AbsoluteDx Cardio

Polygenic risk stratification in familial hypercholesterolemia

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Overview

Allelica's AbsoluteDx Cardio provides a unified, clinically validated framework for cardiovascular risk assessment by combining monogenic variant interpretation and ancestry-informed polygenic risk scores (PRS).

Monogenic variants are interpreted using the Allelica Monogenic interpretation software, following ACMG/AMP guidelines. PRS values are computed using the Allelica PREDICT platform, which applies validated multi-ancestry coronary artery disease (CAD) PRS derived from large, prospective datasets.

This integrated framework enables comprehensive genetic risk evaluation for familial hypercholesterolemia (FH), a monogenic disorder primarily driven by pathogenic variants in LDLR, APOB, PCSK9 or LDLRAP1.

Methods

A meta-analysis was conducted using data from the UK Biobank (UKBB) and the All of Us (AoU) research program to evaluate the ability of the PRS to stratify CAD risk among individuals with familial hypercholesterolemia (FH^+) and to assess how the distribution of PRS values modulates the penetrance of FH. The analysis employed the inverse-variance method to combine cohort-specific estimates in a unified framework. FH carrier status was defined as the presence of *pathogenic* or *pathogenic/likely pathogenic (P/LP)* variants in LDLR, APOB, PCSK9, or LDLRAP1.

The UKBB dataset included ~500,000 participants with exome sequencing and linked clinical data, providing high statistical power for association testing. The AoU dataset comprised participants with whole-genome sequencing and electronic health records, enabling replication across a genetically diverse population. Prior to meta-analysis, genomic annotations, variant definitions, and clinical endpoints were harmonized to ensure consistency in FH carrier identification and CAD outcome evaluation.

Population structure for each cohort is reported in Table 1 (AoU) and Table 2 (UKBB), with the combined dataset summarized in Table 3.

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Table 1. AoU carriers populations description

Gene	# Carriers	# Cases
LDLR	1,039	413
APOB	95	38
PCSK9	55	22
LDLRAP1	7	4
Total	1,196	477

Table 2. UKBB carriers populations description

Gene	# Carriers	# Cases
LDLR	774	135
APOB	71	4
PCSK9	40	22
LDLRAP1	9	4
Total	894	165

Table 3. Meta-analysis population

Gene	# Carriers	# Cases
LDLR	1,813	548
APOB	166	42
PCSK9	95	44
LDLRAP1	16	8
Total	2,090	642

Odds ratio of CAD among FH^+ were estimated using a logistic regression applied separately in UKBB and AoU, adjusted for age, sex, and the first four principal components.

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Cohort-specific hazard estimates for carriers of pathogenic or pathogenic/likely pathogenic variants in LDLR, APOB, PCSK9 or LDLRAP1 were derived separately and then combined using inverse-variance weighting after harmonization of variant annotation, endpoint definition, and censoring criteria across datasets. The resulting meta-analytic estimates reflect the odds ratio of CAD among carriers, providing a unified measure across cohorts.

Results

Integration of the polygenic risk score (PRS) among FH⁺ carriers revealed a wide gradient of coronary artery disease (CAD) risk across PRS percentiles. FH⁺ individuals in the lowest PRS decile exhibited a CAD risk comparable to FH⁻ individuals with an average PRS, reaching an odds ratio of 1.0 at the 6th percentile. Notably, about 25% of FH⁺ carriers remained below the odds ratio of 2 (risk-enhancing threshold). In contrast, FH⁺ carriers in the top PRS percentile showed an odds ratio of 14. Overall, the PRS effectively stratified CAD risk among FH⁺ carriers, with an odds ratio per standard deviation of 1.9 (95% CI: 1.6-2.2).

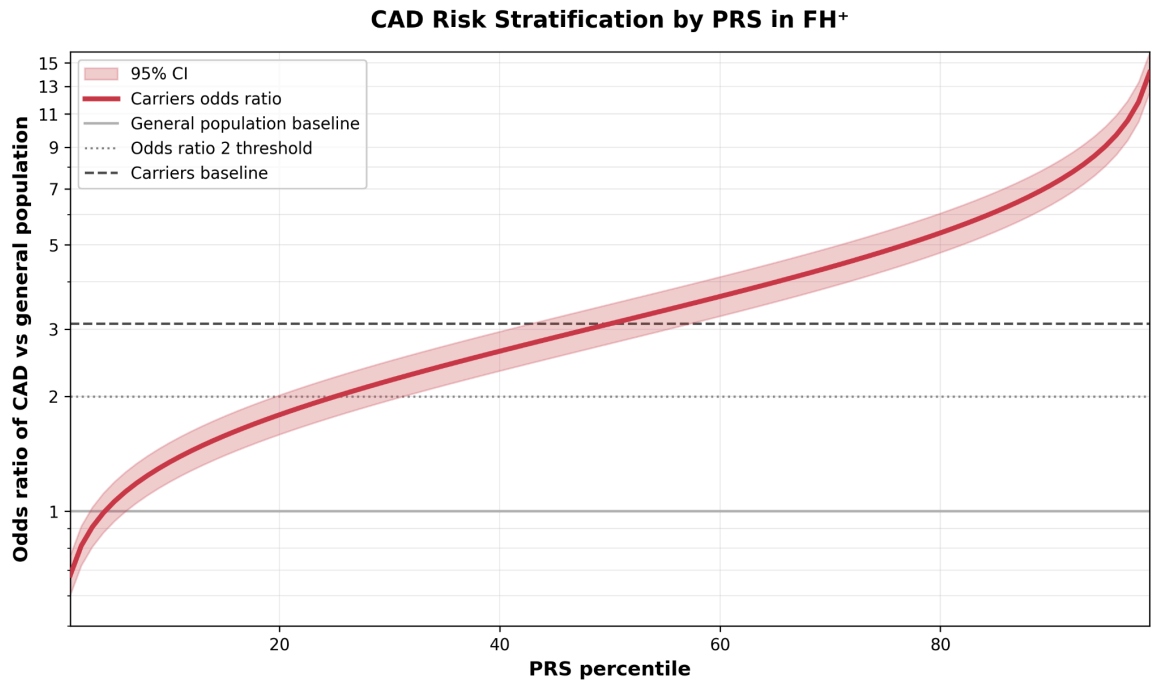

Figure 1. PRS stratifies CAD risk among FH⁺ carriers, revealing that those in the lowest PRS percentiles have risk below the general population average, while those in the top percentiles exceed an odds ratio of 10.

Finally, we evaluated the calibration of the model to ensure that predicted risks accurately reflected the observed incidence of CAD among FH⁺ carriers (Figure 2). The strong alignment

between predicted and observed odds ratio confirms that the PRS captures the quantitative gradient of disease risk without systematic inflation or attenuation, supporting the clinical reliability of PRS-informed risk prediction in FH.

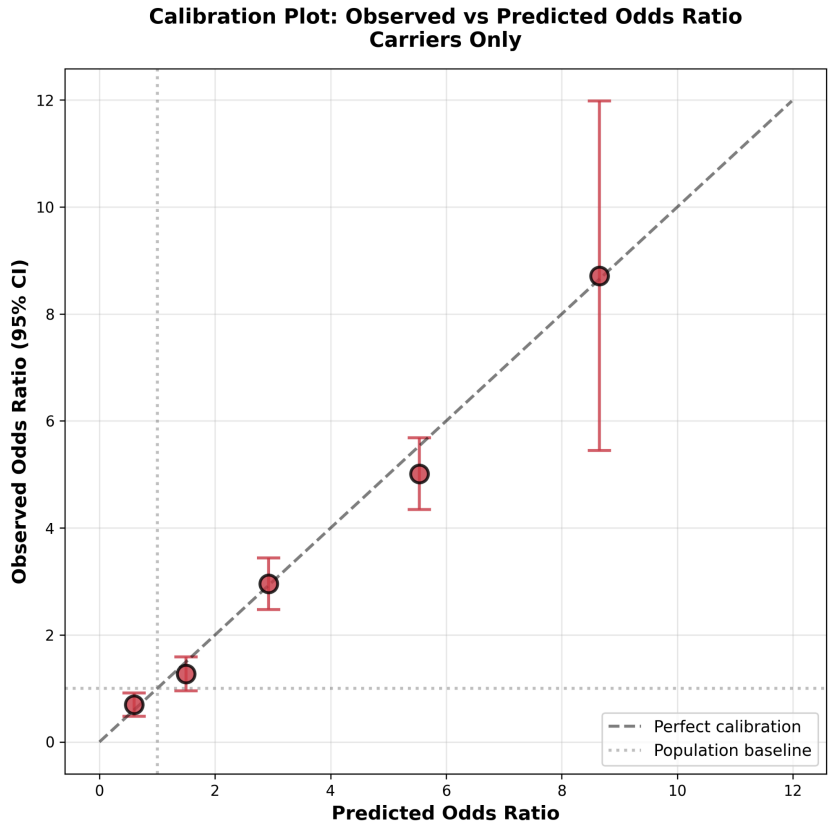

Figure 2. *Calibration of PRS-based risk prediction among FH⁺ carriers.*

Each point represents the observed odds ratio of CAD across bins of predicted odds ratio. The dashed line indicates perfect calibration. The close alignment of points and confidence intervals along the diagonal shows that the model's predictions closely match observed outcomes, confirming accurate quantitative calibration of PRS-derived risk in FH⁺ carriers.

Conclusion

These findings demonstrate that integrating polygenic risk with monogenic FH status transforms risk prediction from categorical to quantitative, uncovering a spectrum of coronary risk that conventional genetic diagnosis alone cannot resolve. Among FH^{+} carriers, PRS identifies 6% of individuals whose risk approximates or even falls below that of the general population, and roughly one-quarter whose risk remains under the odds ratio of 2 risk threshold. Conversely, others exceed an odds ratio of 10. This stratification has immediate clinical implications: it enables precision management of FH carriers by distinguishing those who may benefit most from intensive preventive therapy from those for whom standard lipid-lowering approaches may be sufficient. Integrating PRS into FH screening thus redefines clinical risk assessment, moving from gene-based identification to individualized cardiovascular prevention.