First genetic risk factor for erectile dysfunction identified

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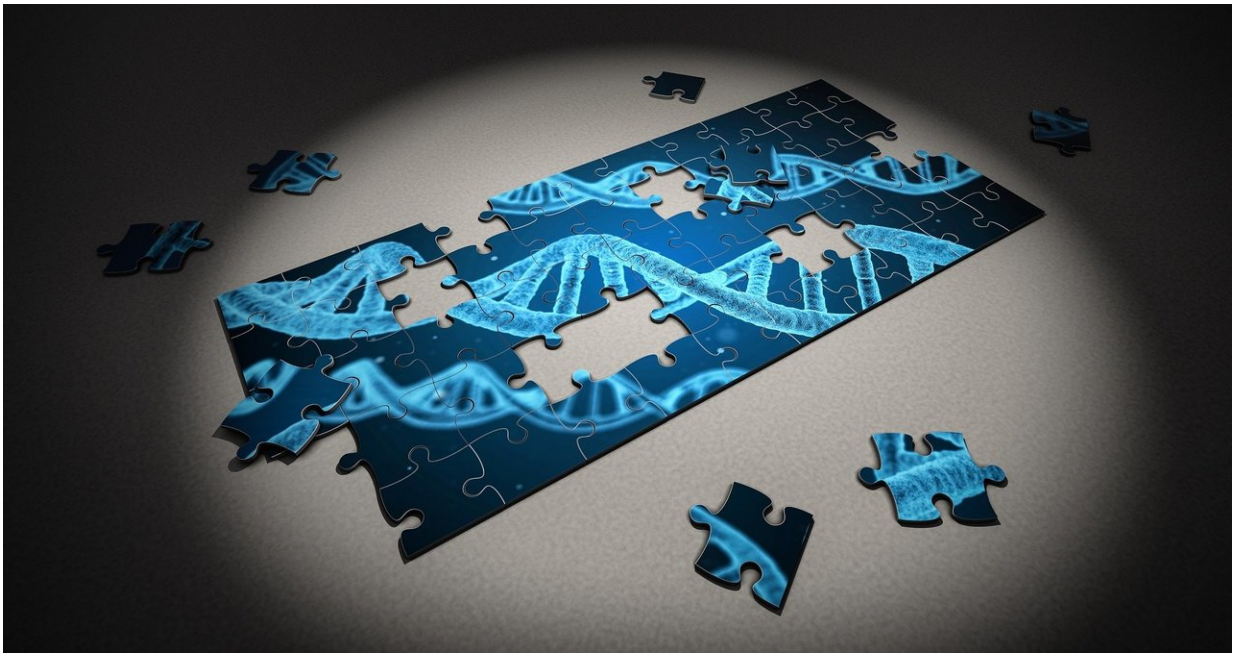

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For the first time, a team of researchers has found a specific place in the human genome that raises a person's risk of erectile dysfunction. The discovery is a significant advancement in the understanding of the genetics underlying erectile dysfunction. The study, "Genetic variation in the SIM1 locus is associated with erectile dysfunction," will be published the week of October 8 in the journal *Proceedings of the National*

Academy of Sciences.

Erectile dysfunction, the inability to obtain and maintain an erection sufficient for sexual activity, is a common and costly condition of men of primarily middle and older ages. The disease is linked to many causes, such as neurological, hormonal and vascular factors.

Therapies based on these factors exist, but many men don't respond to them. Genetics also are suspected as a factor in about one-third of erectile dysfunction cases, but researchers have failed to make an association with any specific genomic locations until now.

The new study found that variations in a specific place in the genome—called a genetic locus—near the SIM1 gene are significantly associated with an increased risk of erectile dysfunction. The researchers ruled out that the risk was due to other known risk factors for erectile dysfunction, such as body mass index, or differences in how men describe their erectile dysfunction. The study also demonstrated a biological role for the genetic location in regulating sexual function, strongly suggesting that these variations can cause erectile dysfunction.

"Identifying this SIM1 locus as a risk factor for erectile dysfunction is a big deal because it provides the long sought-after proof that there is a genetic component to the disease," said the study's lead author, Eric Jorgenson, Ph.D., a research scientist at Kaiser Permanente Northern California's Division of Research. "Identifying the first genetic risk factor for erectile dysfunction is an exciting discovery because it opens the door for investigations into new, genetic-based therapies."

The researchers conducted a genome-wide association study in two large and diverse cohorts to investigate genetic contributors to the risk of erectile dysfunction. The first cohort included 36,648 men from the Genetic Epidemiology Research on Adult Health and Aging (GERA)

cohort, which is part of the Kaiser Permanente Research Program on Genes, Environment and Health, a research program affiliated with the Kaiser Permanente Research Bank. The Research Bank supports external and internal investigation into a variety of health conditions and diseases and includes biospecimens from more than 320,000 consenting Kaiser Permanente members, as well as linked genetic, environmental and health data.

The GERA cohort included male members of Kaiser Permanente who completed a survey on their condition, had a clinical diagnosis of erectile dysfunction based on their electronic health records, and had used drugs or other erectile dysfunction treatments. The findings in the GERA cohort were then verified in a cohort of 222,358 men from the U.K. Biobank.

The study found that variations in the SIM1 locus were associated with a 26 percent increased risk of erectile dysfunction. This risk was independent of known erectile dysfunction risk factors. The association was replicated in the U.K. Biobank sample, providing strong confirmation of the findings.

"This significant advance in our understanding of erectile dysfunction is made possible by the unique ability of the Kaiser Permanente Research Bank to link detailed questionnaires, electronic health records, and genetic data on such a large population," said the study's senior author, Stephen Van Den Eeden, Ph.D., a research scientist at the Division of Research.

Erectile dysfunction has been difficult to study in part because of the differences in how patients report their symptoms. To overcome this challenge, the study looked to see whether the SIM1 locus was a risk factor when considering differences in how men reported their erectile dysfunction to their doctors. The study found that this location was

indeed a risk factor for erectile dysfunction, whether the disorder was defined through clinical diagnoses, prescriptions history, or study participant self-report.

The study then identified a biological role for this location in erectile dysfunction susceptibility. The SIM1 gene is known to be part of a signaling pathway that plays a central role in body weight regulation and sexual function. The erectile dysfunction locus is located near, but not in, the SIM1 gene. Members of the research team at the University of California, San Francisco, were able to show that the implicated location physically interacts with the promoter of the SIM1 gene, and that variants in this location alter the function of a master gene regulator, called an enhancer.

Think of a gene like a light bulb, Jorgenson said: The promoter is like a light switch, and an enhancer acts like the fuse box. Because the erectile dysfunction risk locus showed enhancer activity and interacted with the SIM1 promoter, the erectile dysfunction risk locus likely influences the expression of the SIM1 gene, turning it on and off when needed, the study suggests.

"The different bits of evidence that we present in this study fit together like puzzle pieces to create a picture of how the SIM1 locus can control erectile function," Jorgenson said.

The study highlights the potential of SIM1 as a target for the development of new treatments for erectile dysfunction, which are needed because about half of all men who try currently available pharmaceutical treatments for erectile dysfunction don't respond to them.

"This study points to a new research direction for erectile dysfunction that could help us identify other key genetic variants that trigger the

disease and lead to investigations to better understand the precise mechanisms by which they operate," said Hunter Wessells, MD, chair of urology at the University of Washington School of Medicine, a co-author and one of the study's principal investigators. "Hopefully, this will translate into better treatments and, importantly, prevention approaches for the men and their partners who often suffer silently with this condition."

More information: Eric Jorgenson el al., "Genetic variation in the SIM1 locus is associated with erectile dysfunction," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1809872115

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