Link Uncovered Between Variation In Humans With Extreme Body Mass And Abnormal Splicing

ScienceDaily (Dec. 20, 2007) — Researchers report new insights into how genetic variation may create phenotypic differences between individuals. This study investigates the influence of mutations associated with obesity on the mechanism of splicing.

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Many visible differences are apparent between individuals, ranging from height and weight to hair and eye color. While the extent of genetic variation between individuals is relatively small (0.1%-0.5%), it is estimated that this variation includes approximately 3 million single nucleotide polymorphisms (SNPs). These single base-pair differences in the genome have previously been thought to produce changes in the protein sequence encoded by a gene (non-synonymous SNPs). However, studies have indicated that a significant number of SNPs do not alter the predicted protein sequence (synonymous SNPs), suggesting that other regulatory mechanisms might be influenced.

In the study a research group led by Dr. Gil Ast of Tel Aviv University has analyzed a newly described dataset of SNPs found in individuals with extreme body mass index (BMI) values. Interestingly, nearly 40% of the SNPs associated with obesity do not alter the protein-coding sequence of genes.

"We demonstrated that the SNPs found in extreme BMI individuals that do not alter protein sequence information affect the way genetic information is processed: these SNPs alter mRNA splicing," explains Amir Goren, co-lead author of the study. Splicing is the process whereby the RNA transcribed from a gene is edited by linking together the protein-coding regions (exons) and removing the intervening, non-coding sequences (introns), generating a mature messenger RNA (mRNA). The translation of mRNA into functional proteins requires proper maintenance of the splicing mechanism.

Goren and colleagues find that synonymous SNPs associated with extreme BMI are located near splice sites in exons and exhibit a tendency to reside within splicing regulatory regions,

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suggesting that these SNPs could alter the normal splicing pattern. Furthermore, it was discovered that the exons harboring these SNPs exhibit weak splice sites, indicating that these exons could be prone to reduced frequency of splicing, potentially disrupting function of the translated protein.

"When a certain exon is added only to a fraction of the mRNA molecules and not the others, the mRNA molecules without the exon cannot support proper protein synthesis and the overall level of required protein is reduced," describes co-lead author Eddo Kim, suggesting that in addition to phenotypes attributable to non-synonymous SNPs, alterations in the processing of RNA due to synonymous SNPs could also contribute to phenotypic differences and genetic disorders.

Kim suggests that it is difficult to observe severe shifts in splicing patterns that are likely to result in lethality during development. Slight alterations in splicing are more likely to be non-fatal, yet produce a discernible phenotype. "Subtle changes in genes that are involved, for example, in metabolism of fats might be phenotypically visible later in life as unusual weight gain."

While current genetic variation databases contain millions of SNPs, most were identified from a small number of individuals, hinting that many more SNPs remain undiscovered. "Deep re-sequencing efforts could uncover many otherwise overlooked SNPs," explains Kim. "We might end up finding that SNPs that affect the splicing process explain many of the phenotypic differences between individuals."

Scientists from Tel Aviv University (Tel Aviv, Israel) and the University of California, San Francisco (San Francisco, CA) contributed to this study.

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