Mutations from Mars: Researchers explain why genetic fertility problems can persist in a population

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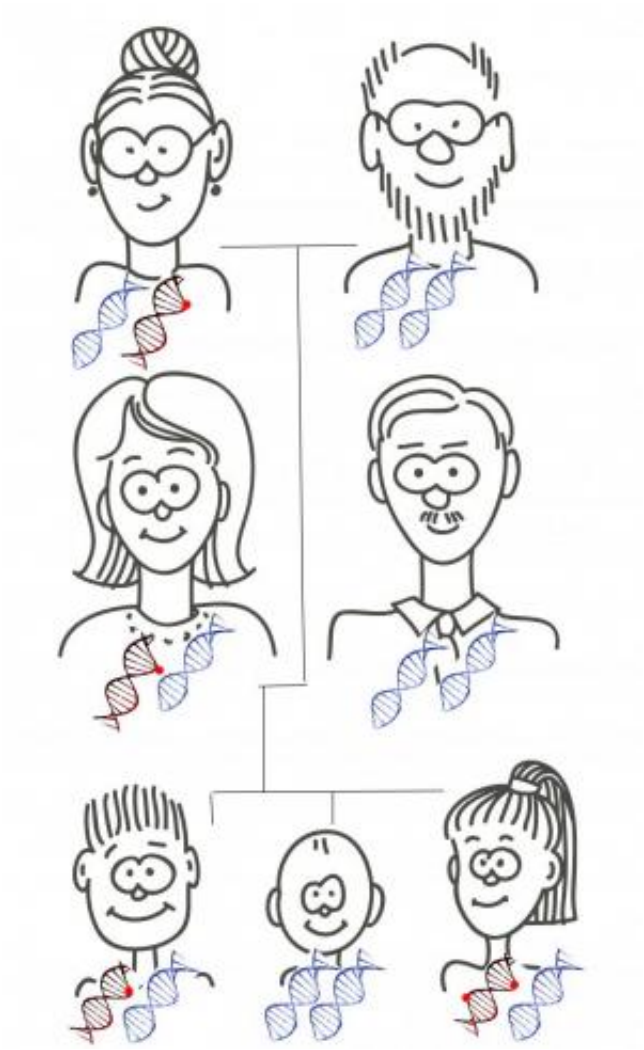

Credit: Weizmann Institute of Science

Some 15% of adults suffer from fertility problems, many of these due to genetic factors. This is something of a paradox: We might expect such genes, which reduce an individual's ability to reproduce, to disappear from the population. Research at the Weizmann Institute of Science that recently appeared in *Nature Communications* may now have solved this riddle. Not only can it explain the high rates of male fertility problems, it may open new avenues in understanding the causes of genetic diseases and their treatment.

Various theories explain the survival of harmful mutations: A gene that today causes obesity, for example may have once granted an evolutionary advantage; or a disease-causing gene may persist because it is passed on in a small, relatively isolated population.

Dr. Moran Gershoni, a postdoctoral fellow in the group of Prof. Shmuel Pietrokovski of the Molecular Genetics Department, decided to investigate another approach – one based on differences between males and females. Although males and females carry nearly identical sets of genes, many are activated differently in each sex. So natural selection works differently on the same genes in males and females.

Take, for example, a mutation that impairs breast milk. It will undergo negative selection only in women. Conversely, a hypothetical gene variant that benefits women but is harmful to men could spread in a population, as it undergoes positive selection in half that population. Gershoni and Pietrokovski created a mathematical model for harmful mutations that affect only half the population; their model showed that these mutations should occur twice as often as those that affect males and females equally.

To test the model, the researchers searched in a computational analysis of the activities of all the human genes that appear in public databases, identifying 95 genes that are exclusively active in the testes. Most of

these genes are vital for procreation; and damage to them leads, in many cases, to male sterility.

The researchers then looked at these 95 genes in people whose genomes had been made available through the 1000 Genomes Project, which gave them a broad cross-section of human populations. Their analysis revealed that genes that are active only in the testes have double the harmful mutation rate of those that are active in both sexes – right in line with the mathematical model. Pietrokovski and his team are now conducting follow-up experiments to see whether the mutations they identified do, indeed, play a role in these problems and whether the "sex-difference" approach can explain their survival.

This new understanding of the persistence of genetic mutations could yield insights into other diseases with genetic components, especially those that affect the sexes asymmetrically, including schizophrenia and Parkinson's, which are more likely to affect men, and depression and autoimmune diseases, which affect more women. And, say Gershoni and Pietrokovski, these findings highlight the need to fit even common medical treatments to the gender of the patient.

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