Technology targets genetic disorders linked to X chromosome

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Geneticists at Emory University School of Medicine have demonstrated a method that enables the routine amplification of all the genes on the X chromosome. The technology allows the rapid and highly accurate sequencing and identification of novel genetic variants affecting X chromosome genes.

The method, developed in cooperation with RainDance Technologies (www.RainDanceTech.com), is described in the Oct. 2011 issue of *Genomics*. Senior author Michael Zwick, PhD, assistant professor of human genetics at Emory University School of Medicine, is using the method to identify genetic variants that contribute to autism spectrum disorders.

Because the X chromosome is a hotspot for genes that are suspected of contributing to autism and intellectual disability, the Emory team's finding could speed new discoveries and eventually make routine clinical diagnosis of autism and intellectual disability easier.

"This technology has the potential to be a valuable tool for genetic researchers across a wide variety of applications," Zwick says. "Our data shows that it can support the routine sequencing of the exons of the human X chromosome in a uniform, accurate and comprehensive way."

The team's sequencing method does not read all the letters of the genetic code in the X chromosome from beginning to end. Instead, it targets more than 800 "exons": all the genes that get read out and made into

RNA.

A direct comparison with another method of target selection called oligonucleotide capture showed that the team's technique needed between three and seven times fewer sequence reads to achieve high levels of accuracy and completeness, potentially meaning lower costs.

The Emory team's experiments showed that their technique could read 97 percent of targeted sequences at high depth with an accuracy of 99.5 percent. The team used data from the HapMap Project, a partnership coordinated by the Human Genome Research Institute, as a reference standard for genetic sequence variation.

Sex is determined by having two X chromosomes (female) or an X and a Y chromosome (male). Because males have only a single X chromosome, a mutation in a gene on the X chromosome is more likely to affect a male than a female because males lack another copy of the same gene to compensate. This pattern of inheritance can contribute to disorders that disproportionately affect males, such as autism spectrum disorder or intellectual disability.

Modern DNA sequencing techniques use the polymerase chain reaction (PCR) to isolate and "amplify" the target DNA scientists want to read. RainDance Technologies has developed a single molecule microdroplet-based technology that enables scientists to target up to 20,000 genomic loci in a single sample, saving time, space and cost while increasing reliability and ease of use. The reactions take place in millions of self-contained droplets, allowing each to amplify a different piece of DNA within an emulsion.

More information: K. Mondal, A.C. Shetty, V. Patel, D.J. Cutler and M.E. Zwick. Targeted sequencing of the human X chromosome exome. *Genomics* Vol. 98, Issue 4, pp. 260-265 (Oct. 2011).