Lives in the balance: Why do we hold onto potentially harmful, disease-causing mutations?

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The persistence of heritable disease raises an evolutionary paradox. When DNA goes awry, and a harmful mutation sprouts up that affects survival, why aren't these simply purged from a population over generations?

Scientists have speculated that there are evolutionary trade-offs at work, that perhaps, carrying a harmful disease mutation may be counterbalanced by other, favorable effects, eventually promoting the long-term survival of a species.

Now, authors Tobias Lenz, Shamil Sunyaev et al. have performed the first systematic test of a counteracting evolutionary force that may work to maintain disease mutations at a higher frequency than expected. This force, called balancing selection, can lead to the maintenance of mutations over long evolutionary times. Their results appear in the advanced online edition of *Molecular Biology and Evolution*.

The most classic disease case of a balancing selection at work is sickle cell anemia, an incurable, painful disease where individuals who inherent mutations in both copies of the hemoglobin gene (one from each parent) cannot get enough oxygen from their red blood cells. Yet those who are carriers, or balanced to carry just one mutated gene, are better protected against malaria.

To perform their study, first, the research team performed computer simulations under different evolutionary selection scenarios and showed that balancing selection could increase the population frequency of deleterious mutations in surrounding genomic regions.

Next, they evaluated their simulation with a direct test by using DNA sequencing data from 6,500 people focused on the most prevalent example of balancing selection in the human genome, the major histocompatibility complex (MHC) of the human immune system. MHC gene products make molecules on the cell surface to play a key role in the adaptive immune response by facilitating the recognition of invading germs. Their mutational dataset included a survey of 17,684 genes, including 124 within the MHC region.

Their results showed that an elevated frequency of harmful mutations occurred in non-HLA genes localized in the MHC region. There was a proximity affect—as long as they were close to the same genomic zip code of HLA genes, the frequency was higher—-more than two orders of magnitude higher than the rest of the genome—-and the further away the mutations, the frequency goes down.

Their results have major implications for the evolution and epidemiology of MHC associated diseases, such as autoimmune disorders, cancer and psychological disorders like Alzheimer's and schizophrenia that have been implicated in previous genome-wide disease scans. Though the authors caution that the genome-wide extent of the observed effect remains to be investigated, this mechanism may significantly contribute to the substantial prevalence of some heritable diseases.

Tobias Lenz, a group leader in Evolutionary Immunogenomics at the Max Planck Institute for Evolutionary Biology in Germany, says: "This trade-off between increased resistance against infectious germs and the

accumulation of harmful mutations has been somewhat expected, but the extent to which even strongly deleterious mutations can be maintained in the human population is surprising. Seeing these results makes me wonder how many of the genetic disorders that we see in humans today are the consequence of continuous exposure to germs during human evolution."

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