Researchers find genome sequencing can be used to identify severe intellectual disability

5 June 2014, by Bob Yirka

(Medical Xpress)—A large team of researchers based in the Netherlands has found that whole genome sequencing can be used to identify a large percentage of patients who have a severe intellectual disability (SID). In their paper published in the journal *Nature*, the team describes how they took a new approach when analyzing gene sequences of SID patients and found that a pattern of genetic abnormalities could be used to diagnose the disorder with an accuracy of 62 percent.

People with a SID (formerly described as various types of severe mental retardation) typically have a very low IQ and associated difficulties in developing both cognitive and functional skills. As medical science has progressed, parents and doctors have been presented with more and more tools for diagnosing various ailments with babies both before and after birth. A diagnosis of SID, however, has been elusive, often only being recognized when a child reaches an age where cognitive skills become apparent. In this new effort, the researchers describe a new type of whole genome sequencing analysis that they claim can be used to diagnose SID in a large number of cases.

SID is unique in that the condition generally comes about due to genetic abnormalities that are not inherited—something happens after conception to alter the genome. Because of this, testing parents for SID risk in offspring is futile. In this new effort, the researchers obtained DNA samples from 50 people who had the condition, and from their parents. They performed whole genome sequencing on all of the samples and then compared the results of each with all the others and with the number of copies of each gene. Doing so revealed 84 previously unknown sequence variations and eight copy number variations. Many of the variations, the researchers found, were mutations that caused genes to stop functioning.

Using what they'd learned, the team turned the results around and applied them as a diagnostic aid—they found that they were able to identify 21 of the original 50 patients as having SID. That means, they claim, that going forward, whole genome sequencing can be used to identify SID with 62 percent accuracy. The data also adds further proof that the majority of cases of SID are the result of non-inherited genetic anomalies, which means research going forward, can focus on the underlying cause of the gene anomalies, rather than continuing to search for something in the parents' genes.

More information: Genome sequencing identifies major causes of severe intellectual disability, *Nature* (2014) doi:10.1038/nature13394

Abstract
Severe intellectual disability (ID) occurs in 0.5% of newborns and is thought to be largely genetic in

origin. The extensive genetic heterogeneity of this disorder requires a genome-wide detection of all types of genetic variation. Microarray studies and, more recently, exome sequencing have demonstrated the importance of de novo copy number variations (CNVs) and single-nucleotide variations (SNVs) in ID, but the majority of cases remain undiagnosed. Here we applied whole-genome sequencing to 50 patients with severe ID and their unaffected parents. All patients included had not received a molecular diagnosis after extensive genetic prescreening, including microarray-based CNV studies and exome sequencing. Notwithstanding this prescreening, 84 de novo SNVs affecting the coding region were identified, which showed a statistically significant enrichment of loss-of-function mutations as well as an enrichment for genes previously implicated in ID-related disorders. In addition, we identified eight de novo CNVs, including single-exon and intra-exonic deletions, as well as interchromosomal duplications. These CNVs affected known ID genes more frequently than expected. On the basis of diagnostic interpretation of all de novo variants, a conclusive genetic diagnosis was reached in 20 patients. Together with one compound heterozygous CNV causing disease in a recessive mode, this results in a diagnostic yield of 42% in this extensively studied cohort, and 62% as a cumulative estimate in an unselected cohort. These results suggest that de novo SNVs and CNVs affecting the coding region are a major cause of severe ID. Genome sequencing can be applied as a single genetic test to reliably identify and characterize the comprehensive spectrum of genetic variation, providing a genetic diagnosis in the majority of patients with severe ID.

Press release

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