Large-scale analysis identifies new genetic alterations associated with height

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A large collaborative study has added to the growing list of genetic variants that determine how tall a person will be. The research, published by Cell Press on December 30 in the *American Journal of Human Genetics*, identifies uncommon and previously unknown variants associated with height and might provide insight into the genetic architecture of other complex traits.

Although environmental variables can impact attained adult height, it is clear that height is primarily determined by specific alleles that an individual inherits. Height is thought to be influenced by variants in a large number of genes, and each variant is thought to have only a small impact on height. However, the genetics of height are still not completely understood. "All of the variants needed to explain height have not yet been identified, and it is likely that the additional genetic variants are uncommon in the population or of very small effect, requiring extremely large samples to be confidently identified," explains Dr. Hakon Hakonarson from The Children's Hospital of Philadelphia.

To search for genetic variants associated with adult height, researchers performed a complex genetic analysis of more than 100,000 individuals. "We set out to replicate previous genetic associations with height and to find relevant genomic locations not previously thought to underpin this complex trait" explains Dr. Brendan Keating, also from The Children's Hospital of Philadelphia. The authors report that they identified 64 height-associated variants, two of which would not have been observed without such a large sample size and the inclusion of direct genotyping of uncommon single-nucleotide polymorphisms (SNPs). A SNP is a variation in just one nucleotide of a genetic sequence; think of it as a spelling change affecting just one letter in an uncommonly long word.

These results suggest that genotyping arrays with SNPs that are relatively rare and occur in less than 5% of the population have the ability to capture new signals and disease variants that the common SNP arrays missed (i.e., 30 new signals in this study), as long as sample sizes are large enough. These low-frequency variants also confer greater effect sizes and, when associated with a disease, could be a lot closer to causative than more common variants. "The increased power to identify variants of small effect afforded by large sample size and dense genetic coverage including low-frequency SNPs within loci of interest has resulted in the identification of association between previously unreported genetic variants and height," concludes Dr. Keating.

Provided by Cell Press