Study examines genetic associations for gastrointestinal condition in infants

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Researchers have identified a new genome-wide significant locus (the place a gene occupies on a chromosome) for infantile hypertrophic pyloric stenosis (IHPS), a serious gastrointestinal condition associated with gastrointestinal obstruction, according to a study in the August 21 issue of *JAMA*. Characteristics of this locus also suggest the possibility of an inverse relationship between levels of circulating cholesterol in neonates and IHPS risk.

"Infantile hypertrophic pyloric stenosis is the leading cause of gastrointestinal obstruction in the first months of life, with an incidence of 1 to 3 per 1,000 live births in Western countries. It affects 4 to 5 times as many boys as girls and typically presents 2 to 8 weeks after birth with projectile vomiting, weight loss, and dehydration. Although IHPS is a clinically well-defined entity, the etiology [cause] of the condition is complex and remains unclear," according to background information in the article. A genetic predisposition is well established; IHPS aggregates strongly in families and has an estimated heritability of more than 80 percent; but knowledge about specific genetic risk variants is limited.

Bjarke Feenstra, Ph.D., of the Statens Serum Institut, Copenhagen, Denmark, and colleagues conducted a study to search the genome for genetic associations with IHPS and to validate findings in 3 independent sample sets. During stage 1, the researchers used reference data from the 1,000 Genomes Project for imputation into a genome-wide data set of 1,001 Danish surgery-confirmed samples (cases diagnosed 1987-2008) and 2,371 disease-free controls. In stage 2, the 5 most significantly

associated loci were tested in independent case-control sample sets from Denmark (cases diagnosed 1983-2010), Sweden (cases diagnosed 1958-2011), and the United States (cases diagnosed 1998-2005), with a total of 1,663 cases and 2,315 controls.

The researchers found a new genome-wide significant locus for IHPS at chromosome 11q23.3 in a region harboring the apolipoprotein (APOA1/C3/A4/A5) gene cluster. APOA1 encodes apolipoprotein A-I, which is the major protein component of high-density lipoprotein (HDL) cholesterol in plasma. "The functional characteristics of the 11q23.3 locus suggest the hypothesis that low levels of circulating lipids in newborns are associated with increased risk of IHPS. We addressed this hypothesis by measuring plasma levels of total, low-density lipoprotein, and HDL cholesterol as well as triglycerides in prospectively collected umbilical cord blood from a set of 46 IHPS cases and 189 controls of Danish ancestry, most of which were also in the discovery sample," the authors write. They found lower cholesterol levels at birth in infants who went on to develop IHPS compared with matched controls who did not develop the disease.

"Further investigation is required to illuminate the functional significance of the association identified here."

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