# BabySeq Researcher Presents Initial Findings at ACMG

Mar 14, 2016 | Andrea Anderson

NEW YORK (GenomeWeb) – The randomized clinical trial known as BabySeq is beginning to yield information on the feasibility of newborn genomic sequencing, according to Mount Sinai Icahn School of Medicine's Ozge Birsoy.

Birsoy presented information on the project and findings from the first 15 sequenced newborns during an oral platform presentation in the whole exome sequencing session at the annual meeting of the American College of Clinical Genetics and Genomics in Tampa, Florida last week.

BabySeq, a best practices pilot study spearheaded by researchers at Brigham and Women's Hospital and Boston Children's Hospital, was launched with the goal of understanding when and how to apply genomic sequencing in the newborn setting, while gauging the impact of newborn sequencing on families and their health-care providers.

Generally speaking, newborn sequencing is expected to help clinicians identify genetic conditions or predispositions in infants, allow for early interventions and disease management, furnish pharmacogenomics clues, and provide information that may aid parents in future family planning, Birsoy noted.

But the approach also presents challenges, she explained, both in generating and interpreting data in an accurate but timely manner, and in determining the types of clinical information that will truly benefit infants and their families.

To begin exploring the potential of newborn sequencing, the researchers are enrolling infants into two cohorts: a group of 240 healthy newborns born at Brigham and Women's Hospital and their parents, when available, who are sequenced in a screening capacity, and 240 infants from Boston Children's Hospital neonatal intensive care unit and their parents. Within each group, half of the newborns are randomized to undergo standardized, state-mandated newborn screening with family history review. The other half receives this current standard-of-care in combination with exome sequencing.

Results from the healthy infant group are being reported in a so-called Genomic Newborn Sequencing Report (GNSR). It includes information on variants — both those that have strong evidence of being pathogenic and those that are likely pathogenic — contributing to childhood onset conditions in a highly

penetrant manner. The GNSR also contains information on carrier status for serious conditions, and, optionally, pharmacogenomic profiles.

Families typically receive the GNSR through a physician, and infants are asked to return for a 10-month follow up to assess their physical health, Birsoy noted. The report is also incorporated into each child's health record.

Meanwhile, information generated through exome sequencing for sick infants from the NICU are returned through an Indication Based Analysis (IBA) report, aimed at identifying variants that may contribute to the condition at hand.

Consequently, the level of evidence required to return information is lower than that required in the GNSR, Birsoy explained. Instead, the IBA report includes information on variants identified in exome sequence data that have been deemed pathogenic and likely pathogenic based on strong or moderate evidence. The team also reports variants of unknown significance in the IBA in the hopes of having the best chance at making a diagnosis in the NICU group.

Both the GNSR and IBA reports are generated with information on variants curated using ClinGen clinical validity classification criteria, and a reporting scheme designed by molecular geneticists, genetic counselors, bioethicists, and other physicians.

Birsoy noted that the BabySeq team has curated some 1,466 gene-disease associations so far. Roughly 65 percent of these variants had strong evidence of disease association, while the remaining variants had moderate, limited, or conflicting evidence of association. The researchers found that more than four-fifths of these variants affected genes implicated in childhood onset diseases and a similar proportion of the curated variants were deemed highly penetrant.

More than half of the curated genes met BabySeq's reporting criteria, with many of these associations involving carrier status for recessively inherited conditions.

Along with insights into this initial gene-disease curation process, Birsoy's presentation touched on the general workflow for the exome sequencing and reporting side of the project, which typically has a turnaround time of around 45 days. She also discussed results from the first 15 BabySeq cases evaluated through the exome sequencing branch of the GNSR screening group.

In these 15 cases, the researchers scrutinized more than 40,000 variants, focusing on more than 200 variants in 163 genes that were selected for further review.

But the gene-disease curation done in advance of these analyses made it possible to quickly rule out a large proportion of potential risk variants, Birsoy explained, with more than 40 percent of the variants failing to meet reporting criteria, falling below the level of evidence needed and/or contributing to adult onset conditions.

The researchers returned carrier status for highly-penetrant childhood-onset conditions for 11 of the 15 sequenced newborns. They are continuing to enroll and evaluate cases for both the GNSR and IBA cohorts and have now analyzed an additional 10 cases.

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