MedicalXpress

Researchers find more genes associated with intelligence and neuroticism

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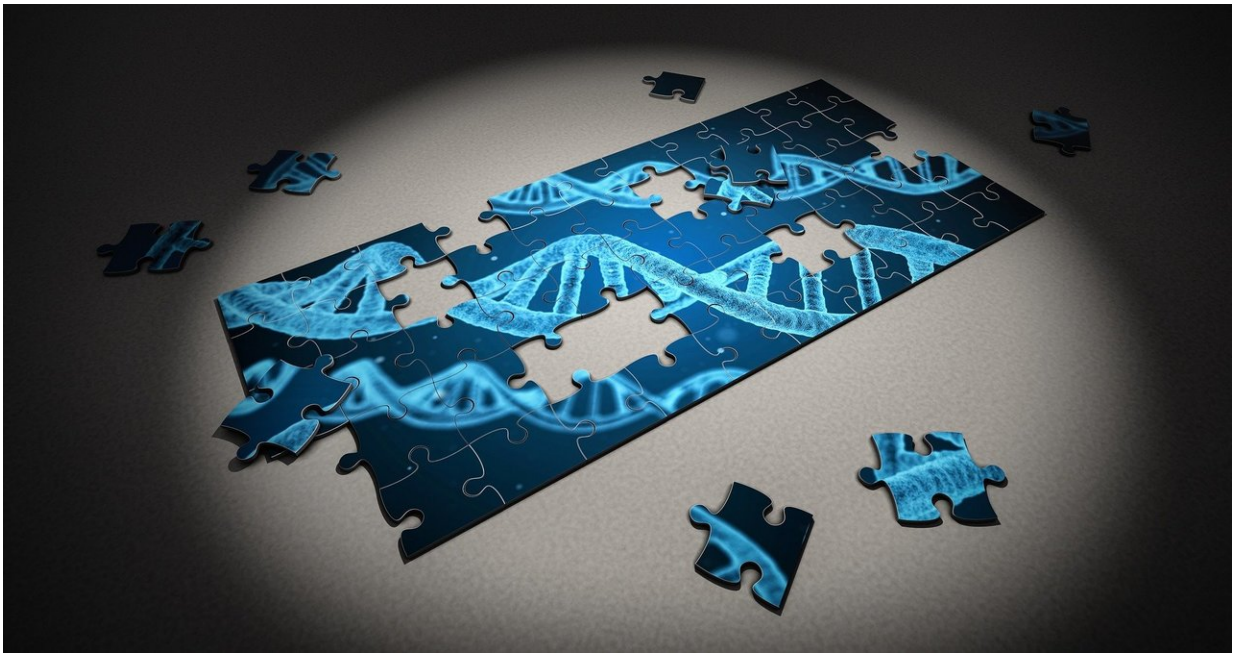

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A single team of researchers from around the globe conducting two different studies has found more genes related to human intelligence and more that are associated with neuroticism. They have published separate papers outlining their work and findings in the journal *Nature Genetics*.

To understand how the human brain functions, scientists conduct work

to isolate the genes that are responsible for individual traits and characteristics. In this new effort, the researchers searched and analyzed information found in databases to isolate genes that appear to be responsible for intelligence and neuroticism.

In the first study, the researchers retrieved information from 14 databases that held health and genetic information. The datasets, they note, contain both genetic information and intelligence test scores. By cross-referencing the data, they were able to isolate 939 genes that had not previously been associated with higher intelligence levels. They report that they also found relationships between higher intelligence and living longer without developing Alzheimer's disease—and also having a higher risk for developing autism.

In the second study, they combed similar databases searching for information surrounding neurotic traits (excessive moodiness, anxiety and nervousness) in patient information. In so doing, they report finding approximately 500 genes that they claim can be associated with neurotic tendencies.

The researchers also report that they used a newly developed statistical method called MAGMA—prior efforts have shown that it can be useful in sifting through genetic data to find pertinent information and associating it with particular parts of the brain. Many of the markers they found regarding intelligence, they note, could be found in the basal ganglia, in what they describe as medium spiny neurons—parts of the brain that have previously been found to be responsible for cognition and learning. In identifying parts of the brain that appear to be involved in neuroticism and other disorders, the researchers note, it might become possible to develop medications to alleviate symptoms. Similarly, they note that discovering why more intelligent people seem to be less susceptible to Alzheimer's disease might lead to new treatments or a cure.

More information: 1. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0151-7

Abstract
Neuroticism is an important risk factor for psychiatric traits, including depression, anxiety, and schizophrenia. At the time of analysis, previous genome-wide association studies (GWAS) reported 16 genomic loci associated to neuroticism. Here we conducted a large GWAS meta-analysis (n = 449,484) of neuroticism and identified 136 independent genome-wide significant loci (124 new at the time of analysis), which implicate 599 genes. Functional follow-up analyses showed enrichment in several brain regions and involvement of specific cell types, including dopaminergic neuroblasts ($P = 3.49 \times 10^{-8}$), medium spiny neurons ($P = 4.23 \times 10^{-8}$), and serotonergic neurons ($P = 1.37 \times 10^{-7}$). Gene set analyses implicated three specific pathways: neurogenesis ($P = 4.43 \times 10^{-9}$), behavioral response to cocaine processes ($P = 1.84 \times 10^{-7}$), and axon part ($P = 5.26 \times 10^{-8}$). We show that neuroticism's genetic signal partly originates in two genetically distinguishable subclusters ('depressed affect' and 'worry'), suggesting distinct causal mechanisms for subtypes of individuals. Mendelian randomization analysis showed unidirectional and bidirectional effects between neuroticism and multiple psychiatric traits. These results enhance neurobiological understanding of neuroticism and provide specific leads for functional follow-up experiments.

2. Jeanne E. Savage et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0152-6

Abstract
Intelligence is highly heritable and a major determinant of human health

and well-being. Recent genome-wide meta-analyses have identified 24 genomic loci linked to variation in intelligence, but much about its genetic underpinnings remains to be discovered. Here, we present a large-scale genetic association study of intelligence (n = 269,867), identifying 205 associated genomic loci (190 new) and 1,016 genes (939 new) via positional mapping, expression quantitative trait locus (eQTL) mapping, chromatin interaction mapping, and gene-based association analysis. We find enrichment of genetic effects in conserved and coding regions and associations with 146 nonsynonymous exonic variants. Associated genes are strongly expressed in the brain, specifically in striatal medium spiny neurons and hippocampal pyramidal neurons. Gene set analyses implicate pathways related to nervous system development and synaptic structure. We confirm previous strong genetic correlations with multiple health-related outcomes, and Mendelian randomization analysis results suggest protective effects of intelligence for Alzheimer's disease and ADHD and bidirectional causation with pleiotropic effects for schizophrenia. These results are a major step forward in understanding the neurobiology of cognitive function as well as genetically related neurological and psychiatric disorders.