Genetic database provides rare disease clues and Parkinson's hope

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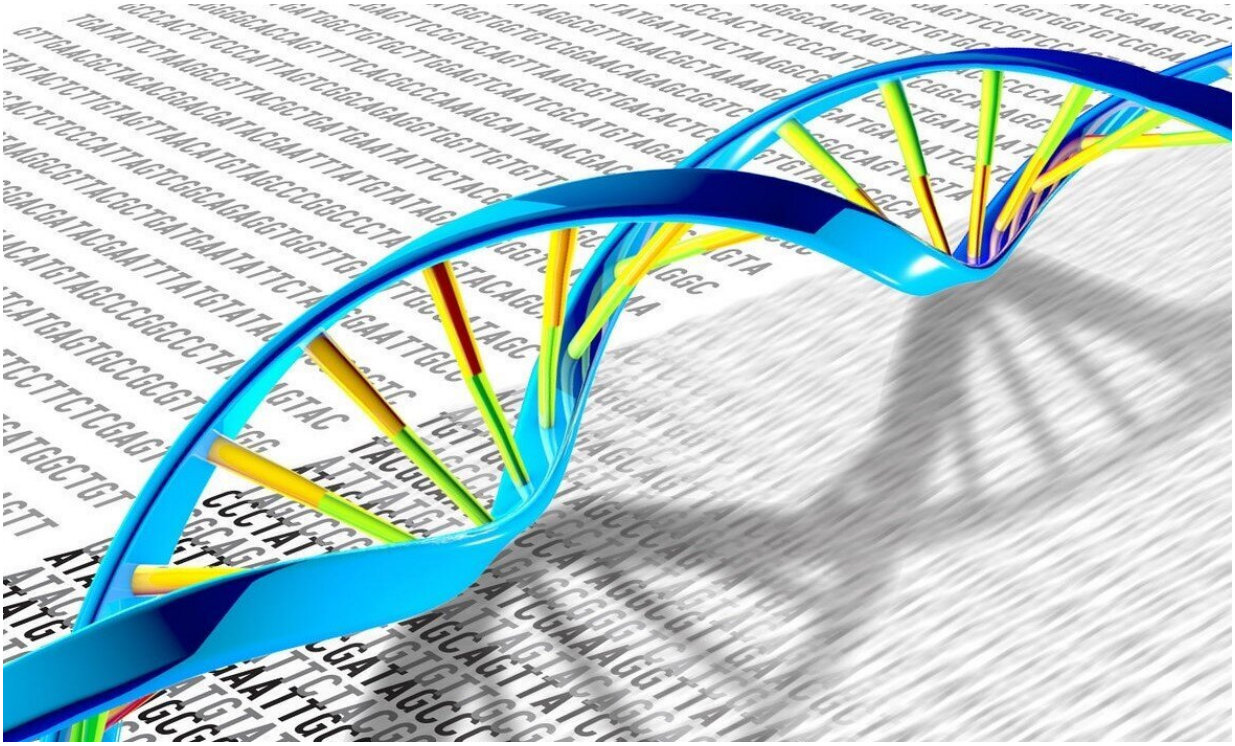

DNA, which has a double-helix structure, can have many genetic mutations and variations. Credit: NIH

Scientists have created the world's largest publicly available database of genetic variants—changes in DNA that can sometimes lead to disease.

The use of this resource, called the Genome Aggregation Database

(gnomAD) and including information from over 140,000 people from across the globe, is described in a landmark collection of seven papers, published today in the journals *Nature*, *Nature Communications* and *Nature Medicine*.

These papers, from international institutions including the Broad Institute of MIT & Harvard and Imperial College London, describe how gnomAD has revealed previously unknown genetic variants that lead to disease, as well as insights into potential drug targets for conditions such as Parkinson's.

Dr. James Ware, from the National Heart and Lung Institute and the MRC London Institute of Medical Sciences, co-author on three of the papers and a member of the gnomAD consortium said: "Reading genomes has become routine in both scientific research and healthcare. However, there are still enormous challenges in understanding what is written in our DNA, and in using that information to improve the health of patients.

"The gnomAD resource is proving hugely valuable to understand which genes are important in human health and disease, and to understand which specific variants in those genes cause problems, and it is already in daily use in genetic testing laboratories around the world. This collection of papers highlights just some of the many uses for this powerful resource, which will become even more informative as the dataset gets bigger. The gnomAD resource is an enormous team effort. More than 100 different research teams have shared data from over 140,000 people. This sort of collaboration and sharing allows to do work that no single team could manage in isolation".

Instructions of the body

Genes hold the instructions for making all proteins in the body. Changes

in the DNA sequence that codes for these genes can lead to genetic diseases. Large genetic sequencing studies provide an opportunity to examine the effects of gene altering variants, so-called loss-of-function variants, providing important insights into human biology and diseases.

By looking across the large number of individuals in gnomAD, scientists can see which genes are frequently disrupted, and which are very rarely altered. If genes are rarely disrupted in healthy people, it could suggest that altering them would lead to disease. A total of 443,769 predicted loss-of-function variants are identified in the new research, far more than in prior genetic databases.

In one paper, led by Dr. Nicky Whiffin from the National Heart and Lung Institute and MRC London Institute of Medical Sciences at Imperial College London, researchers explored the impact of DNA variants arising in an area of the genome that acts as a 'control panel', and manages how much protein the gene makes. These variants can trick a cell to start reading a gene in the wrong place, but previously have not been well-studied. Thanks to the new genetic library, researchers were able to study the impact of these variants and have been able to pin-point those that lead to certain diseases. Once such condition that can be caused by these types of DNA changes is neurofibromatosis, a rare condition that causes tumours to form on nerve tissue.

Dr. Whiffin, who is also a co-author on three of the other papers explained: "Currently we only know the genetic changes that lead to rare diseases in around half of cases, which leaves many patients and their families in the dark about what is causing their often distressing conditions. The use of this new genetic library has already enabled us to tell some patients we have found the genetic causes of their condition, which could open the door for personalised treatments."

Parkinson's treatment hope

In a second paper, Imperial scientists, along with others from the Broad Institute, 23andMe and the Michael J Fox Foundation, used the gnomAD database to suggest a potential treatment for Parkinson's should be safe in humans

In the paper, scientists focused on genetic variants in a gene called LRRK2. Changes in this gene are known to increase the risk of Parkinson's, possibly by affecting nerve function, but initial animal studies showed that blocking the defective protein may lead to lung, liver and kidney damage.

The team used the information from the genetic variant database to show LRRK2 loss-of-function variants do not lead to severe organ dysfunction in humans. This is promising news for Parkinson's disease patients and for drug companies who are currently progressing drugs against LRRK2 through clinical trials.

Dr. Whiffin commented: "Large genetic databases are increasingly giving us a powerful insight into the likely impact of certain drugs. If we see that genetic variants that naturally reduce the amount of protein in our body do not result in severe diseases, we can be more confident that targeting that protein therapeutically will also be safe."

Dr. Whiffin has received co-funding from the Rosetrees Trust, and the Stoneygate Trust. Dr. Whiffin is the Rosetrees/Stoneygate 2018 Imperial College Research Fellow, and this springboard award has enabled her to build her independent research program and advance her research considerably.

More information: Characterising the loss-of-function impact of 5' untranslated region variants in 15,708 individuals, *Nature Communications* (2020). DOI: 10.1038/s41467-019-10717-9

The effect of LRRK2 loss-of-function variants in humans, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-0893-5