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# BabySeq Project Finds Similar Rates of Genetic Risk Variants Across Diverse Groups

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NEW ORLEANS – Similar rates of genetic variants have been reported across demographic groups participating in the BabySeq1 and BabySeq2 projects, according to a new analysis presented at the National Society of Genetic Counselors annual meeting here last week.

The BabySeq Project, a randomized controlled trial led by Robert Green and Ingrid Holm at Harvard Medical School, launched in 2015 with the aim of sequencing the genomes of newborns to ascertain their risk of genetic disease and of studying how that knowledge affects their care compared to a control cohort. The project reported in 2019 that 15 of the 159 infants, or about 9 percent, who underwent sequencing had a genetic variant that put them at risk of developing a childhood-onset disease.

However, the initial BabySeq cohort largely included families of European ancestry and higher socioeconomic status. For the second, expanded study, dubbed BabySeq2, the researchers aimed to address that lack of diversity.

According to Bethany Zettler, a genetic counselor at Brigham and Women's Hospital and project manager for the program, BabySeq2 has so far enrolled 554 infants and sequenced 120 of them. The cohort is more diverse than BabySeq1, as 45 percent of participants are Black or African American, 26 percent Hispanic or Latino, 9 percent White or European American, 3 percent Asian, 2 percent American Indian Native American or Alaska Native, and 1 percent of Middle Eastern or North African/Mediterranean descent. Thirteen percent of participants belong to more than one group and 3 percent did not choose any group.

Zettler and her colleagues analyzed whether the rates of reportable variants associated with Mendelian disease risk or carrier status differs between population demographic groups.

"There's so much bias in genetics," she said, adding that "in the genetic and diagnostic context, there are more VUS among patients from non-White backgrounds, and other screening studies have shown there are lower rates of findings in individuals from non-White backgrounds. So given this context, we thought this was really important to explore within these projects."

In BabySeq1, 11.4 percent of participants had a risk of Mendelian disease, and 87.3 percent were a carrier for a recessive disorder.

Zettler and her colleagues found similar numbers of reported variants in the more diverse BabySeq2 cohort. In this group, 15 percent of participants had a risk of Mendelian disease risk, and 85.8 percent were recessive disease carriers, differences that were not statistically significant.

When they delved into individual demographic groups, the researchers again found no significant differences in the rate of risk between them. In BabySeq2,19.2 percent of Black or African American

participants had a risk of Mendelian disease, while 9.7 percent of Hispanic or Latino participants had such a risk, and 9.1 percent of White or European-American participants did.

The researchers additionally examined whether there were differences in the types of reported variants — variants that altered protein function versus loss-of-function variants — or, by reanalyzing the original variant files, whether they had missed variants that should have been identified and reported.

For a variant that affects protein function to be considered pathogenic or likely pathogenic, it needs to have been observed previously and be included in a database like ClinVar or in the literature, Zettler noted. "Obviously, there's potential for bias because those data sources historically are biased," she added.

Loss-of-function variants, on the other hand, can be novel and still be considered likely pathogenic. In theory, Zettler said, the reporting of those variants could thus be less biased.

She and her colleagues found no significant differences in the average number of variants uncovered per participant or in the types of variants reported in different groups in either BabySeq1 or BabySeq2, though. "This is looking good so far," she said, cautioning that the cohort analyzed was small.

After going back to the raw variant files and examining all the variants that were not reported because there wasn't enough evidence they were pathogenic, they found that there was also no difference in the number of unreported variants between groups.

During her presentation, Zettler described one case in which the BabySeq team uncovered a novel loss-of-function variant in an infant from a mixed-race background who had normal newborn screening and a typical medical and developmental history. The variant was in the ARFGEF1 gene and is associated with risk of a neurodevelopmental disorder including autism, seizures, and developmental delay. When she informed the mother, she learned that the child was just beginning to exhibit related symptoms, and they were able to establish care with specialists and set up early interventions, avoiding a diagnostic odyssey.

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