SickKids Awarded $9M to Complement Array Autism Studies with Sequencing

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By Justin Petrone

The Hospital for Sick Children will use a new CA$8.9 million (US$8.8 million) grant from the Ontario Research Fund's Ministry of Research and Innovation to conduct genomic sequencing studies of autism spectrum disorders — work that will build on nearly a decade's worth of microarray-based autism research at the hospital.

The grant from the Global Leadership Round in Genomics and Life Sciences will support a study aimed at developing new tools to screen genomes and new technologies for diagnosing ASD and other neurological disorders, the hospital, known as SickKids, said last week. In addition to the government funding, SickKids also will receive a new SOLiD DNA sequencer from Life Technologies that is valued at around $700,000.

Stephen Scherer, a senior scientist at Toronto-based SickKids, told *BioArray News* via e-mail that the new funds will support the sequencing of about 1,000 Canadian autism cases and controls. SickKids' main goals are to find rare sequence-level variants associated in autism that might identify monogenic and multigenic factors involved in disease susceptibility.

A "unique aspect" of the project will be to couple SickKids' existing microarray-detected autism-related copy number variants with the smaller sequence-level variants detected by sequencing, with the "ability to go back and test well-phenotyped parents and families for segregating variants, combinations of variants, and phenotypes," Scherer said. Since SickKids' research and diagnostics team "knows all of these families by name, we can work closely with them to get the most clinically relevant data back to them in a timely and informed manner," he said.

Scherer said SickKids will use Agilent Technologies' SureSelect Exome Capture kits and the SOLiD in the study.

Scherer and colleagues have been using genomic technologies, primarily microarrays, to study autism for the past decade. The new sequencing-based project will build on previous research that identified copy number differences associated with ASD susceptibility.

"Our group and collaborators made important contributions to identifying CNVs as etiologic factors in upwards of 10 percent of individuals with autism spectrum disorder," Scherer said. He noted that his team worked with the Autism Genome Project Consortium to discover that CNVs

of the NRXN1 gene, the 1q21.1 and 16p11.2 microdeletion/microduplication regions, DPP6, and others are "significant risk factors" in autism. In addition, Scherer added that his team has "a series of new findings identifying other loci that will increase the association with rare CNVs."

SickKids has used arrays from a number of vendors, including Affymetrix, Illumina, and Agilent Technologies, in its studies. For example, the hospital used the Illumina 1M BeadChip in the latest consortium study, but uses the Affy SNP 6.0 Array for its "day-to-day autism testing," Scherer said. The hospital's molecular diagnostics laboratory is also testing some autism cases for clinical workup on the Agilent platform.

While it is now moving into sequencing-based projects, Scherer predicted SickKids will be using arrays for research and diagnostics "certainly for the next few years.

"Right now [arrays] actually generate significant complementary information to NGS approaches, which are largely aimed at sequencing exomes," Scherer said. "Many CNVs will not be readily detected by the exome approach, either because of complexity, coverage, or their not at all being detected by the exome capture," he said. "We've shown over and over again if you only do the sequencing with no microarrays, at least for now, you will miss interesting variants."

Scherer said that SickKids prefers to use two or more microrrays from different vendors in its studies, since "each platform reveals some 50 percent more variants than just running a single other one."

One planned array-based study will involve running 5,000 autism cases from an Ontario-wide network of pediatric clinics on a high-density platform. "While we have found some rare and inherited CNVs and point mutations to be involved in autism, these findings have been from research cohorts," Scherer said of the basis for the study. "Some of these exciting data already hold prognostic and diagnostic potential, but the findings need to be tested in an unselected autism cohort to see what the prevalence characteristics look like in these non-research populations."

Scherer said there are equivalent microarray studies being run in the UK by Nigel Carter at the Wellcome Trust Sanger Institute and Tony Monaco's lab at Oxford University. "We plan to share data and experiences. We also want to share because we need even more good controls," he said.

SickKids' ultimate goal is to bring its gene discoveries from the research lab to the clinic in order to diagnose ASD earlier. Scherer said that recent studies have yielded markers that can be used clinically in about 10 percent of cases, but that more research is required.

"The next be leap from the 10 percent number will come from running even higher-resolution arrays and doing the NGS sequencing in well-studied cohorts," Scherer predicted. "With these experiments, the diagnostic yield and specificity should continue to get better."

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