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In childhood obesity, gene variants raise risk

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A new study by pediatric researchers has added to the evidence that genes have a strong influence on childhood obesity.

The study team searched across the whole genomes of thousands of obese children for copy number variations (CNVs)--deletions or duplications of DNA sequences. Although the CNVs they found are rare within the population, their data suggest that those individuals harboring such variants are at a very high risk of becoming obese.

"Our study is the first large-scale, unbiased genome-wide scan of CNVs in common pediatric obesity," said study leader Struan F.A. Grant, Ph.D., associate director of the Center for Applied Genomics (CAG) at The Children's Hospital of Philadelphia. "We found CNVs that were exclusive to obese children across two ethnicities—European Americans and African Americans."

The study appears online today in the *American Journal of Human Genetics*. Grant, along with co-study leader Hakon Hakonarson, M.D., Ph.D., director of the CAG, led a team based at The Children's Hospital of Philadelphia and the University of Pennsylvania.

A major health problem in Western societies, obesity has increased dramatically in prevalence in both children and adults over the past decade. Associated with insulin resistance, obesity is a risk factor for type 2 diabetes, heart disease, hypertension and other chronic illnesses. Approximately 70 percent of obese teenagers grow up to become obese adults.

Public health experts have implicated environmental contributors to obesity, such as sedentary lifestyles and the wide availability of high-calorie convenience foods. However, from twin studies and other research, scientists have also recognized that obesity has a strong genetic component as well, although this has been analyzed more frequently in adults than in children.

In the current study, the researchers searched for CNVs in a European American cohort of 1,080 obese children and a control group 2,500 lean children. The obese children were in the top 5th percentile of body mass index, but to avoid confounding their data, the researchers excluded the most severe cases, many of whom were likely to have complicated medical syndromes. After identifying multiple CNVs occurring in the obese children but not the lean controls, the researchers replicated the study in a different cohort, all African American children: 1,479 obese subjects and 1,575 lean controls. All the children were between ages two and 18, recruited from The Children's Hospital of Philadelphia pediatric network.

Of the 17 CNVs they found in obese European Americans, eight, or nearly half, also occurred in obese African Americans. "Because many gene variants have different frequencies in different ethnic groups, detecting these same CNVs in both groups, exclusively in obese subjects, strengthens the probability that these CNVs play a genuine role in the development of obesity," said Hakonarson.

The majority of the genes located at the CNV sites were not previously reported to be associated with obesity. However, at one location, near the gene ARL15, researchers previously linked a gene variant with a higher risk of coronary heart disease and type 2 diabetes via levels of adiponectin, a hormone involved in glucose regulation.

The current study does not have immediate applications to diagnosis and

treatment, but adds another piece to the puzzle of understanding childhood obesity. Grant added that further studies at Children's Hospital and elsewhere will uncover additional genetic influences, and functional studies will investigate the biological details of how genes contribute to childhood obesity. Such knowledge may provide a basis for designing preventive measures and treatments.

More information: "A Genome-Wide Study Reveals Copy Number Variants Exclusive to Childhood Obesity Cases," *American Journal of Human Genetics*, published online Oct. 14, 2010.

Provided by Children's Hospital of Philadelphia