How human disease-causing genes prevent adaptations to remove them

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Scientists have identified a new detrimental effect of genes that cause inherited diseases, publishing their results today in *eLife*.

Their study suggests that these genes prevent adaptation (or the evolution of beneficial genes) from happening around them in the genome, allowing them to persist longer in human populations by preventing their own removal by selective sweeps.

The findings provide new insights on evolutionary processes in the last 50,000 years that have allowed some disease-causing genes to persist in human populations, despite their harmful effects.

"Advanced genome sequencing is allowing scientists to learn more about the evolution of diseases and more beneficial traits in humans. But limited research on disease genes focuses on evolutionary processes occurring in the last 50,000 years," explains first author Chenlu Di, a Ph.D. student at the Enard Lab, Department of Ecology & Evolutionary Biology, University of Arizona, Tucson, US. "Our understanding of the relationship between disease and adaptation in the human genome has been hampered by this gap in more recent information."

To fill this gap, Di and colleagues compared the rates of recent genetic adaptation in disease-linked genes and non-disease genes in 26 distinct human populations around the world that were included in the 1000 Genomes Project. They only included inherited diseases that are caused by mutations in a single gene, which are called Mendelian diseases. These have a simple pattern of inheritance in which a child may inherit a disease if they get one copy of a dominant disease-causing gene from one their parents, or if they get two copies of a recessive disease-causing

gene—one from each parent. The team set out to learn whether genes that cause human Mendelian diseases have undergone more or less positive selection than non-disease-causing genes in the human genome.

They found that recessive Mendelian disease-causing genes were far less likely to be swept out of a population. The patterns suggest that a process called genetic interference may have prevented these genes from adapting to changing environments. "Recessive disease-causing gene variants that prevent adaptation from occurring in the genome can dodge gene sweeps that would normally wipe them out in a population," Di explains.

The team also identified some regional variations in patterns of gene adaptation when they compared different parts of the genome of the same population. African populations had a stronger deficit of gene sweeps at disease genes compared to the rest of their genome. In East Asian and European populations, there was a weaker sweep deficit at disease genes relative to other parts of the genome. The authors say this is likely due to severe population bottlenecks that occurred in human populations that migrated out of Africa and later settled in Asia and Europe. Even a small number of people migrating would have been enough to cause the loss of a significant amount of recessive gene variants that were at low frequencies in the genome.

"We also see a clearer sweep deficit at disease genes in African populations because they have overall clearer genome-wide sweep signals," says senior author David Enard, Assistant Professor at the Ecology & Evolutionary Biology Department, University of Arizona. "This provides a better contrast for us to distinguish between disease genes and the rest of the genome."

While the study provides some interesting new information, Enard cautions that more research is needed to confirm these results and to

ensure that biases in the data they used did not skew the results. For example, he notes that many of the Mendelian diseases in the study were identified in Europe.

"Our work improves on previous studies trying to address this important question by using larger gene datasets and carefully controlling for confounding factors that could result in disease-causing genes and non-disease genes showing different patterns," Enard concludes. "But there is more work to do to better understand recent genetic adaptation in humans."

More information: Chenlu Di et al, Decreased recent adaptation at human mendelian disease genes as a possible consequence of interference between advantageous and deleterious variants, *eLife* (2021). DOI: 10.7554/eLife.69026

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