Reducing VUS rates among ethnic groups: Sequencing smarter not harder

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BACKGROUND
Advances in DNA sequencing have led to genetic testing of many patients with large gene panels. However, it has been reported that the rates of detecting a variant of uncertain significance (VUS) are lower in White/Europeans than in other ethnic groups. Two possible explanations have been proposed for this phenomenon.

- Numerous studies based on White/European cohorts mean that we have more information about this population’s variants.
- Non-White/European populations may carry more variants relative to the human reference genome.

To better understand this issue, we studied rare missense variants in BRCA1 and BRCA2, the most extensively studied hereditary cancer genes, and 78 other hereditary cancer genes.

METHODS
- We identified 123,251 patients for whom BRCA1 and BRCA2, with (13,041) or without (110,210) an additional 78 hereditary cancer genes, were requisitioned at Invitae in 2016 and 2017. Self-reported ethnicity and identified variants were retrieved.
- For each missense variant identified in these patients, the classification and maximal minor allele frequency (MAF) among the 7 populations from gnomAD were recorded.
- MAF <0.1% and MAF <0.01% were used as cutoffs for considering a variant as rare or very rare.
- Differences in VUS rates among ethnic groups were assessed for significance by the chi-square test.

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CONCLUSIONS
- Compared with other ethnicities, White/European or AJ patients have a similar proportion of rare pathogenic missense variants in hereditary cancer syndrome genes, but fewer VUS per patient. This pattern was observed in both well-studied genes (BRCA1 and BRCA2) and in 78 other hereditary cancer syndrome genes. These ethnic differences in the number of VUS per patient were primarily the result of a few rare but recurring variants in White/European and AJ populations for which published studies made a benign interpretation possible.
- Large population databases, such as gnomAD, now provide us with allele frequencies of variants in previously undersequenced populations. In order to reduce VUS rates in non-White/European individuals, we recommend targeted functional and segregation analysis of rare but recurrent variants in these populations. We believe this strategy will be more effective than simply sequencing additional unselected individuals from these populations.

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