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HEALTH

A new database reveals how DNA mutations trigger genetic diseases

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Scientists have created a mega-database revealing how half a million different DNA mutations generate errors in proteins in humans. The researchers hope that the database will be used to develop new, personalised drugs that directly reverse the mutations' effects. The human genome carries instructions for at least 20,000 proteins, which are essential for nearly all physiological processes. Each building block of a protein, called an amino acid, is key to its function, and thus swapping around the amino acids can essentially break a protein.

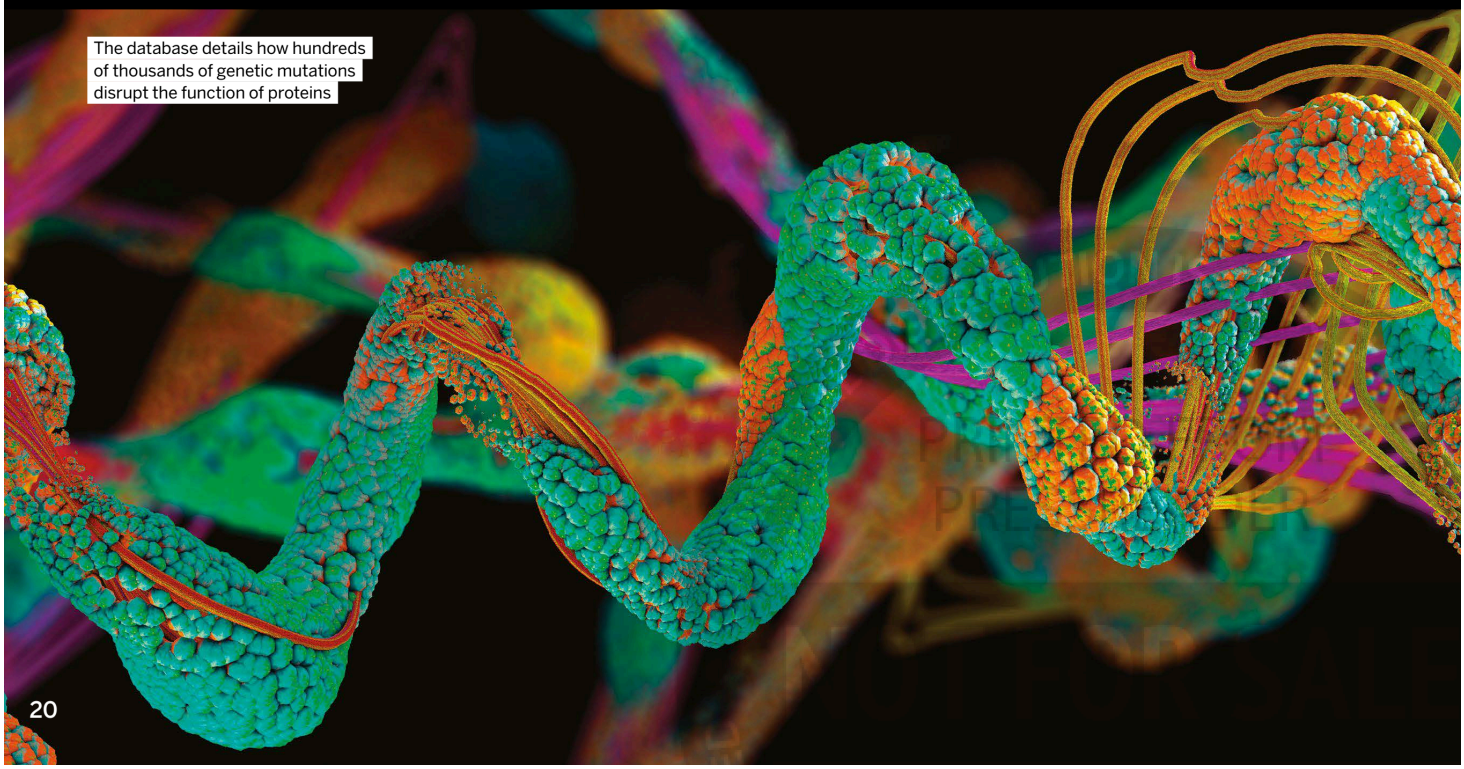
'Missense' mutations – changes in a DNA sequence that swap one amino acid for another – in nearly 5,000 human proteins are known to cause genetic diseases such as Huntington's disease and cystic fibrosis. However, in many cases it's not entirely clear how these mutations affect the structure and function of proteins and thus cause disease. Without this understanding, it's tricky to develop targeted treatments for genetic disorders without altering the genome itself. "Depending on what is happening to the protein, if you were to design a drug to try to fix the disease, then the approach would be completely different depending on the individual mutation," said Antoni Beltran, a postdoctoral researcher at the Centre for Genomic Regulation in Spain.

Beltran and his colleagues have created an enormous database that catalogues the effect of more than 500,000 missense mutations on the stability of 522 protein 'domains' – the regions of proteins that are key to their function. They call the database a human 'domainome', and they built it by systematically triggering mutations in proteins in the lab. They then transferred the mutants into yeast cells and monitored the effects. The team homed in on 621 missense mutations from the database that were already known to cause diseases in humans.

They found that 60 per cent of these mutations made affected proteins less stable. Unstable proteins are more likely to misfold or denature. Proteins must be folded a particular way to reach their intended form. Misfolded proteins can accumulate within cells, causing damage, or simply be degraded by the body, leaving the cells unable to function. For instance, the inherited form of cataracts, an eye disease that clouds the lens of the eye, is triggered by mutations in genes for beta-crystallin proteins, which normally maintain the lens' transparency. In the new study, researchers found that 72 per cent of these mutations destabilise the crystallin proteins, increasing the odds that they clump together and form cloudy areas in the lens.

Rather than causing instability, some missense mutations led to different changes in proteins. For example, some of the mutations behind Rett syndrome, a rare neurodevelopmental disorder, prevent a specific protein from binding to DNA. This process would normally enable the protein to turn genes on and off in the brain, but in the syndrome this goes awry.

Although it's the first and biggest database of its kind, so far it only covers 2.5 per cent of known human proteins, so more work is needed to expand it, Beltran acknowledged. More research will also be needed to determine if the effects seen in isolated domains also show up in full-sized proteins.



The database details how hundreds of thousands of genetic mutations disrupt the function of proteins