MGH INSTITUTE OF HEALTH PROFESSIONS

Impact of gnomAD v4 on BS1 Application

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Background

- The Genome Aggregation Database (gnomAD) is one of the world's largest population databases, and is often used as a resource during variant classification
- **The latest version of gnomAD (v4.1) is ~5x larger than prior versions, but representation of the world's genetic diversity remains a challenge**
  - While the *number* of individuals with non-European genetic ancestry (GA) increased in v4.1, the *percentage* of individuals with non-European GA decreased in v4.1 when compared to earlier versions
- The Richards et al. "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology" guidelines provide evidence criteria and a framework for classifying variants, including BS1 (benign strong)
  - BS1 = variant's allele frequency is greater than expected for a predicted disorder (benign evidence)
  - To apply BS1, the maximum allele frequency (MAF) across GA groups in gnomAD is compared to a BS1 threshold
  - BS1 threshold varies by gene + disorder type

Objectives

To assess if the availability of gnomAD v4.1 changes the number of VUS for which allele frequency data can be used for strong evidence of benign impact (BS1) compared to v2

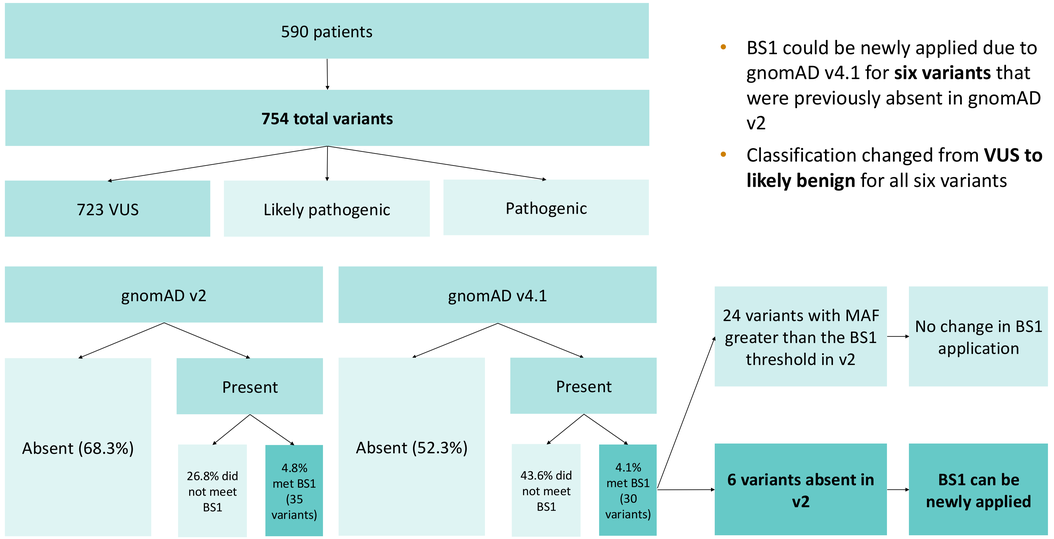
A. To assess if the new application of BS1 changes variant classification

B. To assess differences across reported race/ethnicity groups

Methods

- Retrospective quantitative study of all clinical exomes (2019-2023) with ≥1 VUS at one clinical laboratory
- Data included genomic data and demographic data collected from test requisition forms/clinical documentation
- Variants were mapped from GRCh37 (v2) to GRCh38 (v4.1), and MAF was obtained from gnomAD for each variant
- The BS1 threshold at time of original classification was used for each gene in the dataset
  - Thresholds were set by the laboratory at the time of original classification using the statistical framework described by Whiffin et al. (2017)

Results



- BS1 could be newly applied due to gnomAD v4.1 for **six variants** that were previously absent in gnomAD v2
- Classification changed from **VUS to likely benign** for all six variants

Discussion

- More variants in the cohort are *present in v4*, but the percentage of variants that *pass the BS1 threshold* is lower in v4
  - MAF will decrease in v4.1 if the allele frequency does not change significantly, but the GA group size increases
  - Larger v4 size further refines allele frequencies and highlights the rarity of these variants
- **This study did not identify a significant number of variants for which BS1 could be newly applied due to v4.1**
  - Research Aim B may be assessed in future studies, but was not able to be assessed in this study due to sample size
- The methodology applied in this study may miss variants present in gnomAD v4.1 if there was a transcript change between genome builds

Implications

- Our knowledge of allele frequencies changes over time, fluctuating with data quality, GA representation, and overall size of databases
- Changes in gnomAD data may impact variant classification, though this study identified a limited effect

References: