

# Chromosomal testing expands options for exploring causes of SIDS

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A genetic test known as chromosomal microarray analysis (CMA) could help identify the cause of sudden infant death syndrome (SIDS) or its counterpart in older children, known as sudden unexplained death in

childhood (SUDC), finds a study led by Boston Children's Hospital.

The researchers, led by Richard Goldstein, MD, Ingrid Holm, MD, MPH, and Catherine Brownstein, MPH, Ph.D., call for making CMA routine in investigating SIDS and SUDC. They published their study findings online November 7 in the journal *Advanced Genetics*.

"We think we have enough information to say that CMA is worth considering when a child has died without explanation, and worth exploring further as a way to understand these deaths better," says Goldstein, who directs Robert's Program on Sudden Unexpected Death in Pediatrics at Boston Children's and was a senior author on the study.

The team used CMA to test samples from 116 deceased infants and toddlers up to 28 months old whose deaths were classified as SIDS or SUDC. In 14 children (12 percent), CMA identified deletions or duplications of segments of the child's DNA or small DNA rearrangements that were pathogenic or "favoring pathogenic."

"CMA is already used routinely in children with conditions such as autism, [developmental delay](#), and multiple congenital anomalies, and children with undiagnosed conditions," says Holm, co-senior author of the study.

To further validate their findings, the researchers compared CMA results in SIDS/SUDC patients with those in control groups of children from the community and two cohorts of children with an autism spectrum disorder. When scored for the likelihood of potentially impactful chromosomal changes on CMA, the SIDS/SUDC group scored significantly higher than controls, but had scores similar to those of children with autism spectrum disorder (ASD).

Many of the CMA findings had no obvious relationship to SIDS/SUDC

and call for further investigation. For example, two children had undiagnosed Klinefelter syndrome, in which boys are born with an extra X chromosome but generally have a normal lifespan. Several identified chromosomal deletions/duplications have also been associated with neurodevelopmental conditions, including seizures, ASD, developmental delay, and schizophrenia.

## Adding to the test arsenal

In previous work, Boston Children's researchers used whole-[exome sequencing](#) (sequencing the 1 to 2 percent of the genome that encodes proteins) to evaluate children whose deaths were classified as SIDS or SUDC. In that study, 11 percent of [children](#) had genetic variants (alterations) that likely played a role in their deaths. It remains to be seen to what extent CMA would add to these findings and how much overlap there is between the genes found to be altered on exome sequencing and the genes affected by DNA deletions/duplications.

The team hopes their findings will encourage [medical examiners](#) investigating SIDS deaths to reach out to them for assistance.

"Medical examiners are interested in genetic investigations, but they lack the resources, especially when it comes to interpreting the results," says Goldstein. "We're trying to move that ball forward and provide useful information."

Adding to exome sequencing and [chromosomal abnormalities](#) on CMA, the researchers recently got a grant from the American SIDS Institute to study more complex structural changes in chromosomes that might contribute to SIDS and SUDC, using an advanced genomics platform called the Bionano Saphyr to image extremely long strands of DNA.

"This technique gives us the ability to find structural variations that are

too big for traditional DNA sequencing to pick up but too small for chromosomal microarray to detect," says Brownstein, the study's first author and scientific director of the Manton Center for Orphan Disease Research Gene Discovery Core at Boston Children's. "We can also pick up instances when a segment of DNA 'flips' to a different location on the chromosome."

In the long term, as DNA sequencing costs come down, the researchers want to use whole-genome sequencing to investigate SIDS and SUDC, a single test that could reduce the need for CMA.

**More information:** Catherine A. Brownstein et al, Copy Number Variation and Structural Genomic Findings in 116 Cases of Sudden Unexplained Death between 1 and 28 Months of Age, *Advanced Genetics* (2022). [DOI: 10.1002/ggn2.202200012](https://doi.org/10.1002/ggn2.202200012)

Provided by Children's Hospital Boston

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