Answer to troublesome question of why some genetic assoc. studies have failed replication attempts

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A team of researchers from Harvard School of Public Health (HSPH), Brigham and Women's Hospital (BWH), and elsewhere have described a possible reason why some studies have been unable to replicate associations between genes and traits -- namely that the strength of a gene/trait association might vary with age and that current study designs typically fail to take that into account. The paper was selected for early publication online on the *American Journal of Human Genetics (AJHG)* web site on April 3, 2008, and will appear in the April 11 print issue of the journal.

Said Christoph Lange, HSPH Associate Professor of Biostatistics and senior author: "In reexamining a vast amount of original data from an earlier study, we have illustrated clearly that genetic effects for complex traits can vary by age and that such an interaction can prevent independent replications of the work if this variable is not taken into account in planning and analyzing the study. This insight has implications for all fellow researchers in genetic association studies."

In 2006, Lange was a co-author of a paper in *Science* that found a common genetic variant, or SNP, that is associated with adult and childhood obesity. The association was confirmed in some, but not all, cohorts.

When more data became available, Lange and collaborators reanalyzed

the original data, plus genetic information from 399 additional individuals. Subjects participated in the Framingham Heart Study offspring cohort. More than 116,200 SNPs were initially genotyped, of which 86,604 were used in the association analyses. Measurements of body mass index (BMI) were taken six times over an average of 23 1/2 years. BMI is weight in kilograms divided by the square of height in meters.

The researchers found a second common genetic variant called rs1455832 in the ROBO1 gene that affects obesity. More to the point, the variant's influence on obesity appears to be strongest during childhood and diminishes after age 45.

"This is important because it demonstrates that genetic effects can vary over time," said Jessica Lasky-Su, Instructor at Harvard Medical School and Brigham and Women's Hospital. "In this example, the marker may increase obesity in early life and then as time goes on, other effects become stronger, and the influence of this marker diminishes. It is likely that many other genetic variants also act in this fashion." Lasky-Su is co-lead author of the study with Helen Lyon of Children's Hospital Boston.

To test rs1455832 further, the researchers examined its association with obesity and with age in eight other study populations comprising 13,584 individuals. Five international centers participated, including studies from Costa Rica, Greece, Poland, Iceland, and Germany. The interaction was observed in five of the eight replicate samples with statistically significant results. The authors note that this interaction would have been missed in all but one of the replication samples if they had failed to incorporate the age-dependent effect in the association analysis.

Said Lange, "We are now in an era where scanning entire genomes for associations with diseases is rapid. In assessing the resulting data, it will be important for scientists to keep in mind the significance of age,

otherwise findings may not be replicated or may be overlooked entirely."

The importance of age-dependent genetic effects for BMI was suggested in a 2003 paper published by researchers at the University of Texas MD Anderson Cancer Center in the European Journal of Human Genetics that described a genome-wide scan for genes related to BMI. However, the incorporation of age-dependent genetic effects for BMI into genetic analyses remains uncommon.

Source: Harvard School of Public Health