

Diversity is key for cross-ancestry transferability of glaucoma genetic risk scores in Hispanic Veterans in the Million Veteran Program

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A major goal of precision medicine is to stratify patients based on their genetic risk for a disease to inform future screening and intervention strategies. For conditions like primary open-angle glaucoma (POAG), the genetic risk architecture is complicated with multiple variants contributing small effects on risk. Following the tepid success of genome-wide association studies for high-effect disease risk variant discovery, genetic risk scores (GRS), which collate effects from multiple genetic variants into a single measure, have shown promise for disease risk stratification. We assessed the application of GRS for POAG risk stratification in Hispanic-descent (HIS) and European-descent (EUR) Veterans in the Million Veteran Program. Unweighted and cross-ancestry meta-weighted GRS were calculated based on 127 genomic variants identified in the most recent report of cross-ancestry POAG meta-analyses. We found that both GRS types were associated with POAG case-control status and performed similarly in HIS and EUR Veterans. This trend was also seen in our subset analysis of HIS Veterans with less than 50% EUR global genetic ancestry. Our findings highlight the importance of evaluating GRS based on known POAG risk variants in different ancestry groups and emphasize the need for more multi-ancestry POAG genetic studies.

Keywords: Genetic risk score, primary open-angle glaucoma, ancestral diversity

1. Introduction

Primary open-angle glaucoma (POAG) is the leading cause of irreversible blindness globally (1,2). To mitigate severe POAG outcomes, early intervention is essential (3). POAG is a complex disease with a substantial genetic component (4,5). Comprehensively evaluating individual genetic profiles via genetic risk scores (GRS) may enable POAG risk stratification (6). Specifically, in the era of precision medicine, it is possible that individuals with high genetic risk for developing POAG and experiencing more aggressive disease course could be eligible for earlier and more frequent comprehensive eye examinations and be prioritized for early intervention.

While showing promising clinical utility for diseases with complex disease etiology, GRS are not without limitations (7–9). Historically, studies that inform which variants are included in GRS have been predominantly performed on data from individuals of European descent (EUR), regardless of whether disease burden is highest in EUR or other ancestries (10). GRS also lack cross-ancestry generalizability (9). Although POAG burden is higher in Hispanic (HIS) and African-descent (AFR) individuals (11), most POAG genetic studies have been reported in EUR individuals. Additionally, HIS individuals have a high degree of genetic admixture shaped by Native American, EUR, and AFR ancestries (12), which presents a possible limitation for the clinical use of GRS. We previously found that performance of a POAG GRS was significantly diminished in AFR Veterans compared to EUR Veterans in the Million Veteran Program (MVP) (13). To overcome limitations of contemporary GRS, representation of ancestral diversity in genetic studies must increase. The most recent genome-wide POAG analysis was a cross-ancestry meta-analysis of over 34,000 cases and nearly 350,000 controls that identified 127 POAG-associated loci (14). While this dataset predominantly included EUR individuals, it also included individuals of Asian and African descent (14), representing an important step towards increasing ancestral diversity in POAG genetic studies.

Large-scale, multi-ancestry biobanks linked to electronic health records (EHR) offer another way to increase diversity in genetic studies. We accessed the MVP, which is an ongoing US-based observational research program and mega-biobank funded by the Department of Veterans Affairs (VA) Office of Research and Development (15). To date, over 800,000 Veterans with linked genetic, EHR, health survey, and other clinical data have been enrolled in the MVP (15,16). Representation of diverse ancestral populations (16) is prominent in the MVP; about 29% of participants are from ancestries that have been historically underrepresented in genetic studies, including HIS (16).

In this study, we sought to assess the cross-ancestry transferability of a POAG GRS in HIS and EUR Veterans in the MVP. Among POAG cases and controls in the MVP, we calculated GRS based on 127 variants identified in the 2021 cross-ancestry POAG meta-analysis (14). Finally, we evaluated the GRS performance for POAG case classification in HIS and EUR Veterans.

2. Methods

2.1. Study demographics

We classified POAG cases and controls with a previously published algorithm developed in the VA (17) and applied to the MVP as previously described (13). Ancestry groups were defined using the Harmonized Ancestry and Race/Ethnicity (HARE) algorithm (18), which classifies an individual's

HARE group based on the correspondence of their self-identified race/ethnicity and genetically inferred ancestry.

2.2. *GRS calculations and association tests*

We calculated 127-variant GRS for HIS and EUR Veterans in the MVP. GRS were either unweighted or weighted by published cross-ancestry effect estimates (14) as shown in Equations 1 and 2, respectively. Risk alleles were defined by having odds ratios greater than 1 in the cross-ancestry analysis (14).

$$GRS_{unweighted(i)} = \sum_{j=1}^k M_{ij} \quad (1)$$

where M = risk allele dosage, i = individual, k = 127 variants

$$GRS_{weighted(i)} = \sum_{j=1}^k \beta_j M_{ij} \quad (2)$$

where M = risk allele dosage, i = individual, k = 127 variants, $\beta = \log(\text{odds ratio})$

We tested for association between the GRS and POAG via logistic regression-based analyses using unadjusted models as well as models adjusting for age, sex, and 10 sample-specific principal components (PCs).

2.3. *GRS performance for POAG risk stratification in the MVP*

We compared POAG case classification across GRS deciles and evaluated GRS model performance with area under the curve (AUC) estimates from receiver operating characteristic (ROC) curves, as previously described (13). To elucidate the contributions of each model variable, we estimated the proportion of POAG variance explained by: (i) age, (ii) age and sex, (iii) age, sex, and 10 PCs, and (iv) age, sex, 10 PCs, and each GRS (unweighted and weighted). Coefficients of determination (R^2) were calculated on the observed scale (Nagelkerke's) and the liability scale using a fixed disease prevalence of 2.4% (19) as well as increases in R^2 with the addition of each variable to the model.

2.4. *Subset analyses based on global genetic ancestry*

HIS Veterans are more genetically admixed than EUR Veterans (18); thus, we evaluated GRS performance in a subset of HIS Veterans with less than 50% EUR global genetic ancestry (GGA) as determined via the ADMIXTURE software program (20). We compared these subset results to the full MVP HIS POAG case-control dataset.

3. Results

3.1. *POAG cases and controls in the MVP*

Applying the above-described phenotype and ancestry group definitions to the MVP, our dataset included 3,347 HIS Veterans (382 cases; 2,965 controls) and 62,193 EUR Veterans (3,382 cases; 58,811 controls) (Table 1). Nearly all the study participants were male (Table 1). Among EUR Veterans, 96.48% of POAG cases and 97.76% of controls were male ($p < 0.05$; Table 1); whereas,

among HIS Veterans, 97.12% of POAG cases and 98.01% of controls were male ($p > 0.05$; Table 1). Although the average ages of EUR POAG cases and controls were not significantly different, HIS POAG cases were about 2 years younger, on average, than HIS controls ($p < 0.05$; Table 1).

Table 1. POAG case-control demographics in the MVP. The p -values shown were from Welch's t-test for age and chi-square test for sex. SD: Standard deviation.

	HIS				EUR			
	Cases	Controls	Total	p -value	Cases	Controls	Total	p -value
N (% total)	382 (11.41)	2,965 (88.59)	3,347 (100)		3,382 (5.44)	58,811 (94.56)	62,193 (100)	
Age (SD)	70.24 (9.70)	72.16 (7.23)	71.94 (7.57)	0.0002	73.32 (9.55)	73.11 (7.3)	73.12 (7.44)	0.2021
N Males (% total)	371 (97.12)	2,906 (98.01)	3,277 (97.91)	0.3402	3,263 (96.48)	57,496 (97.76)	60,759 (97.69)	1.8×10^{-6}

3.2. GRS calculations and association tests

We detected association between the 127-variant GRS and POAG case-control status in HIS and EUR Veterans in the MVP. Unweighted and weighted GRS were significantly associated with POAG status in both EUR and HIS Veterans ($p < 0.05$) (Table 2). Although effect estimates were comparable between both datasets for each GRS type, the association signals were more pronounced in the analyses of EUR Veterans compared to HIS Veterans (Table 2).

Table 2. Association test results for unadjusted and adjusted models for unweighted and weighted GRS in HIS and EUR Veterans in the MVP. Effect estimates are calculated as log(odds ratio) for a 1 standard deviation increase in the GRS.

Population	Model	GRS Type	Effect Estimate	Standard Error	z value	p -value
HIS	Unadjusted	Unweighted	0.55	0.057	9.56	1.18×10^{-21}
		Weighted	0.61	0.058	10.54	5.37×10^{-26}
	Adjusted	Unweighted	0.54	0.059	9.20	3.54×10^{-20}
		Weighted	0.61	0.060	10.16	3.13×10^{-24}
EUR	Unadjusted	Unweighted	0.56	0.018	30.63	5.65×10^{-206}
		Weighted	0.61	0.018	34.43	7.62×10^{-260}
	Adjusted	Unweighted	0.56	0.018	30.64	3.36×10^{-206}
		Weighted	0.61	0.018	34.40	2.28×10^{-259}

3.3. GRS performance for POAG risk stratification in the MVP

POAG case proportions generally increased across GRS deciles for both EUR and HIS Veterans (Figure 1). In the top deciles, a higher proportion of EUR POAG cases were consistently categorized compared to HIS POAG cases (Figure 1).

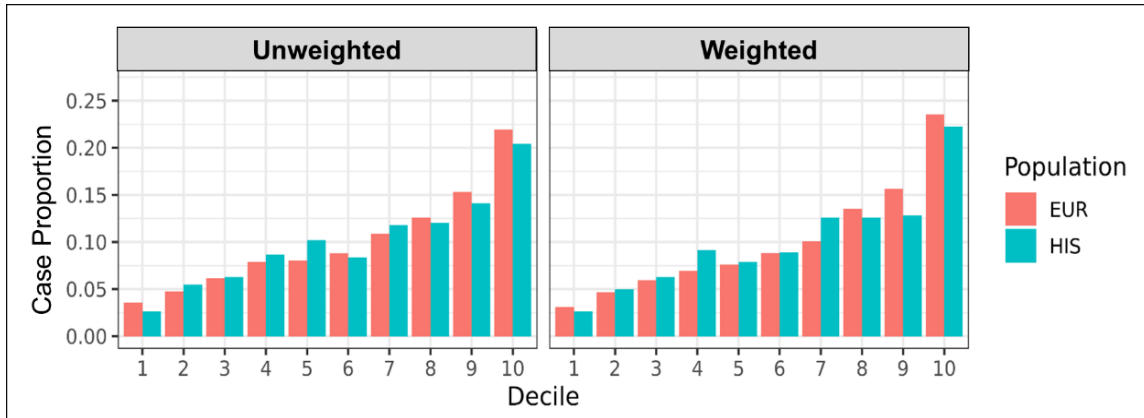


Fig. 1. Case proportions for EUR and HIS Veterans in the MVP for the unweighted and weighted GRS.

For both weighted and unweighted approaches, when we specifically compared the top GRS decile to the bottom 90%, we observed ~3-fold higher odds of POAG case classification for both GRS types in the top decile for both EUR and HIS Veterans (Table 3; Figure 2).

Table 3. Odds ratios (OR) comparing the top GRS decile to bottom 90% in HIS and EUR Veterans.

Population	GRS Type	OR (95% CI)	<i>p</i> -value
HIS	Unweighted	2.70 (2.03-3.56)	3.20 x 10 ⁻¹²
	Weighted	3.11 (2.35-4.07)	4.63 x 10 ⁻¹⁶
EUR	Unweighted	2.74 (2.51-2.98)	2.26 x 10 ⁻¹¹⁶
	Weighted	3.03 (2.78-3.29)	9.05 x 10 ⁻¹⁴⁷

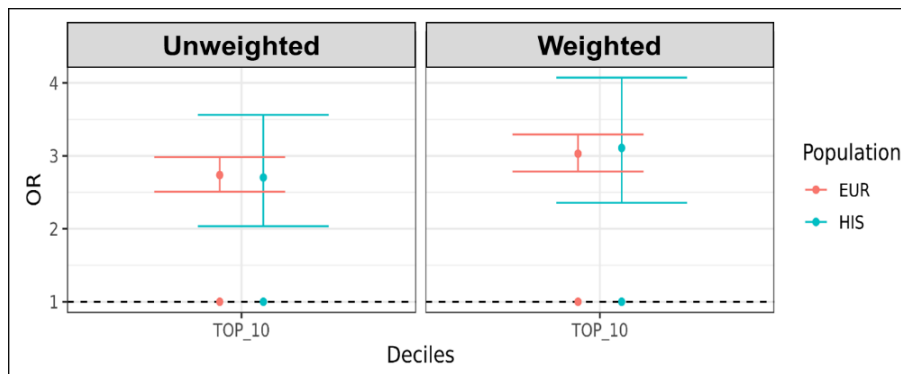


Fig. 2. Comparison of the top GRS decile versus the bottom 90% of the GRS distribution for unweighted and weighted GRS in EUR and HIS Veterans in the MVP.

We found no statistically significant difference in GRS performance based on ROC curve comparisons between HIS and EUR Veterans (AUC range: 0.65-0.69) (Figure 3). This trend was observed for both unadjusted (Figure 3A) and adjusted models (Figure 3B).

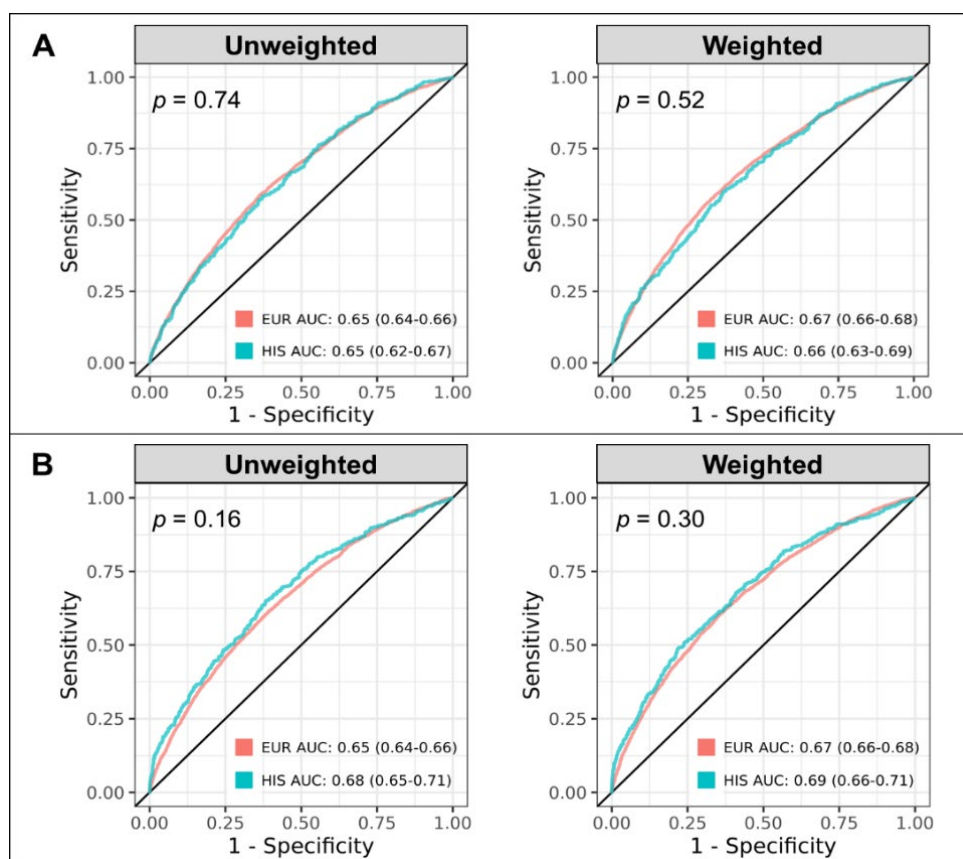


Fig. 3. ROC curve comparisons for (A) unadjusted and (B) adjusted models for unweighted and weighted GRS in HIS and EUR Veterans in the MVP. The p -values shown were calculated from DeLong's comparison of ROC curves.

3.4. Proportion of variance explained by model variables

We found that coefficients of determination (R^2) on the observed (Nagelkerke's) and liability scales were less than 0.1 for all the model variable combinations that we evaluated in our adjusted analyses (Table 4). Covariates alone (age, sex, and 10 PCs) explained a higher proportion of POAG variance in HIS Veterans (Nagelkerke's $R^2 = 0.034$; liability $R^2 = 0.030$) than in EUR Veterans (Nagelkerke's $R^2 = 0.002$; liability $R^2 = 0.0023$) (Table 4). Adding the GRS (unweighted and weighted) to the model resulted in similar increases in R^2 in HIS and EUR Veterans (Table 4).

Table 4. Coefficients of determination (R^2) on the observed scale (Nagelkerke's) and the liability scale for model variables in our adjusted GRS models for HIS and EUR Veterans in the MVP.

Model Variables	HIS		EUR	
	Nagelkerke's R^2 (Observed Scale)	Liability R^2	Nagelkerke's R^2 (Observed Scale)	Liability R^2
Age	0.013	0.012	0.0001	0.0001
Age+Sex	0.014	0.012	0.0011	0.0013
Age+Sex+10PCs	0.034	0.030	0.0020	0.0023
Age+Sex+10PCs+Unweighted GRS	0.085	0.076	0.047	0.054
Age+Sex+10PCs+Weighted GRS	0.096	0.086	0.058	0.067
R^2 Increase				
Unweighted GRS	0.051	0.046	0.045	0.052
Weighted GRS	0.062	0.056	0.056	0.065

3.5. Subset analyses based on global genetic ancestry

Among the 382 HIS POAG cases and 2,965 HIS controls in the MVP, a subset (220 POAG cases and 1,486 controls) had less than 50% EUR GGA (Figure 4). On average, cases in the GGA-based HIS subset were about 70 years old, while controls were about 72 years old ($p = 0.0018$). ROC curves for the GGA-based subset were comparable to those for the full HIS POAG case-control dataset (Table 5).

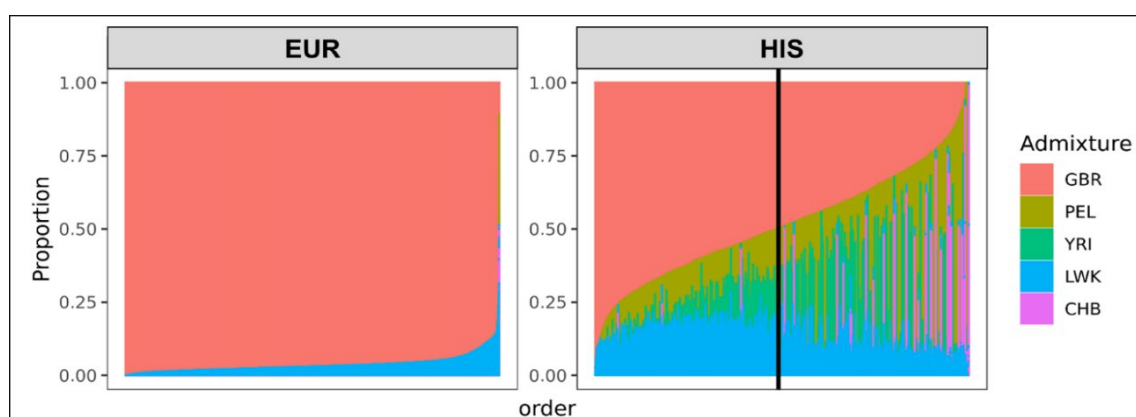


Fig. 4. Admixture proportions for EUR and HIS Veterans in the MVP. Five-way admixture was computed with ADMIXTURE using five 1000 Genomes reference groups (GBR: British in England and Scotland; PEL: Peruvian in Lima, Peru; YRI: Yoruba in Ibadan, Nigeria; LWK: Luhya in Webuye, Kenya; CHB: Han Chinese in Beijing, China). The vertical black line denotes 50% GBR; HIS Veterans to the right of the line were included in the subset analyses.

Table 5. Comparison of ROC curves for full HIS case-control dataset and GGA-based HIS subset.

GRS Type	Area Under the Curve (95% CI)		DeLong's Comparison of ROC curves
	HIS	HIS Subset	p -value
Unweighted	0.65 (0.62-0.67)	0.63 (0.59-0.67)	0.61
Weighted	0.66 (0.63-0.69)	0.65 (0.61-0.69)	0.84

4. Discussion

In this study, we confirmed that GRS based on 127 POAG risk variants identified through cross-ancestry meta-analysis performed similarly in HIS and EUR Veterans in the MVP. We also observed this trend in our subset analyses based on GGA. However, it is important to note that across the highest GRS deciles, a higher proportion of EUR POAG cases were categorized compared to HIS POAG cases in the MVP. This emphasizes the need for more inclusive POAG genetics studies to improve the development of equitable risk prediction models based on genetic data.

The genetic etiology of POAG is complex with heritability estimates from twin studies and GWAS ranging from 0.26 to 0.93 (21–27). To date, over 125 genomic variants have been implicated in the genetic architecture of POAG, but these individual variants only moderately influence disease risk and only account for about 10% of the additive genetic variance of POAG (5,14). Rather than investigating single genetic variant associations, we performed logistic regression-based association analyses on unweighted and weighted GRS in HIS and EUR Veterans and found that both GRS types strongly associated with POAG case-control status in these groups (Table 2). However, when we examined the proportion of POAG variance explained by model variables, we observed varied effects of the addition of covariates alone compared to the combination of covariates and GRS in HIS and EUR Veterans (Table 4). This trend was also observed in our prior study, where covariates were more informative for POAG variance in AFR Veterans while GRS were more informative for EUR Veterans in the MVP (13). We hypothesize that this could be partially explained by the significant difference in the average ages of the AFR (13) and HIS POAG cases and controls (Table 1). Additionally, while the variants included in the 127-variant GRS were identified from a cross-ancestry meta-analysis (14), the variants may still be more informative for EUR individuals than individuals of other ancestries due to the high proportion of EUR individuals included in that study.

Based on our ROC curve comparisons and case classification evaluations, the performance of the 127-variant GRS was not significantly different between HIS and EUR Veterans (Figures 1 and 3). This is in stark contrast to our prior work, which found that GRS performance was significantly reduced when applied to AFR Veterans compared to EUR Veterans (13). Similar trends have been observed in the application of polygenic risk scores (PRS) for coronary heart disease in EUR, HIS, and AFR individuals (28,29) as well as for breast cancer in HIS individuals with varying proportions of EUR and Native American ancestry (30). It was hypothesized that the similar PRS performance in HIS and EUR individuals was attributable to the masking of the breadth of diversity in the HIS group (31), which is more genetically admixed (32). To interrogate this in our study, we evaluated GRS performance in a subset of HIS Veterans with less than 50% EUR GGA and did not detect a significant difference between the full and subset analyses (Table 5). Because AFR and HIS Veterans have a higher admixture proportion than EUR Veterans in the MVP (18), future work should consider the contributions of local genetic ancestry in POAG GRS performance.

While this study describes the application of GRS to a large multi-ancestry POAG case-control dataset, it has limitations. Nearly all the MVP-enrolled Veterans in this study were male due to demographic trends in the US military (15). While previous studies have estimated higher POAG prevalence in males than females (19), future work should evaluate GRS performance in a sex-balanced dataset to ensure that their application is equitable. Also, although this study examined

GRS in both EUR and HIS Veterans, there are substantially more EUR Veterans than HIS Veterans in our analyses. We also limited our GRS to 127 risk variants identified in the largest-to-date multi-ancestry POAG GWAS (14), and we were unable to assess GRS weighted by ancestry-specific effect estimates because the previously published meta-analysis did not include HIS individuals (14). Future studies examining a larger portion of the genetic architecture of POAG in multi-ancestry datasets should be prioritized to facilitate the construction of more informative GRS.

In summary, based on our knowledge of the current GRS limitations (e.g., dearth of diversity in GWAS and lack of transferability of GRS across different ancestries) and what we learned from this study, it is clear that POAG genomics studies need to increase the inclusion of diverse ancestral groups, especially those who have been historically underrepresented in research. This will hopefully improve understanding of the complex genetic architecture of POAG and ensure that GRS can be equitably introduced to the clinic for POAG risk stratification, especially for HIS and AFR individuals for whom POAG burden is higher.

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