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CHOP-led study detects dozens of genes for adult height

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As much as 90 percent of variation in adult height may be caused by genetic inheritance, but a multitude of genes are involved. Most of these have yet to be discovered.

Now a new meta-analysis of data from more than 100,000 people has identified variants in over two dozen genes that were not previously associated with height. The study also confirmed genetic associations in more than 30 previously known height genes. "Although the discoveries may not have immediate clinical use, the approach we used will undoubtedly be helpful in discovering genes that influence other traits and diseases," said the co-study leader, Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia.

Using an existing gene chip customized to include approximately 50,000 SNPs (single-base changes in one letter of DNA's genetic code) in genes having a high likelihood of association with cardiovascular disease, the study team searched variants for SNPs linked to adult height. This study, said Hakonarson, which used height as a lead phenotype for a gene-rich SNP chip enhanced in rare variant coverage, suggests that such platforms will succeed in identifying genetic variants that contribute to multiple other cardiovascular diseases, and potentially to other complex traits.

"This is a proof-of-concept that more dense genotyping of selected gene-rich datasets allows us to find additional genes that have gone undetected in studies using conventional SNP arrays," said Hakonarson. Hakonarson

and co-study leader Brendan J. Keating, D.Phil., also from the Center for Applied Genomics, led the large, international collaborative group whose study appeared online Dec. 30 in the American Journal of Human Genetics.

Many of the variants are in locations with interesting functional roles-in energy metabolism, growth hormones, circadian rhythm and cellular growth-of possible relevance to the biology of growth. The study team identified 64 height-associated genes, 27 of which had not been previously associated with height.

The meta-analysis included DNA from over 114,000 adults from six ethnic groups. The researchers used the IBC array, also called the CardioChip, previously designed by Keating to study genes identified or postulated to play a role in cardiovascular disease. The chip includes some 50,000 SNPs from 2,000 gene regions-about 10 percent of known human genes.

The researchers chose height as an easy-to-measure trait that is highly heritable, usually stable over adult life, and routinely recorded in large population-based studies. The CHOP scientists analyzed gene data from over 65,000 individuals, and Keating collaborated with researchers at dozens of centers throughout the world who genotyped samples from another 48,000 additional study subjects. In all, 47 studies contributed to this meta-analysis.

The specialized gene array provided very dense coverage in known and putative cardiovascular disease regions. The array's design allowed the researchers to capture richer genetic diversity from many resequencing studies and to detect SNPs with low frequency in many diverse human populations. Two of the novel uncommon SNP findings were in genes with compelling evidence of a biological role in determining height. The IL-11 gene is essential to normal bone development and the SMAD3

gene is made active by a growth factor involved with height. Many of the low-frequency SNPs, said the researchers, have strong effects, and may point the way to functional genes.

The researchers used a gene-centric approach, employing an array enriched with specific genes and avoiding non-coding sections of the genome. "The chip we used has high-density genetic coverage in a range of highly prioritized genes, and similar high-density chips may be useful in studying other complex genetic traits," said Hakonarson.

He added that "This discovery method is currently much less expensive than full-genome sequencing, which, as the technology advances, is becoming increasingly prevalent in identifying lower-frequency, disease-related genes. The near future may offer a window of opportunity for this type of technique, using large samples and dense genetic coverage, until whole-genome sequencing becomes more affordable."

Keating said that these results suggest that if the sample sizes are large enough, genotyping arrays with SNP content of less than 5 percent frequency in the population have the ability to capture new disease- and trait-associated variants that common SNP arrays have missed. These low-frequency variants also confer greater effect sizes in this study and may be a lot closer to disease causality.

More information: "Meta-Analysis of Dense Genecentric Association Studies Reveals Common and Uncommon Variants Associated with Height," *American Journal of Human Genetics,* published online Dec. 30, 2010, to publish in January 2011 print edition. doi: 10.1016/j.ajhg.2010.11.007

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