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Researchers develop gene-filtering tool to identify disease-causing mutations

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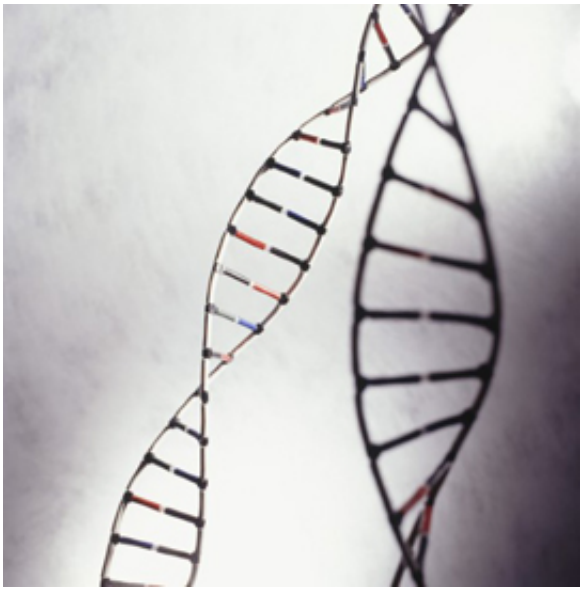

Credit: NIH

Despite their bad reputations, the vast majority of mutations are not harmful. Even in very rare genetic disorders, only one or two genetic variations—out of tens of thousands—is actually the cause of disease. Distinguishing between harmful and harmless mutations has long been a challenge.

A new tool, developed by scientists in Jean-Laurent Casanova's St. Giles Laboratory of Human Genetics of Infectious Diseases at Rockefeller University aims to predict whether a given human gene is likely to

harbor disease-causing mutations. The hope is that their tool, described the *Proceedings of the National Academy of Sciences* this fall, will help researchers who work with genetic data filter out genes that are irrelevant.

"To find a needle in the haystack, it helps to get rid of some of the hay," says Yuval Itan, the study's senior author. "Filtering out the noise, the genes that pollute the data, is crucial."

Through genome analysis, the researchers found that 58 percent of rare genetic variants are located in only 2 percent of human genes. They developed their tool, the Gene Damage Index, from this observation, reasoning that genes that are frequently mutated in the general population are unlikely to cause inherited and rare diseases, because variations to these genes are often found in healthy people.

The Gene Damage Index metric takes into account how much the gene is mutated in the general population, or the "accumulated mutational damage." The calculation also includes how important a given gene is to a specific disease group, including Mendelian disorders, cancer, autism, and primary immunodeficiencies.

"With this method, up to 60 percent of the irrelevant variants can be removed," explains Itan. "The Gene Damage Index will help scientists more easily sort through the large amounts of data produced by next-generation sequencing."

More information: Yuval Itan et al. The human gene damage index as a gene-level approach to prioritizing exome variants, *Proceedings of the National Academy of Sciences* (2015). DOI: 10.1073/pnas.1518646112