CLARITY Genomics Practice Challenge Winner Announced at ASHG

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By Andrea Anderson
SAN FRANCISCO (GenomeWeb News) – At the annual American Society for Human Genetics meeting here today, a clinical genetics team from Brigham and Women's Hospital was named the winner of a genomic sequencing standards contest spearheaded by investigators at Boston Children's Hospital.

The "Children's Leadership Award for the Reliable Interpretation and appropriate Transmission of Your genomic information," or CLARITY, program was launched earlier this year. As GenomeWeb Daily News reported this summer, the challenge focused on three children with rare, undiagnosed genetic conditions.

The program highlights the "incredible advances in massively parallel, or 'next-generation,' sequencing," said National Human Genome Research Institute's Leslie Biesecker, who moderated a related press briefing here today.

Brigham and Women's first place prize comes with a $15,000 award. Two more finalist teams — one from the University of Iowa and another from Genomatix, CeGaT, and the University Hospital of Bonn in Germany — were each awarded $5,000 in recognition of the quality of the entries they submitted.

Five more teams received an honorable mention. Those groups were based at Slovenia's Clinical Institute of Medical Genetics, the Nationwide Children's Hospital in Columbus, Ohio, Sweden's Karolinska Institute, the Scripps Translational Science Institute, and the Massachusetts-based company SimulConsult/Pennsylvania's Geisinger Health System.

Dozens of research groups applied to the CLARITY competition. Each of the 30 teams chosen to compete were tasked with not only analyzing and interpreting the exome and genome sequence data, but also with finding ways to appropriately return the results to patients and their doctors and to deal with issues such as incidental findings.

"We got the best thinking from around the world," CLARITY co-organizer David
Margulies, executive director of the gene partnership at Boston Children's Hospital, said in a statement, "and it has moved us toward a consensus on how to report sequencing data for use in the clinic."

The competition stemmed from the recognition that a lack of standardized guidelines for interpreting genomic data in the clinic — as well as inconsistent or non-specific results or resources — were among the barriers to more widespread use of next-generation sequencing in a clinical setting, Catherine Brownstein, project manager with Boston Children's Hospital's gene partnership program, said at today's briefing.

For the challenge, contest participants were presented with detailed medical histories for three children with unexplained genetic diseases: two with conditions characterized by muscle weakness and a third with a heart rhythm disorder.

In addition to raw whole-exome sequence data for children and their parents, which was generated by SOLiD sequencing at Life Technologies, and whole-genome sequence data from Complete Genomics, the researchers had access to sequence information for some extended family members in some cases.

Generally speaking, Brownstein noted that many of the participating teams used similar data analysis pipelines. And for the most part, each of the highly rated research groups came up with comparable findings for the three families.

Even so, the quality control metrics used for the analyses varied somewhat from one to the next. There were also differences in the way patient results were reported and in the ways that teams dealt with low coverage regions of the genomes or exomes, low confidence data, or variants of unknown significance.

For an affected child from one of the families, eight of the research teams tracked down a mutation in a gene called titin, which has a muscle structure-related role and is believed to be the source of the 11-year-old boy's muscle weakness condition. Six groups identified alterations to the GJB2 gene, which are believed to explain his hearing loss, and three found both gene culprits.

In another family, seven participating groups uncovered a TRPM4 gene mutation suspected of contributing to the heart rhythm problem that claimed the couple's infant son shortly after birth.

For a third family, teams were not able to conclusively diagnose the genetic cause of the affected child's muscle weakening condition. But from the seven variants highlighted by two or more of the groups, researchers at Boston Children's Hospital have selected four for follow-up analyses going forward.
In particular, the winning group was judged highly for its bioinformatics approach as well as the clarity and clinical utility of the reports that it prepared for each of the three families considered.

The specifics of the Brigham and Women's Hospital researchers' scheme are to be described in a future publication, as will strategies developed by other top teams in the competition.

Ideally, CLARITY organizers hope to have co-authors representing all of the teams participating in the competition, according to co-organizer Alan Beggs, director of Boston Children's Hospital's Manton Center for Orphan Diseases Research.

"There are some really outstanding approaches that the various teams have taken," Beggs said.

At today's briefing, members of several teams participating in CLARITY noted that the challenge has spurred a rise in communication and collaboration between the clinical, bioinformatic, and research members from each group — laying the foundation for future clinical genomics efforts at the participating centers.

Meanwhile, the CLARITY team is reportedly gearing up for another challenge related to cancer genome interpretation.

There is also interest in finding ways to improve the level of genomics literacy amongst those directly treating patients, Margulies noted in a statement issued today.

"It is essential that families are cared for by practitioners who are trained in the use of genomic analysis," he said, adding that "[t]raining of care providers will be the next challenge."