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Researchers explore why humans don't purge lethal genetic disorders from the population

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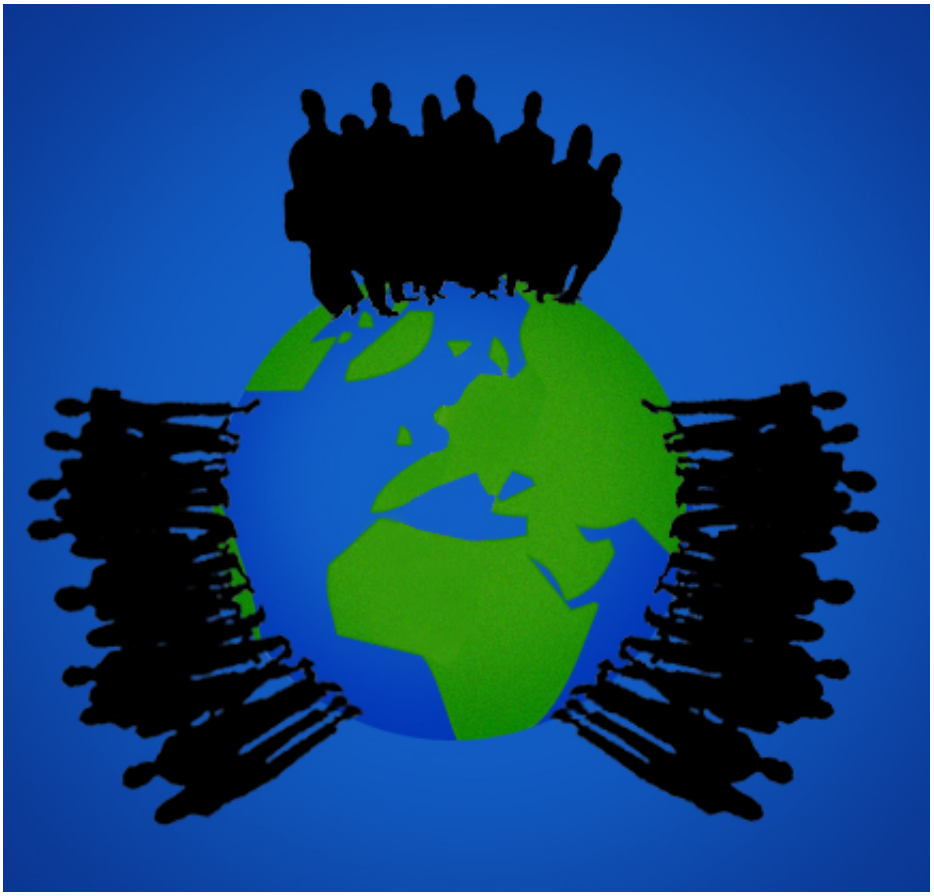

The human population. Credit: Zappys Technology Solutions, Flickr, CC BY

The human population carries around more deadly genetic diseases than would be expected based on a simple comparison of mutation rates and deaths of affected individuals. Carlos Eduardo Guerra Amorim of Stony

Brook University and colleagues, explore potential explanations in a paper published September 28th, 2017 in *PLOS Genetics*.

There are many lethal, recessive diseases that plague the human population, where inheriting a single copy of the defective gene has no effect, but inheriting a copy from each parent is fatal. Due to the lethality of these defective genes, geneticists have long wondered why natural selection has not purged these mutations from the population. In the current study, the researchers generated a handpicked set of 417 mutations in 32 genes that cause recessive lethal disorders, like cystic fibrosis or Tay-Sachs disease. Then they applied analytic models that balance how often these mutations crop up and how often they are eliminated through "purifying selection," when the affected individual dies or is unable to reproduce. When compared to the actual numbers of people carrying lethal recessive disorders, as estimated from 33,370 individuals of European ancestry, the researcher observed that several of the mutations were more common in the human population than the model had predicted.

The researchers propose that lethal, recessive mutations are more common than might be expected due to several factors. These factors include balancing selection, i.e. the selective advantage of carrying a single copy of the defective gene, modulation of the disease severity, stakes in reporting the mutation that causes the disorder, errors in estimates of how often these mutations arise, and the fact that some parents have additional children after the loss of children born with the lethal mutations. Overall, the study highlights the factors that influence the frequencies of deadly, inherited defects. A better understanding of these factors may help researchers to identify overlooked mutations that cause these disorders.

Carlos Eduardo Guerra Amorim adds: "The relevance of our work lies both in the finding that a long-standing theory in population genetics (i.e.

mutation-selection-drift balance) seems to be a good model for explaining the frequencies of disease mutations in human populations, and the broad discussion of factors that are likely to influence disease alleles. This will hopefully help medical geneticists to identify and map harmful mutations in humans.

More information: Amorim CEG, Gao Z, Baker Z, Diesel JF, Simons YB, Haque IS, et al. (2017) The population genetics of human disease: The case of recessive, lethal mutations. *PLoS Genet* 13(9): e1006915. doi.org/10.1371/journal.pgen.1006915