Cord blood DNA can hold clues for early autism diagnosis and intervention

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A new study led by UC Davis MIND Institute researchers found a distinct DNA methylation signature in the cord blood of newborns who were eventually diagnosed with autism spectrum disorder (ASD). This signature mark spanned DNA regions and genes linked to early fetal neurodevelopment. The findings may hold clues for early diagnosis and intervention.

"We found evidence that a DNA methylation signature of ASD exists in cord blood with specific regions consistently differentially methylated," said Janine LaSalle, lead author on the study and professor of microbiology and immunology at UC Davis.

The study published Oct. 14 in *Genome Medicine* also identified sex-specific epigenomic signatures that support the developmental and sex-biased roots of ASD.

The U.S. Centers for Disease Control and Prevention (CDC) estimates that one in 54 children are diagnosed with ASD, a complex neurological condition linked to genetic and environmental factors. It is much more prevalent in males than females.

The role of the epigenome in DNA functioning

The epigenome is a set of chemical compounds and proteins that tell the DNA what to do. These compounds attach to DNA and modify its function. One such compound is CH_3 (known as the methyl group) that could lead to DNA methylation. DNA methylation can change the activity of a DNA segment without changing its sequence. Differentially methylated regions (DMRs) are areas of DNA that have significantly different methylation status.

The epigenome compounds do not change the DNA sequence but affect how cells use the DNA's instructions. These attachments are sometimes passed on from cell to cell as cells divide. They can also be passed down from one generation to the next. The neonatal epigenome has the potential to reflect past interactions between genetic and environmental factors during early development. They may also influence future health outcomes.

Finding factors in fetal cord blood that might predict autism

The researchers studied the development of 152 children born to mothers enrolled in the MARBLES and EARLI studies. These mothers had at least one older child with autism and were considered at high risk of having another child with ASD. When these children were born, the mothers' umbilical cord blood samples were preserved for analysis. At 36 months, these children got diagnostic and developmental assessments. Based on these, the researchers grouped the children under "typically developing" (TD) or "with ASD."

The researchers also analyzed the umbilical cord blood samples taken at birth from the delivering mothers. They performed whole-genome sequencing of these blood samples to identify an

epigenomic signature or mark of ASD at birth. They were checking for any patterns of DNA-epigenome binding that could predict future ASD diagnosis.

They split the samples into discovery and replication sets and stratified them by sex. The discovery set included samples from 74 males (39 TD, 35 ASD) and 32 females (17 TD, 15 ASD). The replication set was obtained from 38 males (17 TD, 21 ASD) and eight females (3TD, 5 ASD).

Using the samples in the discovery set, the researchers looked to identify specific regions in the genomes linked to ASD diagnosis. They tested the DNA methylation profiles for DMRs between ASD and TD cord blood samples. They mapped the DMRs to genes and assessed them in gene function, tissue expression, chromosome location and overlap with prior ASD studies. They later compared the results between discovery and replication sets and between males and females.

Cord blood to reveal insights into genes related to ASD

The researchers identified DMRs stratified by sex that discriminated ASD from TD cord blood samples in discovery and replication sets. They found that seven regions in males and 31 in females replicated, and 537 DMR genes in males and 1762 DMR genes in females replicated by gene association. These DMRs identified in cord blood overlapped with binding sites relevant to fetal brain development. They showed brain and embryonic expression and X chromosome location and matched with prior epigenetic studies of ASD.

"Findings from our study provide key insights for early diagnosis and intervention," LaSalle said. "We were impressed by the ability of cord blood to reveal insights into genes and pathways relevant to the fetal brain."

The researchers pointed out that these results will require further replication before being used diagnostically. Their study serves as an important proof of principle that the cord blood methylome is informative about future ASD risk.

More information: Charles E. Mordaunt et al, Cord blood DNA methylome in newborns later diagnosed with autism spectrum disorder reflects early dysregulation of neurodevelopmental and X-linked genes, *Genome Medicine* (2020). DOI: 10.1186/s13073-020-00785-8

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