New intellectual disability syndrome caused by genetic damage to single gene

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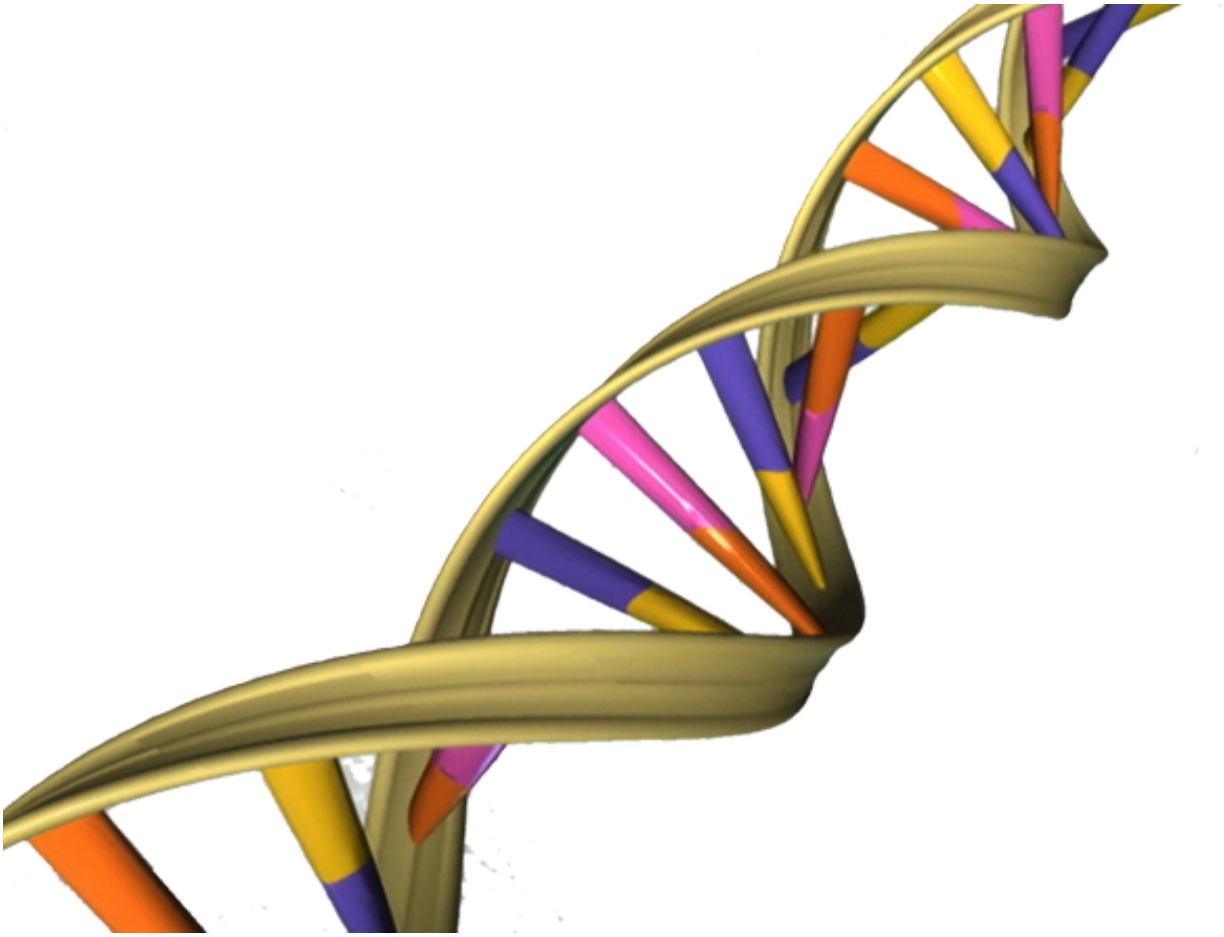

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Scientists at the Wellcome Trust Sanger Institute and Max Planck Institute for Psycholinguistics have found a gene responsible for an intellectual disability disorder and proven how it works. The research, published in the *American Journal of Human Genetics*, details the role of a gene called BCL11A in a new intellectual disability syndrome.

The study showed that if one of a person's two copies of the BCL11A gene is abnormal, or mutated, then they will have the newly described intellectual disability. The team used human cells and a mouse model to show that the body needs two healthy copies of BCL11A to make enough of the BCL11A protein for brain cells to develop normally and work at capacity.

The Sanger Institute's Deciphering Developmental Disorders research programme, has found many new genes associated with intellectual disability. However, relatively little is known about how these genes work because each genetic cause is so rare. By exploring the mechanism in mice, they have been able to show for the first time the impact of these genes on human development.

A team led by Dr Darren Logan and Prof Simon Fisher worked with nine patients, from the UK and abroad, who have an intellectual disability. They found these people share the same genetic profile and symptoms that they now define as a new clinical syndrome. Each person also had the same unusual blood profile which could be used to help diagnose patients in the future.

Dr Darren Logan, lead researcher from the Wellcome Trust Sanger Institute, said: "We worked with patients, studied human cells and made a mouse model to translate research from the gene discovery phase into understanding a cause of intellectual disability. We've shown that the BCL11A gene does cause an intellectual disability syndrome. It's an excellent example of gene discovery by patient DNA sequencing paired

with experimental investigation to prove a link between gene and outcome that is backed up by cellular and animal studies. We plan to follow this model on an even larger scale in the future, to test the role of many other genes associated with intellectual disability."

Nearly three in every 100 people in the human population have some form of learning disability and it can have many different genetic causes. The way conditions present in patients varies too, and so each syndrome is poorly understood. The research also revealed that mutated BCL11A influences many other genes important for brain development and function and so explains why people who carry an abnormal copy have intellectual disability.

Prof Simon Fisher, director of the Max Planck Institute for Psycholinguistics, said: "We were interested to find severe problems with speech and language development as a consistent feature of the syndrome caused by BCL11A mutations. Studies like ours are beginning to reveal intriguing connections between the biological causes of intellectual disability and disorders of spoken language. And although BCL11A mutations are themselves rare, the gene belongs to a bigger network of genes that are crucial for building a healthy brain, and so it can provide much broader insights into the basis of human cognition, and how this might go wrong during development."

Dr Cristina Dias, a clinical geneticist working in Dr. Logan's laboratory at the Sanger Institute, said: "The contribution of patients and their families to this study was essential for us to understand how a mutation in BCL11A affects them as a group. This is a newly recognized condition so it is important we continue patient studies. We will use experimental resources of cells and mouse models to further investigate how the mutations are influencing other genes, and find potential drug targets. Ultimately, these studies will help us better understand intellectual disability and associated health problems, to ensure that

individuals have the best care."

More information: *American Journal of Human Genetics*, DOI: 10.1016/j.ajhg.2016.05.030

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