

Introduction

Myopia, or near-sightedness, is the major form of refractive error. The myopia prevalence drastically rose within the last century. Till 2010 it has been the second leading cause of blindness worldwide, and the global prevalence estimated to be up to 49.8% in 2050. Human ancestors lived under abundant direct sunshine regions (2400–4000 hour/year in Africa), and more time spent outdoors and stronger lighting intensity have been proven to inhibit myopia development. From the evolutionary aspect, sunshine duration might be associated with myopia prevalence and left some trace within the genomes. Since sunshine duration is associated with latitude, and Europe has the most diversity of sunshine duration across the continent, it is suitable for the study. This study compared myopia genetic risk among 4 European cohorts using polygenetic risk score (PRS).

Methods

PRS calculates the weighted sum of effect alleles associated to the trait of interest for an individual, and the associated alleles and corresponding effect sizes are obtained by Genome-wide association study (GWAS). The current study applied previous European myopia GWAS (N=276,065) summary statistics for PRS calculation. The best-fit P -value threshold was estimated by PRS and PCA covariance analysis, and comparison of scored variants in PRS among cohorts using $\Sigma\beta \times \text{MAF}$ based on transformation of PRS formula.

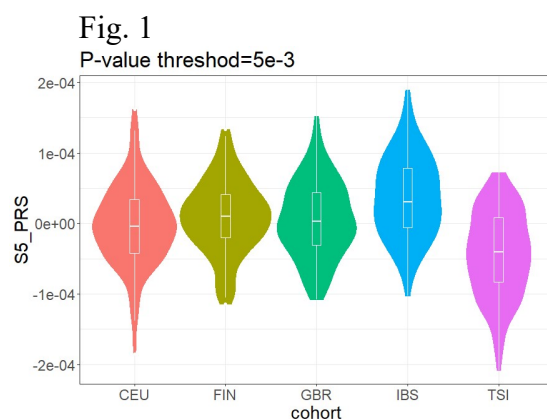
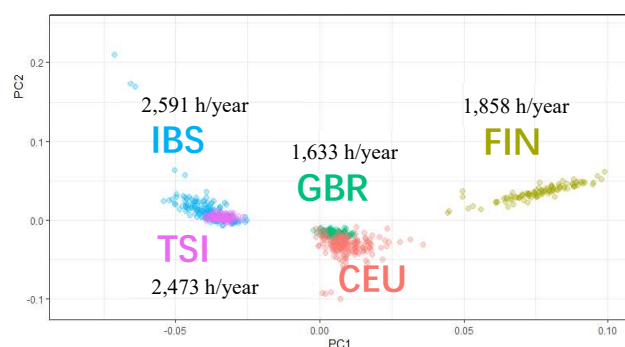


Fig. 2



Results

Five of eight sets of PRSs at different P value thresholds (PT) showing Iberian in Spain (IBS) ranking top and Tosicani in Italy (TSI) ranking the bottom. Finnish (FIN)

and British (GBR) are randomly in the between, and Utah residence (CEU) is as control (Fig. 1). The minus PRS stands for towards more myopic and plus PRS stands for away from being myopic. This pattern is neither in accordance with the general genetic distance among the four cohorts nor with the sunshine duration distribution (Fig. 2). At the best-fit $PT = 5 \times 10^{-3}$, 30,765 variants of the four cohorts were taken into PRS scoring, among which 5,696 variants are mutual, and 2,243 variants are non-overlapped. By comparing the aggregate effect size and variant frequencies, it was the non-overlapped variants driven the unexpected result. Thirty-two unique variants (Minor allele frequency $\leq 1\%$ in at least one cohort) were further identified, while only 3 have distinct frequency difference. The frequencies showed a highly geographic predisposition (Table 1).

Table 1

		rs2844567	rs1053046	rs17086731	Latitude and longitude
<i>Northern Europe</i>	FIN	1.00%	1.00%	1.00%	60°~70° N, 25°~30° E
	Estonian	3.06%	1.85%	4.02%	58°~60° N, 25° E
	Northern Sweden	2.70%	1.30%	6.20%	60°~70° N, 15°~20° E
<i>Western Europe</i>	GBR	8.65%	0.48%	7.21%	51°~59° N, 0°~10° W
	UK10K twins	7.96%	4.94%	7.28%	51°~59° N, 0°~6° W
<i>Southern Europe</i>	IBS	22.00%	11.33%	9.06%	36°~44° N, 0°~8° W
	TSI	8.93%	7.80%	14.29%	37°~46° N, 7°~18° E
<i>Middle East</i>	Qatari	22.20%	16.70%	9.70%	25°~26° N, 51°~52° E
	1000 genomes African	17.17%	49.85%	11.80%	20° N ~ 20° S, 20° W ~ 40° E
	1000 genomes European	10.14%	5.07%	8.05%	-

Discussion

The current study revealed myopia-associated variants vary across European populations and the mutual variant ratio is no more than 60% among the four cohorts. Northern Europeans (FIN) were expected to show being less susceptible to myopia, for whom had living under less sunshine for thousands of years, there could be traces of adaptation to weak-light environment in their genomes. However, the current study did not find a strong correlation between PRS and latitudes among the four European cohorts. The effect size and frequency distribution of myopia-associated variants indicates that myopia was under weak or absence of selective pressure in Europeans. Despite the close relationship in both geography and genome of IBS and TSI, the peculiar PRS order might be induced by this absent selective pressure and gene flow across adjacent continents. The complexity of polygenic traits calls for data with more diversity and depth in the future.