Impact of Variants of Varying Clinical Consequence in Underrepresented Populations and Implications for a Minimum Variant Set for Pan-Ancestry Cystic Fibrosis Carrier Screening

Gary J. Lasthau, Brian C. Haynes, Brad Hall, and John N. Milligan
Asuragen, a Bio-Techne Brand, Austin, TX

Summary

- Toward the goal of equitable cystic fibrosis (CF) testing and improved outcomes for minority patients, the ACMG recently updated the recommended number of CFTR variants for CF carrier screening (GNOAD 100 variants). (ACMG 2022) by filtering candidate variants through the CFTR2 and gnomAD databases and combining them to cover 95% of CF carriers in US ancestry.
- However, this approach resulted in variants of varying clinical consequence (VVC) and pathogenic structural variants (SV) shown in recent US population-level GWAS studies to have high prevalence in minority populations where delayed diagnosis and treatment lead to worse clinical outcomes.
- Here, we leveraged pathogenicity scores calculated from ClinVar as a metric for scrutinizing CFTR2 variants to identify pathogenic/pathway variants, showing that VVC above the threshold represent ≥25% of carriers in African, East Asian, and South Asian ancestry and are underrepresented on most CFTR panels.
- Inclusion of VVC in SV with strong pathogenic evidence in targeted panels may further improve detection rates in minority populations toward the goal of equitable CF testing and screening.

Introduction

Cystic Fibrosis (CF), a progressive autosomal recessive disease, is caused by variants in the CFTR gene. CF carrier screening (CS) is the most common CF test performed among all Ashkenazi and Jewish communities. While a number of evidence-based guidelines exist for CF carrier screening (CS) in minority populations, it is unclear what the appropriate number of CFTR variants to screen for is. One concern is the high frequency of rare CFTR variants that are unique to minority populations.

Methods

Morris et al published the ACMG 2023 guidelines, we generated a base set of pathogenic CFTR variants consisting of all variants listed as CF-causing variants in CFTR2 (April 7th, 2023) release and all variants previously in the recommended ACMG CFTR2 panel. Next, we filtered the variant pathogenic set based on their inclusion in gnomAD (20-1.1.2) in 8 ancestries: African/African American (AFR), Latino/Admixed American (AMR), Ashkenazi Jewish (AJ), East Asian (EAS), East Negroid (ESE), and West Asian (WSA). Two variants (L1102W, S543C) were manually included based on clinical relevance and clinical significance.

Results

Figure 1. Pathogenicity Ratings are Strongly Correlated with Clinical Significance in CFTR2 and ClinVar. Data includes all variants that are present in CFTR2 and variable clinical significance indicated at top. 1= ClinVar benign or likely benign; 2= no data/submissions; 3= conflicting or conflicting interpretations; 4= no data/submissions; 5= likely pathogenic; 6= pathogenic.

- To ensure an equitable panancestry approach, we compared clinical significance from CFTR2 and ClinVar to determine if the 75% prevalence threshold established by pathogenic and probably pathogenic variants in both datasets (Figure 2) is appropriate across all variants and ancestry groups. In minority ancestry, three ancestry groups showed variation in prevalence. For each age group, 1= benign, 2=likely benign, 3=unknown, 4=conflicting interpretations, 5=likely pathogenic and 6= pathogenic.

Figure 2. Percentage of Allele Frequencies Represented by CFTR2 VVCC’s in 6 Ancestries. The percentage of total allele frequencies represented by CFTR2 variants in each of six ancestries, African American (AAR), Ashkenazi Jewish (AJ), East Asian (EAS), non-French European (NFE), and South Asian (SAS). Two rare variants (L1102W, S543C) were manually included based on clinical relevance and clinical significance.

Conclusions

- Pathogenicity ratings (PR) provide a useful means for scrutinizing pathogenicity of VVCC. PR is a ratio of the clinical and functional of variants critical for equitable panancestry CF testing and screening.
- Inclusion of VVCC and SV with strong pathogenic evidence in targeted panels may further improve detection rates in minority populations toward the goal of equitable CF testing and screening.

Table 1. Pathogenic CFTR Structural Variants (SVs) with High Prevalence.

- These data suggest that test panels including just 14 VVCC with strong pathogenic evidence and high prevalence in one or more ancestries would improve equitable coverage, inclusion of pathogenic SVs high prevalence (Table 1) would further improve coverage

References: