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Researchers create map of 'shortcuts' between all human genes

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Some diseases are caused by single gene mutations. Current techniques for identifying the disease-causing gene in a patient produce hundreds of potential gene candidates, making it difficult for scientists to pinpoint the single causative gene. Now, a team of researchers led by Rockefeller University scientists have created a map of gene "shortcuts" to simplify the hunt for disease-causing genes.

The investigation, spearheaded by Yuval Itan, a postdoctoral fellow in the St. Giles Laboratory of Human Genetics of Infectious Diseases, has led to the creation of what he calls the human gene connectome, the full set of distances, routes (the genes on the way), and degrees of separation, between any two human genes. Itan, a computational biologist, says the computer program he developed to generate the connectome uses the same principles that GPS navigation devices use to plan a trip between two locations. The research is reported in the online early edition of the journal *Proceedings of the National Academy of Sciences*.

"High throughput genome sequencing technologies generate a plethora of data, which can take months to search through," says Itan. "We believe the human gene connectome will provide a shortcut in the search for disease-causing mutations in monogenic diseases."

Itan and his colleagues, including researchers from the Necker Hospital for Sick Children, the Pasteur Institute in Paris, and Ben-Gurion University in Israel, designed applications for the use of the human gene connectome. They began with a gene called TLR3, which is important

for resistance to herpes simplex encephalitis, a life-threatening infection from the herpes virus that can cause significant brain damage in genetically susceptible children. Researchers in the St. Giles lab, headed by Jean-Laurent Casanova, previously showed that children with HSE have mutations in TLR3 or in genes that are closely functionally related to TLR3. In other words, these genes are located at a short biological distance from TLR3. As a result, novel herpes simplex encephalitis-causing genes are also expected to have a short biological distance from TLR3.

To test how well the human gene connectome could predict a disease-causing gene, the researchers sequenced exomes – all DNA of the genome that is coding for proteins – of two patients recently shown to carry mutations of a separate gene, TBK1.

"Each patient's exome contained hundreds of genes with potentially morbid mutations," says Itan. "The challenge was to detect the single disease-causing gene." After sorting the genes by their predicted biological proximity to TLR3, Itan and his colleagues found TBK1 at the top of the list of genes in both patients. The researchers also used the TLR3 connectome – the set of all human genes sorted by their predicted distance from TLR3 – to successfully predict two other genes, EFGR and SRC, as part of the TLR3 pathway before they were experimentally validated, and applied other gene connectomes to detect Ehlers-Danlos syndrome and sensorineural hearing loss disease causing genes.

"The human gene connectome is, to the best of our knowledge, the only currently available prediction of the specific route and distance between any two human genes of interest, making it ideal to solve the needle in the haystack problem of detecting the single disease causing gene in a large set of potentially fatal genes," says Itan. "This can now be performed by prioritizing any number of genes by their biological distance from genes that are already known to cause the disease.

"Approaches based on the human gene connectome have the potential to significantly increase the discovery of disease-causing genes for diseases that are genetically understood in some patients as well as for those that are not well studied. The human gene connectome should also progress the general field of human genetics by predicting the nature of unknown genetic mechanisms."

Provided by Rockefeller University