Gene discovered for newly recognized disease in Amish children

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The gene for a newly recognized disease has been identified thanks to the determination of an Amish father and the clinical skills and persistence of Indiana University and Riley Hospital for Children physicians in collaboration with physicians and researchers at the Clinic for Special Children in Lancaster County, Penn., which specializes in disorders of the Amish.

The identification of the new multisystem autoimmune disorder and the recessive gene that causes it have been published early online and are reported in the 12 March 2010 print issue of the American Journal of Human Genetics.

The quest began when Jean P. Molleston, M.D., examined a young Amish boy whose family was looking for answers to why the child was not growing well, was developmentally delayed, had chronic diarrhea, and looked different from other children. In spite of numerous medical tests, which confirmed an enlarged liver and spleen, the cause of his multiple medical problems went undefined.

The search gained impetus for Dr. Molleston, an IU School of Medicine professor of pediatrics and Riley Hospital gastroenterologist, when a younger sibling was born with the same characteristics. Shortly thereafter, it also was recognized that a young cousin had similar problems.

Dr. Molleston and her colleagues had three cases and they reached out to

Eric Puffenberger, Ph.D., Kevin Straus, M.D., and Holmes Morton, M.D., at the Clinic for Special Children, an innovative clinic dedicated to the unique needs of the Amish which employs cutting edge technology to search for genetic disorders. Blood samples and medical data on the children were sent for analysis. There experts were able to determine that an area of chromosome 20 was abnormally prominent in all three boys but not in unaffected children.

At this time Dr. Molleston and then IU School of Medicine pediatric resident Naomi Lohr, M.D., with the help of the father of the first child, conducted field screening in rural northeastern Indiana to search for additional affected children. Meanwhile, the Lancaster County team learned of a fourth child with similar problems who had multiple autoimmune disorders as had several of the Indiana children. Soon they were aware of a total of ten (7 boys and 3 girls) Amish children, with the oldest in his early twenties, who had the unrecognized multisystem disease. All the children were Indiana Old Order Amish (although some no longer lived in Indiana) and were related.

"It was recognizing autoimmune problems, including autoimmune hepatitis and lung and thyroid problems, that led us to focus our efforts to determine that the responsible gene was one identified as ITCH, one of 250 genes in the region of chromosome 20 identified by the Clinic for Special Children team," said Dr. Molleston.

"We found that all the affected children had a mutation in ITCH, a gene which helps in ubiquination, the chaperoning or transporting of proteins around the cell. Ubiquination tells proteins where to go and what to do and it's particularly important in damping down the immune system so it's not overactive. Ubiquitination has many other important roles in the body's cells, possibly explaining some of the other problems these children have," she elaborated.

"Now that the gene has been identified and we are aware of several autoimmune diseases involved, the heavy lifting of identifying and helping these children can begin. We hear often from the father who brought the first child to us. As we all do, he hopes that now that we have identified the gene, we can quickly find effective treatment. But there are a lot of things going on in this disease and it's going to take much more research to find what's wrong with these children, whether environmental or other as yet unidentified factors contribute, and ultimately to develop drugs to affect ITCH without harming the children," she said.

Provided by Indiana University School of Medicine