Inactive genes surprisingly common in humans

February 16 2012

(Medical Xpress) -- Every person carries on average 100 variants that disable genes - yet very few suffer ill effects, an international team of researchers led by Yale University and Wellcome Trust Sanger Institute report in the Feb. 17 issue of the journal *Science*.

Scientists were surprised to find so many of these variants in healthy individuals because loss of gene functions leads to diseases such as cystic fibrosis and muscular dystrophy. The findings will allow researchers to better pinpoint new disease-causing mutations by helping them differentiate between frequently occurring but harmless genetic variants and rare dangerous ones, the authors say.

The study is the latest coming from the 1000 Genomes Project, a

massive international personal genomics effort aiming to provide a comprehensive resource of human genetic variation that will help speed the development of personalized therapies based on the genetic makeup of patients.

The team analyzed the genomes of 185 individuals from Europe, Asia, and Africa looking for so-called loss-of-function variants, mutations that disable a gene's ability to make protein.

"Even though previous studies have shown that loss-of-function variants exist in the general population, their extent has been underappreciated. This is the first time we have a definite sense of variation in the numbers of functional genes between individuals," said Suganthi Balasubramanian, the lead Yale author in the paper.

The study shows no individual has a full complement of functional genes. On average, each individual has 20 genes where both copies of the gene are disabled.

"In total, this study identified 253 such genes. This means at least one percent of human genes can be shut down without causing serious disease," explains Mark Gerstein, Albert L. Williams Professor of Biomedical Informatics, co-senior author from Yale University.

The catalog of loss-of-function variants in healthy genomes will be invaluable to clinicians as they begin to use personalized genomic analysis to help diagnose and treat disease, the authors say.

"Our research will be beneficial for current DNA sequencing studies underway in disease patients," says Dr Chris Tyler-Smith, co-senior author from the Wellcome Trust Sanger Institute. "The common loss-of-function variants were typically in genes that can be shut down without causing serious effects."

Scientists also found a large number of extremely rare variants and “we believe these will be the most interesting cases in terms of a potential role in human disease,” says Dr Daniel MacArthur from the Wellcome Trust Sanger Institute, lead author on the study.

The study also showed that as many as a quarter of the loss-of-function variants involve large stretches of DNA (so-called structural variants), rather than mutations of single base pairs, which were believed to be the primary source of genetic variation. Structural variants are not yet well characterized in the human population and represent a major Yale contribution to 1000 Genomes Project. The Yale team is also looking at variants outside of regions of DNA that code for genes, an area that constitutes the vast majority of the genome.

More information: "A Systematic Survey of Loss-of-Function Variants in Human Protein-Coding Genes," by D.G. MacArthur, *Science*, 2012.

Provided by Yale University