Gene Links Hereditary Intestinal Disorder with Stroke Danger

Posted on Friday, March 12, 2004

DURHAM, N.C. -- Two seemingly disparate hereditary syndromes actually stem, in some patients, from a single genetic defect, according to Duke University Medical Center geneticists. The researchers have linked juvenile polyposis -- characterized by numerous intestinal polyps and an increased colon cancer risk -- and hereditary hemorrhagic telangiectasia (HHT), which causes vascular abnormalities that can lead to stroke.

The finding suggests that anyone with juvenile polyposis should undergo genetic screening, the researchers said. Physicians should then carefully monitor those with the mutation for vascular defects and symptoms that can range from severe nose bleeds to stroke, depending upon where in the body the aberrations occur. Juvenile polyposis occurs approximately once in every 16,000 to 100,000 births.

The Duke team, led by Douglas Marchuk, Ph.D., associate professor of molecular genetics, and research analyst Carol Gallione, report their findings in the March 13, 2004, issue of The Lancet. The work was supported by the National Institutes of Health.

Although anecdotal evidence had indicated that some patients with juvenile polyposis also exhibit vascular anomalies, the current study is the first to clearly define the relationship between the intestinal disorder and HHT, said the researchers.

"This study suggests that the rare cases noted in which patients show intestinal polyps and vascular abnormalities are just the tip of the iceberg," said Marchuk. "The two appear to represent a single syndrome having effects in both the intestine and the blood vessels. Physicians must start looking for the vascular lesions in patients with juvenile polyposis -- with particular attention to those organs that may present suddenly with serious medical consequences."

Juvenile polyposis -- in which as many as 500 polyps line the large bowel and rectum or, less commonly, the stomach and small intestine -- is caused by a defect in one of two different genes, earlier research has shown. Left untreated, patients with the disease have a 50 percent risk of developing colon cancer.

Work done previously in Marchuk's lab found that mutations in two other genes cause HHT. Now, the Duke team reported that mutations in one of the genes linked to juvenile polyposis, called MADH4, also spurs the vessel defects characteristic of HHT.

In HHT patients, some arteries shunt blood directly to veins, rather than diffusing the flow through capillary networks. The high-pressure blood flow in such junctures makes the vessels susceptible to breaks and bleeding.

The investigators collected blood samples from seven families in which some individuals had symptoms of juvenile polyposis and HHT. The team then screened the samples for mutations in the genes known to cause one or the other disorder.

None of the patients had mutations in the genes previously linked to HHT, the researchers found. Rather, the researchers showed, mutations in MADH4 caused both the intestinal polyps and the vascular lesions.

"All patients with MADH4 juvenile polyposis in this study have at least some vascular symptoms," said Gallione. "Our results suggest that genetic screening of JP patients might identify those individuals most at risk for developing vascular symptoms. In patients at risk, aggressive screening protocols for blood vessel malformations in the visceral organs may be warranted."

The protein encoded by the MADH4 gene, SMAD4, plays a role in a key cellular pathway that governs cell growth and differentiation, Marchuk said. Therefore, he speculates, the genetic defect might lead to a drop in the SMAD4 protein below some threshold required for blood vessels to sprout into capillary beds normally, resulting in the vascular deformities seen in patients with HHT. A similar mechanism is thought to underlie the vessel lesions in patients with the earlier established HHT genes.

Collaborators in the research included Gabriela Repetto, M.D., of the Universidad del Desarrollo in Chile; Eric Leguis, M.D., and Sabine Tejpar, M.D., of University Hospital Gasthuisberg in Belgium; Anil Rustgi, M.D., of the University of Pennsylvania in Philadelphia; Susan Schelley, M.D., of Stanford University; Grant Mitchell, M.D., and Eric Drouin, M.D., of Ste Justine Hospital in Montreal; and Cornelius Westermann, M.D., of St. Antonius Hospital in the Netherlands.

A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5

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Patients with hereditary haemorrhagic telangiectasia (HHT, or Osler-Weber-Rendu syndrome) have variable presentation patterns and a high risk of preventable complications. Diagnostic tests for mutations in *endoglin* (HHT type 1) and *ALK-1* (HHT type 2) are available. Some HHT patients are now known to have HHT-juvenile polyposis overlap syndrome due to *Smad4* mutations. Families were ascertained following the presentation of probands for embolization of pulmonary arteriovenous malformations. Genome-wide linkage studies using over 700 polymorphic markers, and sequencing of candidate genes, were performed. In a previously described HHT family unlinked to *endoglin* or *ALK-1*, linkage to *Smad4* was excluded, and no mutations were identified in the *endoglin*, *ALK-1*, or *Smad4* genes. Two point LOD scores and recombination mapping identified a 5.4 cM *HHT3* disease gene interval on chromosome 5 in which a single haplotype was inherited by all affected members of the pedigree. The remainder of the genome was excluded to a 25 cM resolution. We are currently studying a further family potentially linked to *HHT3*. We conclude that classical HHT with pulmonary involvement can result from mutations in an unidentified gene on chromosome 5. Identification of *HHT3* should further illuminate HHT pathogenic mechanisms in which aberrant transforming growth factor (TGF)- signalling is implicated.

Gene links intestinal problem with stroke

Two hereditary defects leading to an intestinal disorder and stroke may, in fact, be linked, according to new research.
Juvenile polyposis is characterized by numerous polyps in the intestine. Previous work has suggested that

there is an association with blood vessel abnormalities that can lead to stroke. This is now confirmed by a new study from Duke University Medical Center in the US.

The team has been looking at genes linked to the blood vessel disorder known as hereditary hemorrhagic telangiectasia (HHT) and found that one mutation, in a gene called MADH4, is also linked to juvenile polyposis. It may therefore be useful to screen young patients with polyposis - which, itself, carries a 50 per cent risk of colon cancer - to see if they are also at risk of HHT. The gene governs cell growth and differentiation, so maybe in its mutated form it causes problems with both blood vessels and the lining of the colon.

Source
The Lancet 13th March 2004