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Wide range of differences, mostly unseen, among humans

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No two human beings are the same. Although we all possess the same genes, our genetic code varies in many places. And since genes provide the blueprint for all proteins, these variants usually result in numerous differences in protein function. But what impact does this diversity have? Bioinformatics researchers at Rutgers University and the Technische Universitaet Muenchen (TUM) have investigated how protein function is affected by changes at the DNA level. Their findings bring new clarity to the wide range of variants, many of which disturb protein function but have no discernible health effect, and highlight especially the role of rare variants in differentiating individuals from their neighbors.

The slightest changes in human DNA can result in an incorrect amino acid being incorporated into a protein. In some cases, all it takes is for a single base to be substituted in a person's DNA, a variant known as a single nucleotide polymorphism (SNP). "Many of these point mutations have no impact on human health. However, of the roughly 10,000 'missense' SNPs in the human genome – that is, SNPs affecting the protein sequence – at least a fifth can change the function of the protein," explains Prof. Yana Bromberg of the Department of Biochemistry and Microbiology at Rutgers University. "And in some cases, the affected protein is so important and the change so large that we have to wonder why the person with this mutation is still healthy."

Furthermore, two unrelated individuals have thousands of different mutations that affect proteins. Previously, scientists did not fully

understand how this large number of mutations affects the coding sequences of DNA. To investigate these "silent" mutations, Bromberg joined forces with Rutgers colleague Prof. Peter Kahn and Prof. Burkhard Rost at TUM.

Silent mutations more significant than previously thought

"We found that many of the mutations are anything but silent," declares Rost, head of the TUM Chair for Bioinformatics and a fellow of the TUM Institute for Advanced Study. The research indicates an extremely wide range of mutations. Many SNPs, for example, are neutral and do not affect protein function. Some, however, cause pathogenic disruption to protein functionality. "There is a gray area between these extremes," Rost explains. "Some proteins have a reduced biological function but are tolerated by the organism and therefore do not directly trigger any disease."

The research team analyzed over one million SNPs from a number of DNA databases. They used artificial learning methods to simulate the impact of DNA mutations on the function of proteins. This approach enabled them to investigate the impact of a large number of SNPs quickly and efficiently.

Insight into human evolution

The study's findings suggest that, with respect to diversity in protein function, the individual differences between two people are greater than previously assumed. "It seems that humans can live with many small changes in protein function," says Rost. One conclusion the researchers draw is that the wide functional spectrum of proteins must play a key role in evolution. In addition, Bromberg says, "Protein functional

diversity may also hold the key to developing personalized medicine."

More information: Neutral and weakly nonneutral sequence variants may define neutrality; Yana Bromberg, Peter C. Kahn and Burkhard Rost, *Proceedings of the National Academy of Sciences*, DOI: 10.1073/pnas.1216613110 . www.pnas.org/cgi/doi/10.1073/pnas.1216613110

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