome, which has many similarities to ASD. However, Dup15 syndrome, when the same region is duplicated, is one of the most frequently found chromosome change in ASD patients.

A gene called UBE3A, common to both deleted and duplicated DNA regions, is thought to be the risk gene. However, as there are other genes in these regions how can we know that UBE3A is responsible? The authors of the study report an extremely rare case of a small UBE3A mutation in a child with ASD. It is not present in their unaffected parents, so it must have newly mutated in that individual.

Genes can act like on/off switches for the protein they are responsible for coding. Usually mutations like this one would deactivate the protein and permanently turn the switch off, but in this case the change permanently switches it on. This is a rare instance where mutations detected by Genome-Wide Association Studies can be assigned to a specific change in a protein – and here it arises in an individual who then develops ASD.

What goes up, must come down.

This is very strong evidence, but it raises the question of how both a gain of UBE3A activity (as seen in the new mutation and in Dup15 syndrome), and a loss of UBE3A (as seen in Angelman syndrome) can be associated with ASD. The answer may lie in how UBE3A works.

UBE3A turns out to be important for learning. When nerve cells in the brain fire, UBE3A activity rises, but it then switches itself off. This activity cycle in the brain is required when we learn, but loss or gain of UBE3A prevents the cycle from occurring. This may explain why either loss or gain could be associated with the learning difficulties experienced by people with ASD.

Does this help towards a treatment? Zylka and Yi show that the drug Rolipram may suppress overactive UBE3A. By using genetic screening to identify individuals with increased UBE3A, it may be possible to design precise treatments to alleviate some ASD symptoms. Whether or not UBE3A ultimately makes it as a clinically useful target, it shows how finding rare genetic cases offers a powerful strategy in the search for a cure.

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