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Tiny genetic differences have huge consequences

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A study led by McGill University researchers has demonstrated that small differences between individuals at the DNA level can lead to dramatic differences in the way genes produce proteins. These, in turn, are responsible for the vast array of differences in physical characteristics between individuals.

The study, part of the Genome Regulators in Disease (GRID) Project funded by Genome Canada and Genome Quebec, was led by Dr. Jacek Majewski of McGill University's Department of Human Genetics and the McGill University and Genome Quebec Innovation Centre, and first-authored by his research associate Dr. Tony Kwan. It was published January 13 in the journal *Nature Genetics*.

The study was originally initiated by Dr. Tom Hudson, former director of the McGill University and Genome Quebec Innovation Centre, and drew upon the data collected by the vast HapMap (Haplotype Map) Project, a global comparative map of the human genome, which Hudson and his colleagues were instrumental in completing.

This study solves in part the mystery of how a relatively small number of differences within DNA protein coding sequences could be responsible for the enormous variety of phenotypic differences between individuals. It had previously been shown that individual differences reside in simple, relatively small variations in the DNA sequence called single nucleotide polymorphisms (SNPs, often pronounced "snips"), which exist primarily in the "junk code" of the DNA not previously known to

have any profound genetic effect.

“There are many SNPs,” explained Dr. Majewski. “If you add them all together, you'd expect that two individuals would differ at more than a million of those positions. So we have a million or more small differences that distinguish you and me, and yet it would be very hard to explain all the phenotypic differences in the way we look, grow, and behave just by the handful of these protein coding differences.”

Majewski and his colleagues have demonstrated that the natural processing of messenger RNA (mRNA), via a process called splicing, is genetically controlled by these SNPs. The SNPs in certain individuals lead to changes in splicing and result in the production of drastically altered forms of the protein. These out-of-proportion consequences may lead to the development of genetic diseases such as cystic fibrosis and Type 1 diabetes.

Source: McGill University