Hidden burden: Most people carry recessive disease mutations

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Humans carry an average of one to two mutations per person that can cause severe genetic disorders or prenatal death when two copies of the same mutation are inherited, according to estimates published today in the journal *Genetics*. The new numbers were made possible by a long-term collaboration between medical researchers and a unique community that has maintained detailed family histories for many generations.

"These records offered a fantastic opportunity to estimate disease mutation carrier rates in a new way that disentangles the effects of genetic and socioeconomic factors," said lead author Ziyue Gao of the University of Chicago.

Most genetic disorders that result in sterility or childhood death are

caused by recessive mutations, DNA sequence variants that are harmless when a person carries only one copy. But if such mutations are present at both copies (where one copy was inherited from each parent), they can cause devastating diseases like cystic fibrosis.

Recessive disease mutations are much more common than those that are harmful even in a single copy, because such "dominant" mutations are more easily eliminated by natural selection. But exactly how common are the recessive disease-causing mutations in humans?

Previous efforts to estimate the number have relied on studies of disease in children born to related parents. In this method, the increased rates of childhood mortality and disease in these families are assumed to be due to recessive mutations. But this method mixes up the effects of genetics and socioeconomic factors.

For example, in some places, marriage between close relatives correlates with poverty. In those cases, children with related parents can have higher disease and death rates simply because their families suffer from poor nutrition or lack of access to medical care. "There are many different non-genetic factors that can bias this kind of approach," said Gao.

But the new method elegantly sidesteps this problem. It relies on the fact that the Hutterites, a religious community that settled in North America in the 1870s, keep meticulous genealogical records and live a communal lifestyle that ensures uniform access to healthcare and food.

Co-author Carole Ober of the University of Chicago has worked closely with a group of Hutterites from South Dakota for two decades, studying genetic contributions to disease using a large 13-generation family tree that traces the ancestry of more than 1,500 living people.

Molly Przeworski, a population geneticist at Columbia University, realized that this ancestry tree could be used to estimate the number of recessive disease mutations carried by the group's founders in the 18th and 19th century. This calculation was possible because Ober's team and other medical researchers had compiled comprehensive records on the frequency of disorders that cause sterility or childhood death in the study population.

Using this information, the team estimated that there were around three mutations of this type for every five people among the original founders. But that only counted mutations that allow children carrying two copies to survive at least until birth. Based on estimates of the proportion of recessive mutations that cause death during fetal development, the team concluded that each founder carried approximately one to two recessive mutations that cause sterility or death before adolescence.

"This number is probably lower than the real average for most populations, but it is in the right ballpark," said Gao. "Most importantly, unlike previous estimates, it is unaffected by socioeconomic factors."

Gao explained that isolated founder populations like those in the study are expected to carry fewer harmful recessive mutations than the general population, which is one of several reasons why we expect a slightly higher number than one to two mutations on average. This number also excludes recessive mutations carried on the sex chromosomes.

Gao cautions that the number of recessive disease mutations will vary from person to person, and the new number doesn't necessarily help predict a specific couple's risk for passing on a genetic disorder. She also points out that most infant mortality worldwide is caused by non-genetic factors like nutrition and infectious disease, rather than inherited disorders.

Surprisingly, the recessive disease mutation estimate for humans is similar to those from fruit fly and fish species, even though these organisms all have different total genome sizes. "We don't yet understand why the number of recessive lethal mutations might be relatively constant across distantly related organisms," said Gao. "It's an interesting evolutionary question for further research."

More information: An Estimate of the Average Number of Recessive Lethal Mutations Carried by Humans Ziyue Gao, Darrel Waggoner, Matthew Stephens, Carole Ober, and Molly Przeworski, *Genetics* April 2015 199: 1243-1254 DOI: 10.1534/genetics.114.173351

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