New method helps link genomic variation to protein production

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Scientists have adopted a novel laboratory approach for determining the effect of genetic variation on the efficiency of the biological process that translates a gene's DNA sequence into a protein, such as hemoglobin, according to a presentation, Nov. 6, at the American Society of Human Genetics 2012 meeting in San Francisco.

In the 0.1% of the DNA that differs between any two individuals, scientists search for the biological mechanisms underlying human genetic differences, including disease susceptibility.

"How exactly these slight changes in the DNA affect the biology of the human body is not known in most cases," said Constantin Polychronakos, M.D., professor of pediatrics, experimental medicine and human genetics at McGill University, Montreal, Canada.

"We decided to investigate the possibility that some of these changes may alter the translation of RNA into protein, a question that had not been systematically examined before," he added.

Translation is the final stage of gene expression at which the gene's DNA recipe for a protein can be modified, said McGill University scientist Quan Li, Ph.D., who presented the research.

In general, genomic studies have focused on finding links between diseases and variation in DNA. However, the new study takes a big step toward understanding how that variation affects the production of

proteins, which are the molecules that most directly affect health and disease.

The study was designed to determine the effect of single-nucleotide polymorphisms (SNPs), which are variations in the DNA sequence, on the process of translation, Dr. Li said.

Translation begins when a gene's DNA sequence is transcribed into the messenger RNA (mRNA) molecule that carries the transcript, or the blueprint for the protein encoded by the gene, to ribosomes, where proteins are manufactured in a cell.

Dr. Li and his colleagues developed a novel and scalable method that uses the binding of mRNAs to ribosomes as a proxy for translational efficiency of mRNAs that differ from one another because of SNPs.

"Because efficiently translated transcripts associate with multiple ribosomes while less active ones with fewer or no ribosomes, we hypothesized that functional transcripts would show a detectable shift in this distribution," said Dr. Li.

Huiqi Qu, Ph.D., co-investigator of this study and assistant professor at the University of Texas School of Public Health, Brownsville, said, "The results of the proof-of-principle pilot study have clearly shown translational differences between mRNAs that differ only slightly from one another can be detected at a transcriptome-wide scale."

The transcriptome refers to the multiple types of RNAs that function in a cell.

"This study may represent the 'tip of the iceberg,' and its application to larger sample sizes will facilitate a shift toward functional genomics," said Dr. Polychronakos. "Functional genomics tells us how genetic

variation affects disease and points more directly toward possible therapies."

"It will add an important tool in the evaluation of genetic loci associated with complex disorders," Dr. Polychronakos added.

More information: The researchers' presentation is titled, "Translational cis-regulation of gene expression in the human genome: the effect of human single nucleotide polymorphisms."

Provided by American Society of Human Genetics