New study identifies thousands of novel brain-expressed gene isoforms

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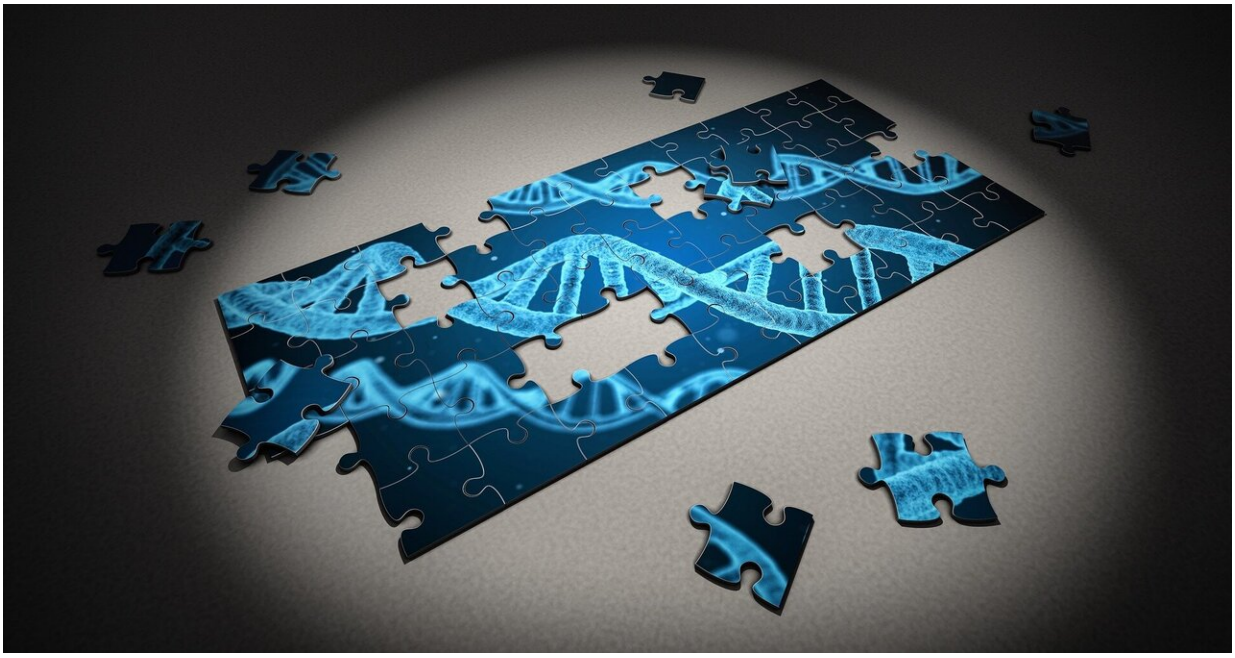

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New research led by the University of Exeter has shed light on the complexity of gene expression in the brain by characterizing the extent of isoform diversity in the human and mouse cortex, including the identification of novel isoforms of genes involved in diseases including Alzheimer's disease, autism and schizophrenia. The research suggests that the genes expressed in our brains may produce far more proteins

than previously thought.

We have approximately 20,000 genes encoded in our DNA sequence, but each gene can be expressed in many different versions—or isoforms—that are generated by a process called 'alternative splicing'. This process can produce many isoforms of an expressed gene by sticking together different parts of the coding sequence in different combinations. Alternative splicing greatly increases the coding complexity of the genome and is important because these isoforms can have different functional properties that might play a role in health and disease.

Alternative splicing is known to be particularly important in the central nervous system, where it plays a role in the development and function of the brain. In recent research published in *Cell Reports*, and funded by the Medical Research Council and the Simons Foundation for Autism Research (SFARI), a team led by Professor Jonathan Mill used novel long-read sequencing approaches in Exeter to characterize complete transcripts and describe the full repertoire of isoforms present in the human and mouse brain. Around half the isoforms they detected had not previously been described, and the majority of these novel isoforms have the potential to encode proteins.

Lead author Szi Kay Leung said: "Isoforms have a wide range of functions, and we've long known that alternative splicing plays an important role in regulating gene function in the brain, being implicated in many brain diseases. Now, we've characterized for the first time the different isoforms present in the human and mouse brain, and also explored differences occurring across brain development. Our study identifies thousands of novel brain expressed isoforms, and confirm the importance of alternative splicing in the cortex, dramatically increasing transcriptional diversity and representing an important mechanism underpinning gene regulation in the brain."

The team found major differences in isoform diversity for specific genes between human and mouse brains, and also big shifts between fetal and adult cortex suggesting an important role for alternative splicing in neurodevelopment.

Senior author Professor Jonathan Mill, of the University of Exeter, said: "We're excited to find that genes associated with three brain diseases, Alzheimer's disease, autism and schizophrenia, are characterized by lots of new isoforms not previously described. We are now in the process of exploring how these isoforms might play a role in the onset of disease."

The team has made their isoform annotations available to the community to enable further research, at http://genome.exeter.ac.uk/BrainIsoforms.html

The paper is entitled "Full-length transcript sequencing of human and mouse cerebral cortex identifies widespread isoform diversity and alternative splicing" and is published in *Cell Reports*.

More information: Jonathan Mill, Full-length transcript sequencing of human and mouse cerebral cortex identifies widespread isoform diversity and alternative splicing, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.110022. www.cell.com/cell-reports/full … 2211-1247(21)01504-7

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