

Evaluation of Shared Genetic Susceptibility to High and Low Myopia and Hyperopia

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IMPORTANCE Uncertainty currently exists about whether the same genetic variants are associated with susceptibility to low myopia (LM) and high myopia (HM) and to myopia and hyperopia. Addressing this question is fundamental to understanding the genetics of refractive error and has clinical relevance for genotype-based prediction of children at risk for HM and for identification of new therapeutic targets.

OBJECTIVE To assess whether a common set of genetic variants are associated with susceptibility to HM, LM, and hyperopia.

DESIGN, SETTING, AND PARTICIPANTS This genetic association study assessed unrelated UK Biobank participants 40 to 69 years of age of European and Asian ancestry. Participants 40 to 69 years of age living in the United Kingdom were recruited from January 1, 2006, to October 31, 2010. Of the total sample of 502 682 participants, 117 279 (23.3%) underwent an ophthalmic assessment. Data analysis was performed from December 12, 2019, to June 23, 2020.

EXPOSURES Four refractive error groups were defined: HM, -6.00 diopters (D) or less; LM, -3.00 to -1.00 D; hyperopia, $+2.00$ D or greater; and emmetropia, 0.00 to $+1.00$ D. Four genome-wide association study (GWAS) analyses were performed in participants of European ancestry: (1) HM vs emmetropia, (2) LM vs emmetropia, (3) hyperopia vs emmetropia, and (4) LM vs hyperopia. Polygenic risk scores were generated from GWAS summary statistics, yielding 4 sets of polygenic risk scores. Performance was assessed in independent replication samples of European and Asian ancestry.

MAIN OUTCOMES AND MEASURES Odds ratios (ORs) of polygenic risk scores in replication samples.

RESULTS A total of 51 841 unrelated individuals of European ancestry and 2165 unrelated individuals of Asian ancestry were assigned to a specific refractive error group and included in our analyses. Polygenic risk scores derived from all 4 GWAS analyses were predictive of all categories of refractive error in both European and Asian replication samples. For example, the polygenic risk score derived from the HM vs emmetropia GWAS was predictive in the European sample of HM vs emmetropia (OR, 1.58; 95% CI, 1.41-1.77; $P = 1.54 \times 10^{-15}$) as well as LM vs emmetropia (OR, 1.15; 95% CI, 1.07-1.23; $P = 8.14 \times 10^{-5}$), hyperopia vs emmetropia (OR, 0.83; 95% CI, 0.77-0.89; $P = 4.18 \times 10^{-7}$), and LM vs hyperopia (OR, 1.45; 95% CI, 1.33-1.59; $P = 1.43 \times 10^{-16}$).

CONCLUSIONS AND RELEVANCE Genetic risk variants were shared across HM, LM, and hyperopia and across European and Asian samples. Individuals with HM inherited a higher number of variants from among the same set of myopia-predisposing alleles and not different risk alleles compared with individuals with LM. These findings suggest that treatment interventions targeting common genetic risk variants associated with refractive error could be effective against both LM and HM.

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Refractive errors are associated with adverse effects, including amblyopia, strabismus, retinal detachment, and myopic maculopathy.¹⁻³ Myopia is an increasingly common cause of visual impairment and blindness, especially in East and Southeast Asia.⁴ The rapid increase in myopia prevalence has occurred too quickly to be explained by positive selection of myopia-predisposing risk alleles. Thus, this increased prevalence is likely associated most with lifestyle exposures; the strongest support to date is for insufficient time spent outdoors and additional years of education (which may include insufficient time outdoors and/or greater levels of near work).⁵⁻⁹ Nevertheless, the high heritability of refractive error underscores an important genetic contribution.¹⁰⁻¹³ A parsimonious explanation for these findings is that genetic risk factors confer susceptibility to the effects of lifestyle risk factors for myopia.¹³⁻¹⁵

Clinical studies often classify refractive error by severity (eg, low myopia [LM], moderate myopia, and high myopia [HM]). Coupled with the discovery of rare genetic variants that cause monogenic HM or high hyperopia, these studies¹⁶⁻²⁰ have led some researchers to assume that the genetic risk for each category of refractive error is distinct. The aim of the current study was to evaluate the extent to which common genetic risk variants are shared across refractive error categories. Past evidence led us to hypothesize that risk variants are shared across refractive error categories.^{13,14,21}

Methods

Participants and Phenotypes

UK Biobank is a prospective cohort study that investigates genetic and lifestyle influences on well-being and disease.²² Participants 40 to 69 years of age living in the United Kingdom were recruited from January 1, 2006, to October 31, 2010. Data analysis was performed from December 12, 2019, to June 23, 2020. All participants provided written informed consent. All data were deidentified. Ethical approval was obtained from the National Health Service Research Ethics Committee. This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline.

Of the total sample of 502 682 participants, 117 279 (23.3%) underwent an ophthalmic assessment.²³ Noncycloplegic autorefraction (Tomey RC 5000; Tomey Corp) readings were averaged, and mean spherical equivalent (MSE) refractive error was calculated as sphere power plus half the cylinder power. MSE was averaged between fellow eyes. Refractive error categories were defined with a separation of at least 0.75 diopters (D) between groups to reduce misclassification: HM, -6.00 D or less; LM, -3.00 to -1.00 D; hyperopia, $+2.00$ D or greater; and emmetropia, 0.00 to $+1.00$ D.

Participant selection is described in the eMethods in Supplement 1. Briefly, 51 841 participants of European genetic ancestry met the inclusion criteria. A random sample of approximately 10% of participants within each refractive error group were assigned as European ancestry replication samples, whereas the remaining 90% were assigned as European ancestry discovery samples. A total of 2165 participants

Key Points

Question Is susceptibility to high and low myopia and hyperopia associated with a common set of genetic variants or with different sets of variants for each refractive error category?

Findings In this genetic association study of 54 006 individuals, polygenic risk scores derived from a genome-wide association study for high myopia were predictive of high and low myopia and hyperopia. Polygenic risk scores from a genome-wide association study for hyperopia were predictive of high and low myopia.

Meaning These results support a single set of common genetic variants being associated with susceptibility to high myopia, low myopia, and hyperopia (in addition to rare mutations for monogenic high myopia or high hyperopia, already known to exist).

of Asian ancestry met the inclusion criteria (1921 who self-reported their ethnicity as Asian and 244 as Chinese). These participants were assigned as the Asian ancestry replication samples. (Because of limited numbers of individuals of Asian ancestry, we did not create an Asian ancestry discovery sample.)

GWAS and Creation of Polygenic Risk Scores

Four genome-wide association study (GWAS) analyses were performed for the European ancestry discovery samples: (1) GWAS for HM vs emmetropia, comprising 3164 HM cases and 21 416 emmetropia controls; (2) GWAS for LM vs emmetropia, comprising 11 197 LM cases and 21 416 emmetropia controls; (3) GWAS for hyperopia vs emmetropia, comprising 10 828 hyperopia cases and 21 416 emmetropia controls; and (4) GWAS for LM vs hyperopia, comprising 11 197 LM cases and 10 828 hyperopia controls. Single-marker tests were performed with Firth logistic regression, a penalized likelihood-based method for binary traits robust to unbalanced case-control ratios even for markers with low minor allele frequency, implemented in PLINK, version 2.0.^{24,25} A total of 13 958 389 biallelic markers with a minor allele frequency greater than 0.1% and imputation quality metric greater than 0.6 were tested. Age, age squared, sex, a binary indicator of genotyping array, and the first 10 ancestry principal components were included as covariates. Genetic variants independently associated with the phenotype were identified by clumping and thresholding to remove variants within 500 kb and in linkage disequilibrium $r^2 \geq 0.1$ with the lead variant in each region. Independently associated variants were then selected as meeting a series of increasingly stringent P value thresholds: $P < 1 \times 10^{-2}$, $P < 1 \times 10^{-3}$, $P < 1 \times 10^{-4}$, $P < 1 \times 10^{-5}$, $P < 1 \times 10^{-6}$, $P < 1 \times 10^{-7}$, and $P < 1 \times 10^{-8}$. Clumped GWAS summary statistics are presented in Supplement 2.

Predictive Performance of Polygenic Risk Scores

Individuals in the 4 European ancestry replication samples were assigned a total of 28 polygenic risk scores (4 GWAS analyses \times 7 P value clumping thresholds). A polygenic risk score is the cumulative sum of the number of risk alleles of a variant carried by a person multiplied by a weighting factor.²⁶ Here,

Table. Number of Markers Included in Each Polygenic Risk Score

P value threshold	No. of genetic variants included in polygenic risk score			
	GWAS for HM vs emmetropia	GWAS for LM vs emmetropia	GWAS for hyperopia vs emmetropia	GWAS for LM vs hyperopia
1×10^{-2}	38 512	35 490	36 345	38 354
1×10^{-3}	5635	4048	4264	4690
1×10^{-4}	884	471	525	653
1×10^{-5}	164	67	81	156
1×10^{-6}	45	15	26	67
1×10^{-7}	17	8	14	31
1×10^{-8}	11	4	9	22

Abbreviations: GWAS, genome-wide association study; HM, high myopia; LM, low myopia.

the log odds ratio (OR) for variants in the GWAS analyses described above in the GWAS and Creation of Polygenic Risk Scores section were used as weighting factors. The Table lists the number of genetic variants that contribute to each polygenic risk score. For each of the 28 polygenic risk scores, a logistic regression analysis (R, version 3.6.3 [R Foundation for Statistical Computing]) was performed for each of the 4 European ancestry replication samples: (1) 341 HM cases vs 2426 emmetropia controls, (2) 1242 LM cases vs 2426 emmetropia controls, (3) 1227 hyperopia cases vs 2426 emmetropia controls, and (4) 1242 LM cases vs 1227 hyperopia controls. Individuals in the 4 Asian ancestry replication samples were similarly assigned 28 polygenic risk scores, as above, and logistic regression prediction analyses were performed for these Asian ancestry samples: (1) 207 HM cases vs 1219 emmetropia controls, (2) 490 LM cases vs 1219 emmetropia controls, (3) 249 hyperopia cases vs 1219 emmetropia controls, and (4) 490 LM cases vs 249 hyperopia controls. The logistic regression models included the same covariates as in the GWAS analyses. The OR for a 1-SD change in the polygenic risk score in the logistic regression analysis was used as the measure of predictive performance.

In a separate set of analyses, polygenic risk scores were calculated in the European ancestry replication samples as the count of risk alleles (equivalent to setting the weighting factor equal to 1 for all variants). A Spearman correlation was used to perform a 2-sided test for a monotonic trend of increasing or decreasing counts of risk alleles across the HM, LM, emmetropia, and hyperopia groups. A 2-sided $P < .05$ was considered to be statistically significant.

Results

Participants and Phenotypes

A total of 51 841 unrelated individuals of European ancestry and 2165 unrelated individuals of Asian ancestry were assigned to a specific refractive error group and included in our analyses. The numbers of European ancestry participants in each group were as follows: HM, 3505; LM, 12 439; hyperopia, 12 055; and emmetropia, 23 842. The numbers of Asian ancestry participants in each group were as follows: HM, 207; LM, 490; hyperopia, 249; and emmetropia, 1219. This left 43 073 European and 1887 Asian individuals who were not analyzed further because of relatedness or because their refrac-

tive error did not fall within any of the 4 categories. Demographic characteristics of the participants are presented in eTables 1 and 2 and eFigure 1 in Supplement 1.

A total of 46 605 European ancestry participants (90%) selected at random from each refractive error group were assigned as European ancestry discovery samples for the GWAS analyses. The remaining 5236 European ancestry participants (10%), along with the Asian ancestry samples, were used to test the predictive performance of polygenic risk scores.

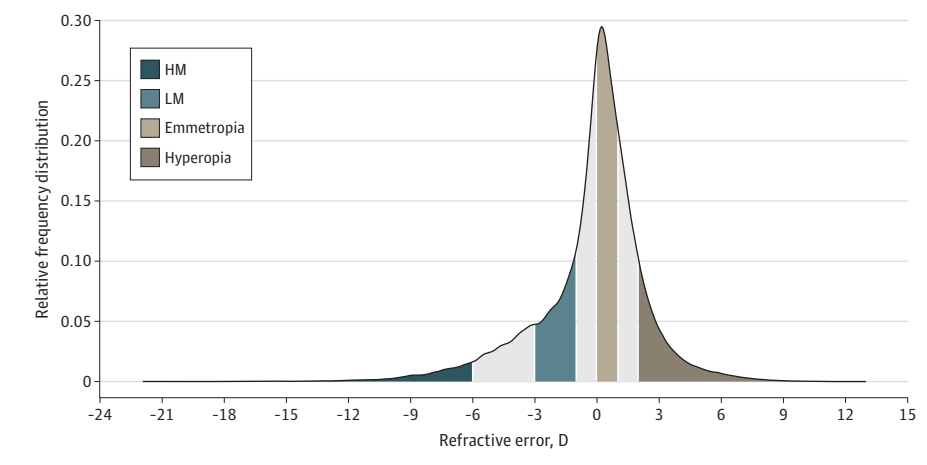
GWASs and Creation of Polygenic Risk Scores

Four GWAS analyses were performed (Figure 1). After P value-based clumping and thresholding, 11 variants met the most stringent threshold of $P < 1 \times 10^{-8}$ in the GWAS for HM vs emmetropia, 4 for LM vs emmetropia, 9 for hyperopia vs emmetropia, and 22 for LM vs hyperopia. Increasing leniency in the choice of P value threshold led to increasing numbers of independently associated variants (Table). The log OR (β) coefficients from the GWAS analyses were used as single-nucleotide variant weights for creating polygenic risk scores. A total of 28 ($4 \times 7 = 28$) polygenic risk scores were created, corresponding to 4 GWAS traits and 7 P value thresholds.

Predictive Performance of Polygenic Risk Scores

The predictive performance of the 28 polygenic risk scores was evaluated in the replication samples. The replication samples were statistically independent of the GWAS samples (ie, the individuals in the replication samples were not included in any of the GWAS analyses and composed of participants unrelated to any person in the GWAS analyses). As shown in Figure 2 and eTable 3 in Supplement 1, most of the 28 polygenic risk scores were effective at predicting all 4 categories of refractive error in the European ancestry replication samples (evident by 95% CIs for prediction that did not overlap with an OR of 1.0). The best performance was for polygenic risk scores derived from the GWAS for LM vs hyperopia. Not only did these polygenic risk scores successfully predict LM vs hyperopia, they also were predictive of HM vs emmetropia, LM vs emmetropia, and hyperopia vs emmetropia. For example, the LM vs hyperopia GWAS polygenic risk score derived using a P value threshold of $P < 1 \times 10^{-5}$ had ORs of 1.83 (95% CI, 1.62-2.06; $P = 2.31 \times 10^{-23}$) for HM vs emmetropia, 1.27 (95% CI, 1.18-1.36; $P = 4.19 \times 10^{-11}$) for LM vs emmetropia, 0.74 (95% CI, 0.68-0.79; $P = 1.16 \times 10^{-15}$) for hyperopia vs emmetropia, and 1.72 (95% CI, 1.57-1.89; $P = 6.90 \times 10^{-31}$) for LM vs

Figure 1. Refractive Groups of European Ancestry Samples



Relative frequency distribution of refractive groups ($n = 94\,914$). Genome-wide association studies (GWAS) were as follows: GWAS 1, high myopia (HM) vs emmetropia; GWAS 2, low myopia (LM) vs emmetropia; GWAS 3, hyperopia vs emmetropia; and GWAS 4, LM vs hyperopia.

hyperopia. There was an approximately linear association between the OR for prediction and the difference in refractive error between groups (Figure 3). Polygenic risk scores derived from the GWAS for HM vs emmetropia and the GWAS for hyperopia vs emmetropia also demonstrated good predictive performance (Figure 2), being predictive of all 4 types of refractive error. However, predictive performance was lower for polygenic risk scores derived from the GWAS for LM vs emmetropia. This GWAS examined the groups with the smallest difference in refractive error (Figure 3 and eTable 1 in Supplement 1) and yielded polygenic risk scores with the lowest number of included variants (Table). However, even this polygenic risk score was effective in predicting comparisons other than LM vs emmetropia (Figure 2).

Predictive performance of the polygenic risk scores was worse in the Asian ancestry replication samples than in European ancestry replication samples (Figure 2 and eTable 4 in Supplement 1). For example, the median OR was 1.24 in the European sample and 1.13 in the Asian sample (after taking the reciprocal of ORs for predicting hyperopia vs emmetropia, such that all ORs were in the same direction, ie, OR >1.0 rather than OR <1.0). Nevertheless, prediction of LM vs emmetropia and LM vs hyperopia in the Asian replication samples was significantly better than chance (95% CI did not overlap with an OR of 1.0 for polygenic risk scores derived from at least 1 of the 7 P value thresholds tested) for polygenic risk scores derived from all 4 GWAS analyses, and for 2 and 3 of the GWAS analyses, respectively, for predicting hyperopia vs emmetropia and HM vs emmetropia (eTable 4 in Supplement 1).

An exploratory analysis was performed to count the number of myopia-predisposing risk alleles carried by participants in the European ancestry replication samples. For allele counts based on the GWAS for HM vs emmetropia, for instance, a decreasing number of risk alleles were being carried across groups (HM greater than LM greater than emmetropia greater than hyperopia) (eFigure 2 and eTable 5 in Supplement 1).

To evaluate the predictive capacity of individual genetic variants across the 3 GWAS analyses for HM vs emmetropia, LM vs emmetropia, and hyperopia vs emmetropia, we se-

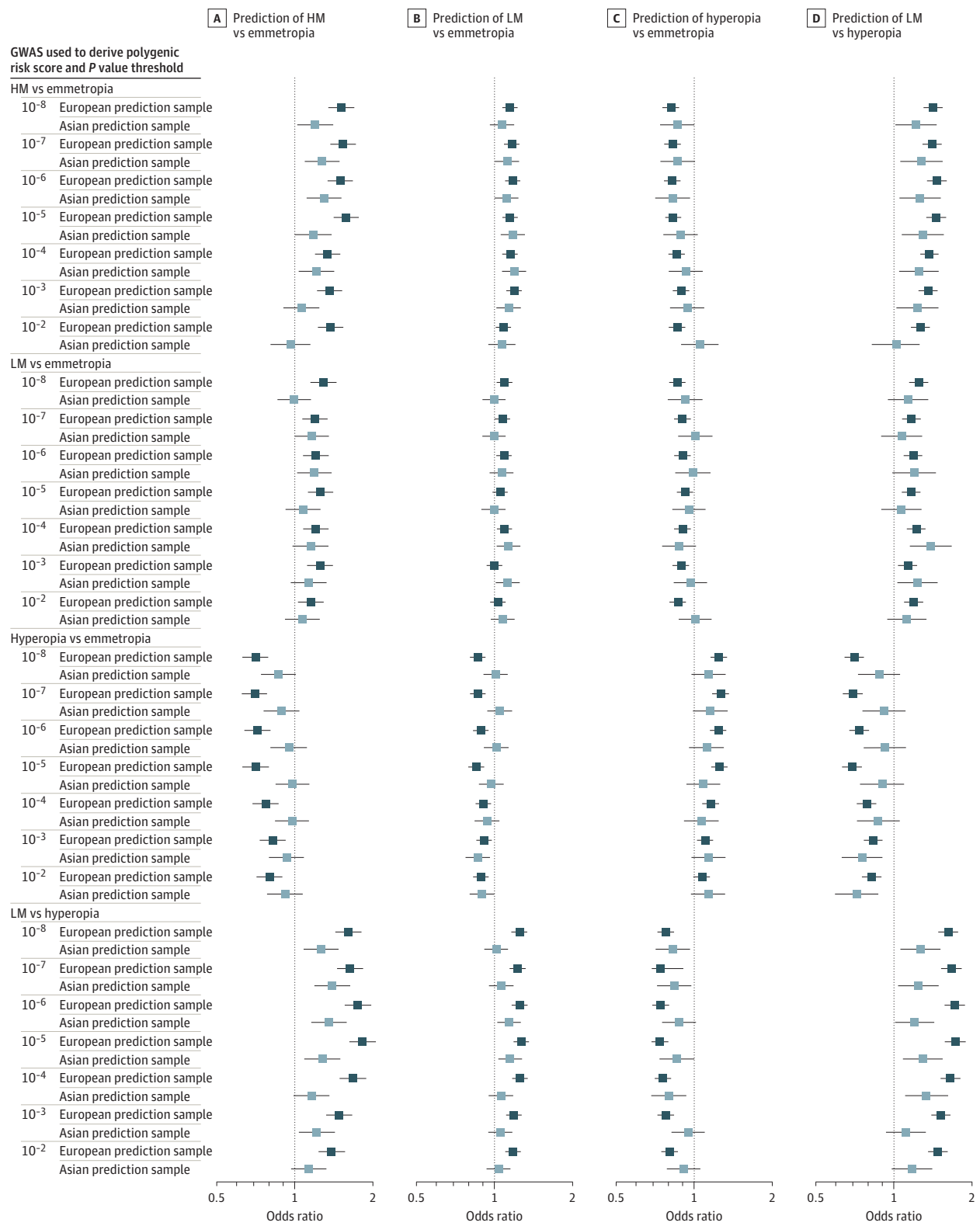
lected variants strongly associated with 1 phenotype (GWAS $P < 1 \times 10^{-5}$) that also displayed some evidence of association with one or both of the other 2 phenotypes (GWAS $P < 1 \times 10^{-2}$). A scatterplot of GWAS effect sizes for these variants demonstrated a high degree of concordance (eFigure 3 in Supplement 1). This concordance constituted evidence that specific individual genetic variants were associated with a shared risk for HM, LM, and hyperopia. In addition, eTable 6 in Supplement 1 provides GWAS summary statistics for individual variants reported by Tedja et al²¹ as genome-wide significantly associated with refractive error.

Discussion

The results of this genetic association study support the concept that susceptibility to ocular refraction is associated with many common variants that act across the distribution of the trait.^{14,21,26,27} For example, as a group, individuals with HM have a higher genetic predisposition to myopia than those with LM, emmetropia, or hyperopia because of the inheritance of a greater number of common myopia risk alleles (especially risk alleles for variants with larger effect sizes). This concept is not new (see, for example, Figure 3 in the article by Tedja et al²¹). However, by demonstrating the efficacy of polygenic risk scores across HM, LM, emmetropia, and hyperopia, the current work provides novel evidence to support this concept.

These findings are consistent, with some individuals having monogenic HM because of a rare genetic variant. However, the fact that, as a group, individuals with HM are enriched for common LM-predisposing variants detected in a GWAS for LM vs emmetropia implies that these common LM-predisposing variants are enriched within the HM group. Moreover, this phenomenon held true not only for the 4 top GWAS variants identified in the GWAS for LM vs emmetropia at the most stringent P value threshold; even the 35 490 LM-predisposing variants selected at the most lenient P value threshold (Table) were enriched in individuals with HM. The opposite holds true for individuals with hyperopia, who on

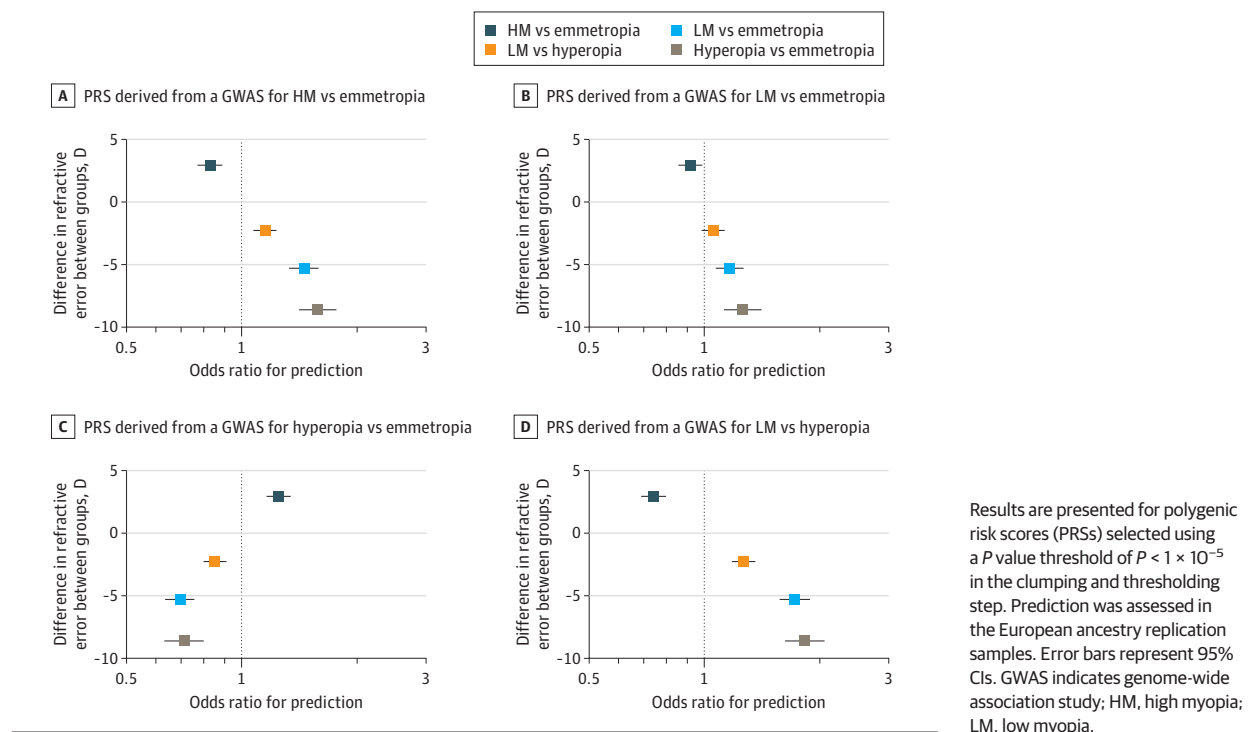
Figure 2. Prediction of Refractive Error Categories Using Polygenic Risk Scores



Polygenic risk scores derived from specific case-control genome-wide association study (GWAS) analyses in individuals of European ancestry were used to predict all categories of refractive error in European ancestry and Asian

ancestry replication samples. Error bars represent 95% CI. HM indicates high myopia; LM, low myopia.

Figure 3. Association Between Odds Ratio for Prediction and Difference in Refractive Error Between Groups



average inherit the lowest number of myopia risk alleles (again, especially risk alleles for variants with larger effect sizes).

The cross-ancestry prediction results provide further support that genetic variants associated with refractive error are shared across European and Asian ancestry groups and that genetic differences are unlikely to explain the higher prevalence of myopia in East Asia compared with Europe.²¹ For example, the 471 variants selected at the P value threshold of $P < 1 \times 10^{-4}$ from the LM vs emmetropia GWAS as predisposing to LM in the European sample were predictive of HM, LM, and hyperopia in participants of Asian ancestry. Predictive performance in the Asian ancestry replication samples was lower and had wider CIs than that in the European sample. Previous studies^{28,29} that investigated a range of traits have demonstrated that this consistently worse performance of polygenic risk scores in predicting traits in those of Asian ancestry compared with those of European ancestry using a polygenic risk score derived from individuals of European ancestry is primarily attributable to differences in patterns of linkage disequilibrium between individuals of Asian and European ancestry.

Overlap of the variants that contribute to the inheritance of ocular refraction has 2 additional implications. First, it implies that gene-environment interactions will have effects across the whole refractive error spectrum. Thus, time outdoors and near work likely contribute to refractive error in individuals with LM, HM, and hyperopia who inherit a myopia-predisposing risk allele.¹⁵ Second, the ability to predict HM using commonly occurring variants identified in a GWAS for LM vs hyperopia implies that rare variants are not usually the cause of HM. As mentioned above, this conclusion is not in con-

flict with reports of rare mutations that cause HM or high hyperopia with a monogenic inheritance pattern.³⁰⁻⁴³ Such rare genetic variants are expected even for a polygenic trait (the apparent monogenic inheritance pattern occurs because the massive effect of the specific risk allele swamps the background polygenic effect). However, the rarity of very large-effect risk alleles means that they make no contribution to the phenotype in many individuals with HM or high hyperopia.

Strengths and Limitations

This study has strengths and limitations. Strengths include the standardized phenotyping and genotyping of all participants. Firth logistic regression, which has been recommended to appropriately control the type I error rate when testing low-frequency genetic variants in imbalanced case-control samples,⁴⁴ provided no evidence of systematic inflation of P values (eFigure 4 in Supplement 1).

One limitation of the current study was the modest size of the GWAS analyses, which limited predictive accuracy for the polygenic risk scores (being especially evident for the polygenic risk score derived from the GWAS of LM vs emmetropia) (Figure 3). Polygenic risk scores with much better predictive accuracy (eg, providing an OR >6 for detecting future risk of HM) have been derived using larger GWAS samples.^{14,26} A second limitation was that our Asian ancestry replication sample included both South Asian and East Asian participants and that these groups were imbalanced (1921 and 244 South Asian and East Asian individuals, respectively). This imbalance precluded an evaluation of the performance of polygenic risk scores in separate South Asian and East Asian samples. Third, the analyses assumed that genetic variants

acted additively, and they ignored the influence of gene-environment and epistatic interactions.^{15,45,46}

Previous work^{21,29} has demonstrated that genetic risk for myopia is shared between individuals of European and Asian ancestry. Coupled with the current findings, this suggests that many recent molecular genetic studies of myopia are of limited value.¹⁶⁻²⁰ For instance, if a genetic variant is associated with refractive error in a large-scale GWAS in individuals of European ancestry, then it can be assumed with high confidence that the variant will be associated with the whole spectrum of refractive error (hyperopia, emmetropia, LM, and HM) in that ethnic group. Furthermore, interethnic replication is likely to be the rule for alleles with similar frequencies in the relevant ethnic groups.

Conclusions

This work provides further evidence that the genetic contribution to refractive error is primarily polygenic. Genetic variants with risk alleles associated with myopia were common in individuals with LM, even more common in those with HM, but less common in those with hyperopia. These findings support the hypothesis that the same set of variants is responsible for conferring the polygenic portion of genetic risk of HM, LM, and hyperopia in most of the general population, including individuals of European and Asian ancestry.

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Group Information: The Consortium for Refractive Error and Myopia (CREAM Consortium) and the

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REFERENCES

- Chua SYL, Foster PJ. The Economic and Societal Impact of Myopia and High Myopia. In: Ang M, Wong TY, eds. *Updates on Myopia: A Clinical Perspective*. Springer Singapore; 2020:53-63. doi:10.1007/978-981-13-8491-2_3
- Flitcroft DJ. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res*. 2012;31(6):622-660. doi:10.1016/j.preteyeres.2012.06.004
- Ip JM, Robaei D, Kifley A, Wang JJ, Rose KA, Mitchell P. Prevalence of hyperopia and associations with eye findings in 6- and 12-year-olds. *Ophthalmology*. 2008;115(4):678-685.e1. doi:10.1016/j.ophtha.2007.04.061
- Morgan IG, French AN, Ashby RS, et al. The epidemics of myopia: aetiology and prevention. *Prog Retin Eye Res*. 2018;62:134-149. doi:10.1016/j.preteyeres.2017.09.004
- He M, Xiang F, Zeng Y, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA*. 2015;314(11):1142-1148. doi:10.1001/jama.2015.10803
- Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK. Outdoor activity during class recess reduces myopia onset and progression in school children. *Ophthalmology*. 2013;120(5):1080-1085. doi:10.1016/j.ophtha.2012.11.009
- Cuellar-Partida G, Lu Y, Kho PF, et al. Assessing the genetic predisposition of education on myopia: a mendelian randomization study. *Genet Epidemiol*. 2016;40(1):66-72. doi:10.1002/gepi.21936
- Mountjoy E, Davies NM, Plotnikov D, et al. Education and myopia: assessing the direction of causality by mendelian randomisation. *BMJ*. 2018;361:k2022. doi:10.1136/bmj.k2022
- Huang HM, Chang DS, Wu PC. The association between near work activities and myopia in children: a systematic review and meta-analysis. *PLoS One*. 2015;10(10):e0140419. doi:10.1371/journal.pone.0140419
- Lopes MC, Andrew T, Carbonaro F, Spector TD, Hammond CJ. Estimating heritability and shared environmental effects for refractive error in twin and family studies. *Invest Ophthalmol Vis Sci*. 2009;50(1):126-131. doi:10.1167/iovs.08-2385
- Pärssinen O, Jauhanen HM, Kauppinen M, Kaprio J, Koskenvuo M, Rantanen T. Heritability of spherical equivalent: a population-based twin study among 63- to 76-year-old female twins. *Ophthalmology*. 2010;117(10):1908-1911. doi:10.1016/j.ophtha.2010.02.008
- Guggenheim JA, St Pourcain B, McMahon G, Timpson NJ, Evans DM, Williams C. Assumption-free estimation of the genetic contribution to refractive error across childhood. *Mol Vis*. 2015;21:621-632.
- Tedja MS, Haarman AEG, Meester-Smoor MA, et al; CREAM Consortium. IMI: myopia genetics report. *Invest Ophthalmol Vis Sci*. 2019;60(3):M89-M105. doi:10.1167/iovs.18-25965
- Hysi PG, Choquet H, Khawaja AP, et al; Consortium for Refractive Error and Myopia; UK Eye and Vision Consortium; 23andMe Inc. Meta-analysis of 542,934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nat Genet*. 2020;52(4):401-407. doi:10.1038/s41588-020-0599-0
- Pozarickij A, Williams C, Hysi PG, Guggenheim JA; UK Biobank Eye and Vision Consortium. Quantile regression analysis reveals widespread evidence for gene-environment or gene-gene interactions in myopia development. *Commun Biol*. 2019;2:167. doi:10.1038/s42003-019-0387-5
- Cheong KX, Yong RYY, Tan MMH, Tey FLK, Ang BCH. Association of VIPR2 and ZMAT4 with high myopia. *Ophthalmic Genet*. 2020;41(1):41-48. doi:10.1080/13816810.2020.1737951
- Cheng T, Wang J, Xiong S, et al. Association of IGF1 single-nucleotide polymorphisms with myopia in Chinese children. *PeerJ*. 2020;8:e8436. doi:10.7717/peerj.8436
- Li L, Cui YJ, Zou Y, et al. Genetic association study of SOX2 gene polymorphisms with high myopia in a Chinese population. *Eur J Ophthalmol*. 2020;1120672120904666. doi:10.1177/1120672120904666
- Xu C, Wu J, Wang J. Associations of rs524952 and rs634990 gene polymorphisms in 15q14 with high myopia: a meta-analysis. *Mol Vis*. 2019;25:603-609.
- Tang SM, Li FF, Lu SY, et al. Association of the ZC3H11B, ZFH1B and SNTB1 genes with myopia of different severities. *Br J Ophthalmol*. 2020;104(10):1472-1476. doi:10.1136/bjophthalmol-2019-314203
- Tedja MS, Wojciechowski R, Hysi PG, et al; CREAM Consortium; 23andMe Research Team; UK Biobank Eye and Vision Consortium. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nat Genet*. 2018;50(6):834-848. doi:10.1038/s41588-018-0127-7
- Allen N, Sudlow C, Downey P, et al. UK Biobank: current status and what it means for epidemiology. *Health Policy Technol*. 2012;1(3):123-126. doi:10.1016/j.hlpt.2012.07.003
- Cumberland PM, Bao Y, Hysi PG, Foster PJ, Hammond CJ, Rahi JS; UK Biobank Eyes & Vision Consortium. Frequency and distribution of refractive error in adult life: methodology and findings of the UK Biobank study. *PLoS One*. 2015;10(10):e0139780. doi:10.1371/journal.pone.0139780
- Bi W, Zhao Z, Dey R, Fritsche LG, Mukherjee B, Lee S. A fast and accurate method for genome-wide scale phenome-wide G × E analysis and its application to UK Biobank. *Am J Hum Genet*. 2019;105(6):1182-1192. doi:10.1016/j.ajhg.2019.10.008
- Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*. 2015;4:7. doi:10.1186/s13742-015-0047-8
- Ghorbani Mojarrad N, Plotnikov D, Williams C, Guggenheim JA; UK Biobank Eye and Vision Consortium. Association between polygenic risk score and risk of myopia. *JAMA Ophthalmol*. 2019;138:7-13. doi:10.1001/jamaophthalmol.2019.4421
- Verhoeven VJM, Hysi PG, Wojciechowski R, et al; Consortium for Refractive Error and Myopia (CREAM); Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group; Wellcome Trust Case Control Consortium 2 (WTCCC2); Fuchs' Genetics Multi-Center Study Group. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat Genet*. 2013;45(3):314-318. doi:10.1038/ng.2554
- Márquez-Luna C, Loh PR, Price AL; South Asian Type 2 Diabetes (SAT2D) Consortium; SIGMA Type 2 Diabetes Consortium. Multiethnic polygenic risk scores improve risk prediction in diverse populations. *Genet Epidemiol*. 2017;41(8):811-823. doi:10.1002/gepi.22083
- Ghorbani Mojarrad N, Williams C, Guggenheim Jeremy A. Accuracy of genetic prediction of myopia in individuals of non-European ancestry. Paper presented at: 17th International Myopia Conference; September 12, 2019; Tokyo, Japan.
- Xiao X, Li S, Jia X, Guo X, Zhang Q. X-linked heterozygous mutations in *ARR3* cause female-limited early onset high myopia. *Mol Vis*. 2016;22:1257-1266.
- Jin ZB, Wu J, Huang XF, et al. Trio-based exome sequencing arrests de novo mutations in early-onset high myopia. *Proc Natl Acad Sci U S A*. 2017;114(16):4219-4224. doi:10.1073/pnas.1615970114
- Zhao F, Wu J, Xue A, et al. Exome sequencing reveals *CCDC111* mutation associated with high myopia. *Hum Genet*. 2013;132(8):913-921. doi:10.1007/s00439-013-1303-6
- Aldahmesh MA, Khan AO, Alkuraya H, et al. Mutations in *LRPAP1* are associated with severe myopia in humans. *Am J Hum Genet*. 2013;93(2):313-320. doi:10.1016/j.ajhg.2013.06.002
- Mordechai S, Gradstein L, Pasanen A, et al. High myopia caused by a mutation in *LEPREL1*, encoding prolyl 3-hydroxylase 2. *Am J Hum Genet*. 2011;89(3):438-445. doi:10.1016/j.ajhg.2011.08.003
- Li J, Gao B, Xiao X, et al. Exome sequencing identified null mutations in *LOXL3* associated with early-onset high myopia. *Mol Vis*. 2016;22:161-167.
- Wang B, Liu Y, Chen S, et al. A novel potentially causative variant of *NDUFAF7* revealed by mutation screening in a Chinese family with pathologic myopia. *Invest Ophthalmol Vis Sci*. 2017;58(10):4182-4192. doi:10.1167/iovs.16-20941
- Napolitano F, Di Iorio V, Testa F, et al. Autosomal-dominant myopia associated to a novel P4HA2 missense variant and defective collagen hydroxylation. *Clin Genet*. 2018;93(5):982-991. doi:10.1111/cge.13217
- Tran-Viet K-N, Powell C, Barathi VA, et al. Mutations in *SCO2* are associated with autosomal-dominant high-grade myopia. *Am J Hum Genet*. 2013;92(5):820-826. doi:10.1016/j.ajhg.2013.04.005
- Wakazono T, Miyake M, Yamashiro K, Yoshikawa M, Yoshimura N. Association between *SCO2* mutation and extreme myopia in Japanese

- patients. *Jpn J Ophthalmol*. 2016;60(4):319-325. doi:10.1007/s10384-016-0442-4
40. Guo H, Jin X, Zhu T, et al. SLC39A5 mutations interfering with the BMP/TGF- β pathway in non-syndromic high myopia. *J Med Genet*. 2014;51(8):518-525. doi:10.1136/jmedgenet-2014-102351
41. Shi Y, Li Y, Zhang D, et al. Exome sequencing identifies ZNF644 mutations in high myopia. *PLoS Genet*. 2011;7(6):e1002084. doi:10.1371/journal.pgen.1002084
42. Sundin OH, Leppert GS, Silva ED, et al. Extreme hyperopia is the result of null mutations in MFRP, which encodes a Frizzled-related protein. *Proc Natl Acad Sci U S A*. 2005;102(27):9553-9558. doi:10.1073/pnas.0501451102
43. Gal A, Rau I, El Matri L, et al. Autosomal-recessive posterior microphthalmos is caused by mutations in PRSS56, a gene encoding a trypsin-like serine protease. *Am J Hum Genet*. 2011;88(3):382-390. doi:10.1016/j.ajhg.2011.02.006
44. Ma C, Blackwell T, Boehnke M, Scott LJ; GoT2D Investigators. Recommended joint and meta-analysis strategies for case-control association testing of single low-count variants. *Genet Epidemiol*. 2013;37(6):539-550.
45. Pozarickij A, Williams C, Guggenheim JA; and the UK Biobank Eye and Vision Consortium. Non-additive (dominance) effects of genetic variants associated with refractive error and myopia. *Mol Genet Genomics*. 2020;295(4):843-853. doi:10.1007/s00438-020-01666-w
46. Pozarickij A, Enthoven CA, Ghorbani Mojarad N, et al. Evidence that emmetropization buffers against both genetic and environmental risk factors for myopia. *Invest Ophthalmol Vis Sci*. 2020;61(2):41. doi:10.1167/iovs.61.2.41