Epigenetic Variations Could Underlie Neurodevelopmental Disorders, Congenital Anomalies

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NEW YORK (GenomeWeb) – Epigenetic variations may contribute to the development of neurodevelopmental disorders and congenital anomalies, a new study has found, explaining cases where no genetic mutations could be found.

Genetics are thought to underlie many types of neurodevelopmental disorders and congenital anomalies, but for a lot of cases, genomic analysis has been unable to give answers. An international team of researchers has now suggested that instead, epigenetic changes could be involved.

As the researchers, led by Andrew Sharp at the Icahn School of Medicine at Mount Sinai, reported today in *Nature Communications*, they compared the DNA methylation profiles of nearly 500 individuals with neurodevelopmental disorders and congenital anomalies to those of about 1,500 controls. While they found that epigenetic variants — dubbed epivariations — are common in the human genome, they also discovered that *de novo* epivariations are more common among affected individuals than controls. They further noted that these epivariations appear to influence gene expression, which could affect disease.

"Our study suggests that these epigenetic mutations are a significant contributor to human disease," Sharp said in a statement.

He and his colleagues studied a cohort of 489 individuals with neurodevelopmental disorders and congenital anomalies for whom exome or whole-genome sequencing and copy-number array analysis had found no pathogenic variants. They generated methylation profiles for them using Illumina's Infinium Human Methylation 450 BeadChip.

Within the cohort, the researchers identified 143 epivariations. Using PCR and bisulfite sequencing, they confirmed methylation changes for 55 of the 58 samples they could assay.

At the same time, the team examined epivariations within two large population control cohorts. In these, they also uncovered a number of differentially methylated regions, suggesting that epivariations are rather

common in the human genome.

However, the researchers noted that there was an enrichment of epivariations within the disease cohort compared to the controls. Cases, they reported, had a 2.8-fold increase in the rate of *de novo* epivariations.

They also noted recurrent *de novo* epivariations among the cases, including near the promoters of two genes previously linked to congenital disease. This indicted to the researchers that these could be pathogenic epivariations.

Also, some epivariations could be due to underlying DNA mutations in regulatory sequences, Sharp and his colleagues said. Through high-resolution array CGH and targeted DNA sequencing of 50 differentially methylated regions and surrounding areas, they found that rare sequence mutations co-segregated with epivariations, and could affect regulatory elements, about a quarter of the time.

Three of these rare segregating single nucleotide variants were at binding sites for CTCF, a transcription factor with a key role in chromatin organization. These included a *de novo* SNV affecting a CTCF binding site paired with a *de novo* epivariation. This, the researchers said, indicates there is an enrichment of rare segregating SNVs at CTCF binding sites. They added that these variants could be causing the epivariation and that epigenetic profiling could help in the interpretation of non-coding genetic variation.

Epivariations could have functional consequences akin to those of loss-of-function mutations, the researchers wrote. Using RNA-seq and DNA methylation data from the 1000 Genomes Project, they found that epivariations at promoters led to large changes in gene expression: Decreased methylation resulted in increased expression, while increased methylation led to decreased expression.

Based on this, the researches argued that epivariations could contribute to disease pathogenesis in some patients and may have diagnostic relevance.

"These findings can open up a whole new world in what we know about disease and genetic profiling," Sharp said. "Investigating DNA methylation when profiling genomes for disease mutations could help us uncover causative defects in congenital and neurodevelopmental diseases that have eluded us for years."

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