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New insights into intellectual disability genetics emerge

Researchers highlight repetitious DNA as a previously under-recognized factor

Date: September 23, 2024

Source: The Mount Sinai Hospital / Mount Sinai School of Medicine

Summary: Researchers have published a pivotal study that sheds light on a novel genetic variant associated with intellectual capacities and educational outcomes. This discovery offers new insights into intellectual disability diagnostics and potential therapeutic avenues.

FULL STORY

Researchers at the Icahn School of Medicine at Mount Sinai have published a pivotal study in *Nature Genetics* that sheds light on a novel genetic variant associated with intellectual capacities and educational outcomes. This discovery offers new insights into intellectual disability diagnostics and potential therapeutic avenues.

The study reveals the significant impact of tandem repeats -- sequences of DNA where a pattern of nucleotides is repeated multiple times in a head-to-tail manner on a chromosome -- on intellectual functioning.

"The genome contains a myriad of these tandem repeats that, when expanded, can disrupt the function of genes," explained Andrew Sharp, PhD, Professor of Genetics and Genomic Sciences at Icahn Mount Sinai and lead author of the study. "Our research brings to light how these previously underappreciated genetic features can have a profound impact on human intelligence."

Tandem repeats can be compared to sentences within the book of the human genome that are repeated several times. An excessive number of these repeats can lead to a disruption in the genetic instructions, impacting an individual's development and cognitive abilities, say the investigators.

Using advanced DNA methylation profiling and genotyping, the research team identified a repeat expansion of a specific nucleotide sequence, consisting of a series of guanine (G) and cytosine (C) bases followed by another cytosine (C) base (GCC), within the *AFF3* gene, which is strongly associated with educational attainment. This discovery could explain the genetic basis of at least 0.3 percent of intellectual disability cases, improving the precision of genetic testing and diagnostics.

The study's phenome-wide association approach, which links genetic variants to human phenotypes, underscores the broader implications of these genetic variations on public health. "Identifying the *AFF3*expansion as a contributor to intellectual disability is a step toward more accurate and timely diagnoses," noted Dr. Sharp.

Future research is expected to build on these findings. Although the current study focuses on a limited number of tandem repeat expansions, the human genome contains hundreds of thousands, many of which are likely to play a role in disease, explained Dr. Sharp. The team plans to expand their research to explore more of these repeat expansions, deepening our understanding of their prevalence and impact on the human population.

Funding support for this study was provided by National Institutes of Health (NIH) grants AG075051, NS105781, HD103782 and NS120241; NIH National Heart, Lung, and Blood Institute Fellowship 5120339; the Prinses Beatrix Spierfonds (W.OR20-08); the European Research Council under the European Union's Horizon 202 research and innovation program, grant 772376 -- EScORIAL; UK Research and Innovation (MR/S006753/1); Barts Charity (MGU0569); and a Medical Research Council Clinician Scientist Award (MR/S006753/1).

Competing Interest Statement Pacific Biosciences provided research support for HiFi sequencing performed in this study. Study authors Egor Dolzhenko and Tom Mokveld are employees and shareholders of Pacific Biosciences.

Story Source:

Materials provided by **The Mount Sinai Hospital / Mount Sinai School of Medicine**. *Note: Content may be edited for style and length.*

Journal Reference:

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Cite This Page:

MLA APA Chicago

The Mount Sinai Hospital / Mount Sinai School of Medicine. "New insights into intellectual disability genetics emerge." ScienceDaily. ScienceDaily, 23 September 2024.