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First reproducible connection made between genes and height in humans

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It became clear nearly a century ago that many genes likely influence how tall a person grows, though little progress, if any, has followed in defining the myriad genes. Now an international research team brings light to this age-old question by pinpointing a genetic variant associated with human height — the first consistent genetic link to be reported.

The findings, published in the September 2 advance online edition of *Nature Genetics*, stem from a large-scale effort led by scientists at the Broad Institute of Harvard and MIT, Children's Hospital Boston, the University of Oxford and Peninsula Medical School, Exeter. Using a new "genome-wide association" method, the research team searched the human genome for single letter differences in the genetic code that appear more often in tall individuals compared to shorter individuals. By analyzing DNA from nearly 35,000 people, the researchers zeroed in on a difference in the HMGA2 gene — a 'C' written in the DNA code instead of a 'T'. Inheriting the 'C'-containing copy of the gene often makes people taller: one copy can add about a half centimeter in height while two copies can add almost a full centimeter.

"This is the first convincing result that explains how DNA can affect normal variation in human height," said co-senior author Joel Hirschhorn, an associate member of the Broad Institute, a pediatric endocrinologist at Children's Hospital Boston, and an associate professor of genetics at Harvard Medical School. "Because height is a complex trait, involving a variety of genetic and non-genetic factors, it can teach us valuable lessons about the genetic framework of other complex traits

— such as diabetes, cancer and other common human diseases."

In addition to being a textbook example of a complex trait, height is a common reason children are referred to medical specialists. Although short stature by itself typically does not signal cause for concern, delayed growth can sometimes reflect a serious underlying health condition. "By defining the genes that normally affect stature, we might someday be able to better reassure parents that their child's height is within the range predicted by DNA, rather than a consequence of disease," said Hirschhorn.

Nearly 90% of the variation in height among most human populations can be attributed to DNA. The remainder is due to environmental and lifestyle factors, such as nutrition. Although a few genes have been uncovered through studies of rare, single-gene stature disorders, most do not seem to be associated with height in the general population. Recent advances, including the completion of the HapMap project and the availability of large-scale research tools, enabled the scientists to take a systematic approach to understand how common genetic differences can impact a person's height.

The results of the research team, which also includes co-senior authors Timothy Frayling of the Peninsula Medical School, Exeter and Mark McCarthy of the University of Oxford, spring from data made available in two recent genome-wide association studies of type 2 diabetes. The studies, one led by the Diabetes Genetics Initiative and the other by the Wellcome Trust Case Control Consortium, involved nearly 5,000 patients who generously volunteered DNA samples as well as pertinent clinical information, such as height and weight.

After scrutinizing the initial data, the scientists identified a single letter change — known as a single nucleotide polymorphism or SNP — in the HMGA2 gene as the most promising result. They collaborated with

additional researchers to study this SNP through a second phase of analysis that encompassed nearly 30,000 individuals: adults and children from the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Exeter Family Study of Childhood Health (EFSOCH), European adults taking part in a study of type 2 diabetes risk (UKT2D GCC), Finnish individuals participating in the FINRISK1997 health survey, and a set of tall and short European American and Polish adults assembled for studies of height. This two-pronged approach enabled co-first author Guillaume Lettre, a researcher at the Broad Institute and Children's Hospital Boston, and his colleagues to convincingly prove that the DNA variation in HMGA2 influences height.

The genomic find, though, is not the only indication that HMGA2 affects height. Previous studies in mice and humans revealed that a handful of rare stature disorders result from severe mutations in the gene. Taken together, the findings provide strong evidence for a role for HMGA2 in height. However, the identified SNP accounts for just 0.3% of the normal variability in human stature, which means there are probably many others yet to be found. To do this, researchers will need to study even larger groups of individuals.

"Unlike most other complex traits, height is something that can be easily defined and measured in very large numbers of people," said Hirschhorn. "Soon the scientific community will have access to many more large-scale genomic data sets, making it feasible to identify additional genes involved in height."

While surprisingly little is known about how genes hardwire humans for growth, some initial clues have already surfaced as a result of the HMGA2 discovery. The gene is active in the first months of fetal growth and shuts off shortly before birth, suggesting it orchestrates growth-related events early in human development. Moreover, it appears to influence the overall longitudinal growth of the skeleton, as scientists

found that the T-to-C change in the gene's DNA sequence correlates with an increased length of both the limbs and spine in young children. HMGA2 has also been implicated in certain forms of cancer. Thus, further studies may help dissect the relationship between normal growth and the deranged growth central to cancer.

Source: MIT