Study explores why some children exposed to the coronavirus develop inflammatory syndrome

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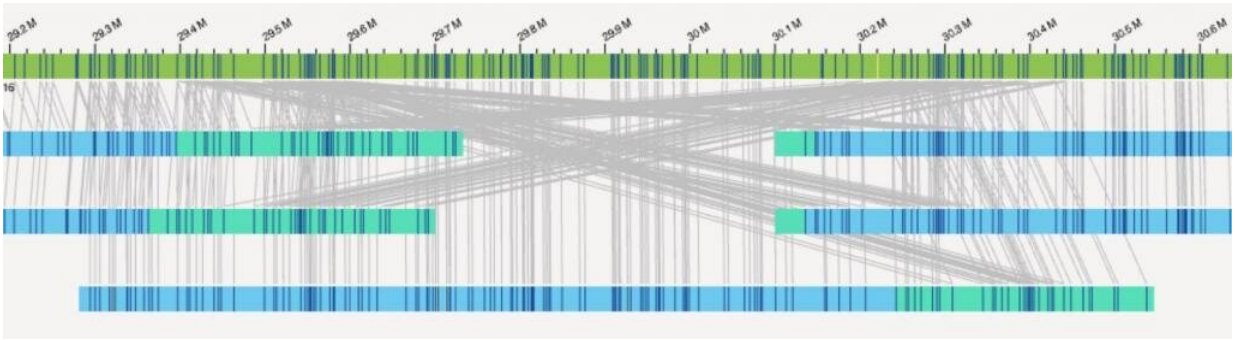

This readout from Saphyr shows areas of a patient's DNA that have "flipped" to a different location on the chromosome, indicated by the grey diagonal lines. The green line at the top represents the normal organization of DNA at that part of the chromosome. Credit: Bionano Genomics

Most children exposed to SARS-CoV-2 have few or no symptoms, but a small number become sick enough to go to the hospital—and a tiny handful develop a severe inflammatory illness called multisystem inflammatory syndrome (MIS-C), often weeks after initial exposure to the virus.

A team at Harvard Medical School and Boston Children's Hospital is using a cutting-edge genetics technology to try to find out why.

"We're looking for variations in the structure of DNA that make children susceptible to MIS-C," said Catherine Brownstein, assistant professor of pediatrics at HMS and assistant director of the Molecular Genetics Core Facility at Boston Children's.

Brownstein is co-leading the new study with Alan Beggs, the Sir Edwin and Lady Manton Professor of Pediatrics at HMS and director of the Manton Center for Orphan Disease Research at Boston Children's.

Genetic sequencing and beyond

The study builds on work already underway at HMS and Boston Children's.

The Children's Rare Disease Cohort Initiative, led by David A. Williams, Piotr Sliz and Shira Rockowitz, is providing blood samples. A team led by critical care physician Adrienne Randolph and immunologist Janet Chou has been sequencing children's entire genomes or exomes (a smaller group of genes that code for proteins).

These traditional methods can identify "spelling" changes in the genetic code. Another method, called chromosomal microarray analysis, can pick up duplicated or missing segments of DNA in our 23 chromosomes. But there are other kinds of genetic changes that neither of these technologies can pick up.

"This new project takes the next step, looking at changes in the deeper structure of a person's genome," said Randolph, HMS professor of anesthesia and of pediatrics at Boston Children's. "These changes help could explain why some young individuals develop rare complications from COVID-19 or [develop] very severe illness."

Imaging children's DNA

Brownstein and Beggs are using a sophisticated platform called Saphyr, provided by Bionano Genomics, to image and map the structure of the genome. Their plan is to analyze the DNA of children with MIS-C, children with severe COVID-19 but not MIS-C and children with mild or asymptomatic infections.

In all, they hope to enroll 50 children in each group, looking for hard-to-find differences in the chromosome structure.

Brownstein said that the team has one of only two Saphyr machines on the East Coast.

"Its unique power is its ability to identify structural variations that are too big for traditional DNA sequencing to detect, but too small for chromosomal microarray to pick up," he said. "Our hypothesis is that some of these variations might influence genes important for the development of MIS-C or might interact with triggers in the environment."

"In addition to finding deletions and duplications, the system can also identify chromosome rearrangements, like a piece of DNA that's flipped around or moved to a different location on the chromosome," added Beggs.

Understanding immune differences

Randolph and Chou will lend their medical expertise to the project.

Randolph's research focuses on the immune system's role in critical illness in children. As leader of the nationwide Overcoming COVID-19

study, she has been tracking the health, immune responses and inflammatory responses of children with MIS-C.

Chou, assistant professor of pediatrics at HMS and director of the Primary Immunodeficiency Program and Immunogenomics Program at Boston Children's, will provide input on how chromosomal changes affect genes involved with the immune response.

The research could also shed light on why some adults with COVID-19 develop life-threatening inflammation. The researchers have joined the COVID-19 Host Genome Structural Variation Consortium, which is studying patients of all ages. They hope to compare their findings with those in up to 850 adult cases.

If Saphyr can crack the genetics behind susceptibility to MIS-C, its uses could be expanded to other diseases, the researchers said. Ultimately, the hope is that the genetics will reveal more about the immune system and how to strengthen the body's defenses against a variety of threats.

Provided by Harvard Medical School

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