NEWS

Analysis unearths common genetic roots for disparate traits

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Using a new genetic approach, researchers are finding shared risk factors for seemingly unrelated conditions, ranging from autism to obesity[1].

The method, described in the November issue of *Nature Genetics*, provides intriguing hints about the role of genes in the distribution of certain traits and disorders across the population. For example, large epidemiological studies have shown that the risk of coronary artery disease drops with increasing height[2]. The new work suggests that the link between height and heart disease stems partly from shared genetics.

The researchers found 276 of these associations; included among them is a curious association between autism risk and educational attainment.

The tentative ties between these diverse factors provide fodder for epidemiological studies that could verify the relationships, says lead researcher **Benjamin Neale**, assistant professor of analytic and translational genetics at Massachusetts General Hospital in Boston.

“It is one of the tools in our arsenal to explore a variety of considerations about how different [traits] relate together,” Neale says. “This is extremely powerful, because large-scale cross-sectional epidemiological studies are challenging.”

But many of these links are hard to interpret, researchers say. For instance, many factors — genetic and environmental — contribute to the odds of attending college. These include intelligence, personality and socioeconomic status. So exactly which factors contribute to autism’s link to higher education, and to what extent, remains uncertain.

Power in numbers:

Genetic studies aim to directly link an individual's genes with a certain characteristic. But environmental factors can influence genetic data, says **Bernie Devlin**, professor of psychiatry at the University of Pittsburgh. For example, people who have had more education may be more likely than less-educated individuals to participate in genetic studies.

"Epidemiologists have spent decades worrying about hidden biases in data, which, if not controlled for, can lead to erroneous associations," he says. "We genetic epidemiologists will also have to worry about these issues."

The new method relies on data from genome-wide association studies (GWAS), which ferret out common variations in the genetic code that are unusually prevalent among people with a given feature or trait. Combinations of many different variants — single-letter swaps called single nucleotide polymorphisms (SNPs) — dictate traits ranging from height to intelligence.

Researchers need data from tens of thousands of people to get a statistically valid tie between a single variant and a trait. But the combined effect of thousands of variants can show that as a whole, these variants boost the odds of a condition.

Neale and his colleagues started with data from 24 GWAS, each of which associates a set of variants with an individual condition or trait, such as autism, Alzheimer's disease, body mass index or educational attainment. They then merged the data and looked for conditions and traits that share some of the same genetic risk factors.

A diagnosis of autism or schizophrenia is equivalent to a "diagnostic peak" that results from a particular combination of genetic risk factors, says **Stephan Sanders**, assistant professor of psychiatry at the University of California, San Francisco. "This paper is a remarkable insight into which peaks are closely related, such as schizophrenia and bipolar disorder, and which are far apart, such as autism and coronary artery disease," he says.

In a study published yesterday, researchers reported that some of the same rare, harmful mutations may underlie congenital heart disease and neurodevelopmental disorders[3].

Smoking gun:

One of the study's most intriguing findings is that the genetic risk factors for anorexia overlap with those that underlie a low, but healthy, body mass index. This finding suggests that extremes of behavior and more moderate variation have common genetic underpinnings, says Neale.

The study also suggests that the tendency to smoke and schizophrenia have little genetic overlap, despite the fact that people with the disorder are significantly more likely to smoke than are people in the general population. The result suggests that from a genetic point of view, what drives people with schizophrenia to smoke is different from the factors at work in the general population.

The autism findings from the study are perhaps the least robust, because GWAS in the field are still small, says **Elise Robinson**, instructor in medicine at Harvard University and a researcher on the study. The link to higher education may not hold up when researchers use the method with new, unpublished GWAS data that include roughly three times more participants than those in the current study, she says.

What's more, no one is sure why autism and education level would be genetically linked. The most likely explanation is that the flagged variants boost both intelligence quotients (IQ) and autism risk. But the variants probably produce these divergent effects under separate sets of conditions, Sanders says.

"A common genetic variant that increases IQ in the population may not have the same effect in a child with autism," he says. "Rather, it might reflect a biological process that is advantageous in one situation but has a negative effect in combination with other risk factors."

REFERENCES:

1. Bulik-Sullivan B. *et al. Nat. Genet.* **47**, 1236-1241 (2015) **PubMed**
2. Wang N. *et al. Int. J. Epidemiol.* **40**, 1715-1726 (2011) **PubMed**
3. Homsy J. *et al. Science* **350**, 1262-1266 (2015) **Abstract**