New clinical RNA sequencing platform may improve rare disease diagnostics in pediatrics

April 13 2023

Dr. Kyoko Yuki and Dr. Lianna Kyriakopoulou are moving the needle on precision diagnostics for rare diseases through a new clinical RNA sequencing platform at SickKids. Credit: The Hospital for Sick Children (SickKids)

A new clinical RNA sequencing platform at The Hospital for Sick

Children (SickKids) is helping to facilitate research into rare genetic conditions and carve a path for Precision Child Health, a movement at SickKids to deliver individualized care for every patient.

RNA sequencing provides a different way of looking at the genes, by looking at how the body interprets the genetic code rather than looking directly at the genetic code itself. While DNA-based tests like genome sequencing take a picture of a person's genetic code, scientists can better understand how the DNA is being read by also looking at RNA, which carries instructions for making proteins in our body.

Across the SickKids Research Institute, scientists have been working closely together over the last six years to build and incorporate RNA sequencing into the research pipeline. Now, championed by Dr. Lianna Kyriakopoulou, a Clinical Laboratory Director in the Division of Genome Diagnostics, and Laboratory Specialist Dr. Kyoko Yuki, this technology is, for the first time in Canada, validated to be used in the clinical space as a new tool for precision diagnostics.

"The clinical RNA sequencing platform at SickKids is helping to move the needle in achieving a diagnosis for patients with rare genetic conditions through patient-centered care, or what SickKids calls Precision Child Health," says Dr. Lianna Kyriakopoulou. "Used together, genome sequencing and RNA sequencing can potentially further inform which findings are relevant to help guide clinical decision-making."

Combined DNA and RNA sequencing offers improved diagnostic information for complex genetic conditions

Using this clinical RNA sequencing platform, a team of SickKids researchers, in collaboration with Dr. Panagiota Klentrou at Brock

University, performed genome sequencing and RNA sequencing on 97 individuals from 39 different families in the Complex Care Program, a clinical program focused on diagnosis and care of children with unexplained medical complexity.

In a study published in the *American Journal of Human Genetics*, the RNA analysis provided useful diagnostic information for an additional 8% of the patients whose diagnosis was not confirmed using genome sequencing alone, either confirming or ruling out the impact of a DNA variant identified during genome sequencing.

"Our findings demonstrate a clear benefit to pairing RNA sequencing with genome sequencing in a cohort of children who are suspected to have a genetic diagnosis," explains co-first author Dr. Ashish Deshwar, a resident physician in Medical Genetics & Genomics.

This study is also one of the first to examine the utility of a trio-approach to RNA sequencing, a process which involves conducting RNA sequencing on the affected individual and both parents. While trio RNA sequencing with this population did not uncover any new genetic variants, it decreased the amount of time researchers needed to spend reviewing results and made the analysis more efficient.

Deshwar, alongside other first-authors Yuki and Dr. Huayun Hou, a Bioinformatician in the Wilson Lab, also noticed inherited RNA patterns between family members and are optimistic about its potential use in further research.

"We hope that the results of our study will help support the inclusion of clinical based RNA-testing in diagnostic workflows for children with rare conditions," say co-leads and physician-scientists Drs. Gregory Costain and Jim Dowling, Scientist-Track Investigator and Senior Scientist (respectively) in the Genetics & Genome Biology program.

RNA sequencing platform sparks new research into genetic conditions

The study is just one of the many research programs harnessing RNA sequencing at SickKids.

At The Centre for Applied Genomics (TCAG) in the SickKids Research Institute, automated screening platforms are also available to researchers thanks to a collaborative effort including the Wilson Lab, Dowling Lab, Costain Lab, Shlien Lab, Brudno Lab, and others as well as the equipment and expertise at The Centre for Computational Medicine (CCM).

Current research already underway includes the study of allergic responses with Dr. Thomas Eiwegger and blood samples from individuals with lupus with Dr. Linda Hiraki.

Bridging clinical and research for the future of Precision Child Health

As more research is done into the benefits of RNA sequencing, scientists and clinicians are excited to better define the scenarios where clinical RNA sequencing can provide real insights for patients with rare genetic conditions, as well as other patient groups. This will be essential to providing the evidence needed to inform decisions about making RNA sequencing more broadly available for precision diagnostics.

"We have built a strong bridge between the research and clinical labs at SickKids which will benefit ongoing and future studies contributing to precision medicine becoming standard of care, as well as patients throughout the hospital," says Dr. Michael Wilson, a Senior Scientist in the Genetics & Genome Biology program, who previously held a Canada

Research Chair in Comparative Genomics. "By carefully sequencing and analyzing RNA from diverse populations of sick and healthy children, we have the potential to improve how we find diagnoses for patients with rare genetic conditions."

More information: Ashish R. Deshwar et al, Trio RNA sequencing in a cohort of medically complex children, *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.03.006

Provided by The Hospital for Sick Children