MedicalXpress

Next generation sequencing establishes genetic link between two rare diseases

July 29 2010

Scientists have successfully used "next generation sequencing" to identify mutations that may cause a rare and mysterious genetic disorder. The research, published by Cell Press on July 29th in the *American Journal of Human Genetics,* demonstrates that sequencing an affected individual's entire "exome"; that is, all of the genes that carry instructions for producing proteins, can reveal critical genes that when mutant, cause inherited disorders.

Perrault syndrome is a recessive disorder that is associated with hearing loss in both boys and girls, and failure of ovarian function in girls. Some individuals with Perrault syndrome also have neurological symptoms. Prior to the current study, no genes for Perrault syndrome had been identified.

A research group led by Mary-Claire King, PhD, from the University of Washington in Seattle studied the genetics of Perrault syndrome in a small family, originally of Irish and Italian ancestry, that included two sisters with well-characterized Perrault syndrome.

"Because the family is small and not consanguineous (both parents descended from a common ancestor), standard genetic mapping techniques would not have been informative in identifying the responsible gene," explains Dr. King. "Instead, we attempted to identify the gene responsible for Perrault syndrome in this family through the use of whole exome sequencing." The exome can be thought of as a kind of genetic blueprint for the synthesis of proteins.

After sequencing the entire exome of one of the sisters, the researchers identified a single gene (HSD17B4) that exhibited two rare functional variants. This gene encodes D-bifunctional protein (DBP), a multifunctional enzyme involved in lipid metabolism. Underscoring the genetic diversity of the disease, the researchers went on to show that six other families with Perrault syndrome had normal HSD17B4.

"Other mutations in HSD17B4 are known to cause a very severe congenital syndrome called DBP deficiency that is generally fatal within the first two years of life," says Dr. King. "No girls with DBP deficiency have been reported to survive past puberty, so ovarian abnormalities have not previously been known to be associated with this illness. The few reported long term survivors of DBP deficiency exhibit hearing loss and neurological dysfunction."

Taken together, the findings indicate that Perrault syndrome and DBP deficiency share some clinical symptoms and that very mild cases of DBP deficiency may be under-diagnosed. "Our research also demonstrates that whole exome sequencing can reveal critical genes in small nonconsanguinous families," concludes Dr. King.

More information: Pierce et al.: “Report: Mutations in the DBP-Deficiency Protein HSD17B4 Cause Ovarian Dysgenesis, Hearing Loss, and Ataxia of Perrault Syndrome.” Publishing in the American Journal of Human Genetics, August 13, 2010.

Provided by Cell Press