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The genetic architecture of 25 hydroxyvitamin D concentration

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Abstract

Vitamin D deficiency is associated with a range of adverse health outcomes. It is highly impacted by environmental factors (e.g. season, skin covering, outdoor behaviour), but family and genome-wide association studies (GWAS) have shown that genetic risk factors also have an impact. Here, we used data from the UK Biobank to describe the genetic architecture of 25 hydroxyvitamin D (25OHD), the main metabolite used to assess vitamin D status. These findings provide new insights into the genetic basis underlying 25OHD status.

Heritability and SNP-based estimation

GCTA-GREML was used to estimate heritability from a UKB subset that included all pairs of individuals related with coefficient of relationship >0.2 (N=58,738). **Estimate: 0.32 s.e. 0.01**

GCTA-GREML was used to estimate SNP-based heritability from 50K unrelated individuals randomly drawn from the UKB. **Estimate: 0.13 s.e. 0.01**

SNP-based heritability was also estimated from GWAS summary statistics (N=417,580; ~1.1M HapMap3 SNPs). **Outcome:** The estimates from SbayesS and SbayesR were similar to the GCTA-GREML estimates but those from linkage disequilibrium (LD) Score regression were lower.

Genetic Architecture

SNP-based heritability estimated using GCTA-LDMS (stratified by five minor allele frequency groups and two linkage disequilibrium (LD) groups. **Estimate: 0.13 s.e. 0.01** (i.e. little impact for this approach).

Using SBayesS, we estimated that about 0.8% of the ~1.1 million HapMap3 panel common SNPs affect variation in 25OHD, a lower polygenicity estimate than that of most complex traits.

Controlling for Body Mass Index (BMI)

Given the negative phenotypic relationship with body mass index (BMI), analyses were conducted fitting BMI as a covariate as well as bivariate GREML analyses. **Outcome:** BMI has little impact on estimates despite genetic genetic correlation of -0.19.

Season

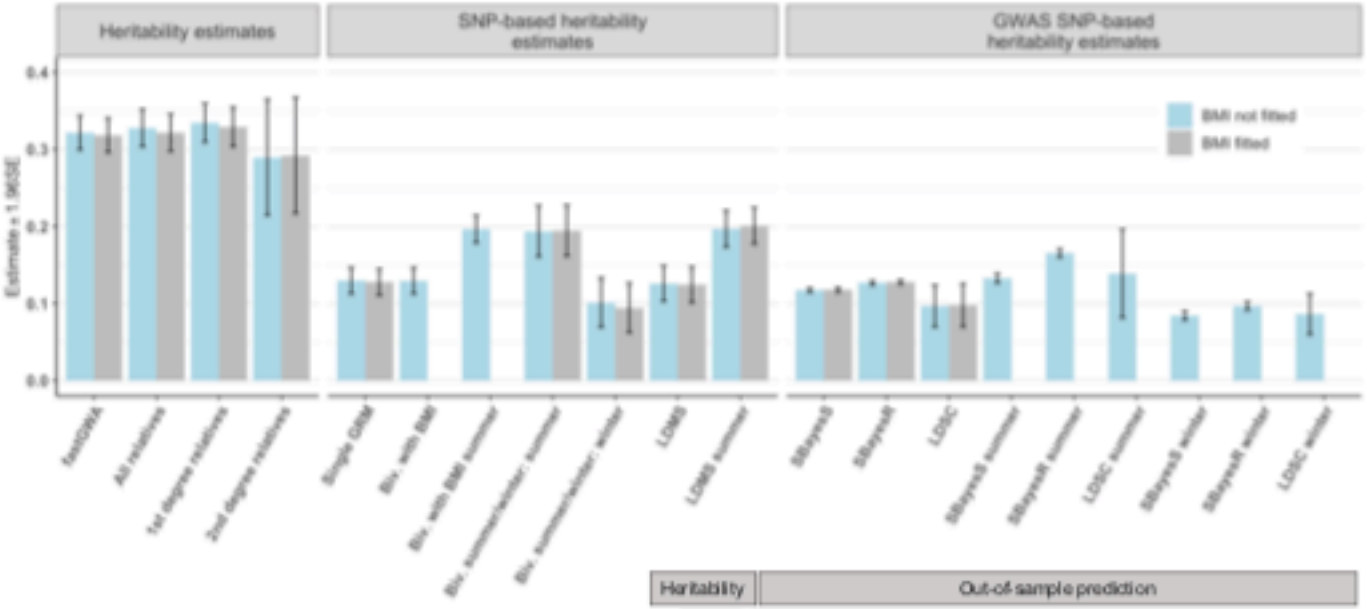
Vitamin D levels are seasonal (higher in summer). Bivariate GREML for vitD assessed in summer and winter as two different phenotypes.

Estimate SNP-based heritability summer estimate 0.19, s.e. = 0.02 significantly higher ($P = 1.5 \times 10^{-3}$) than winter estimate (vs. 0.10, s.e. = 0.02). Genetic correlation estimate between the seasons 0.89 s.e. 0.05 (LDSC).

Genetic correlation

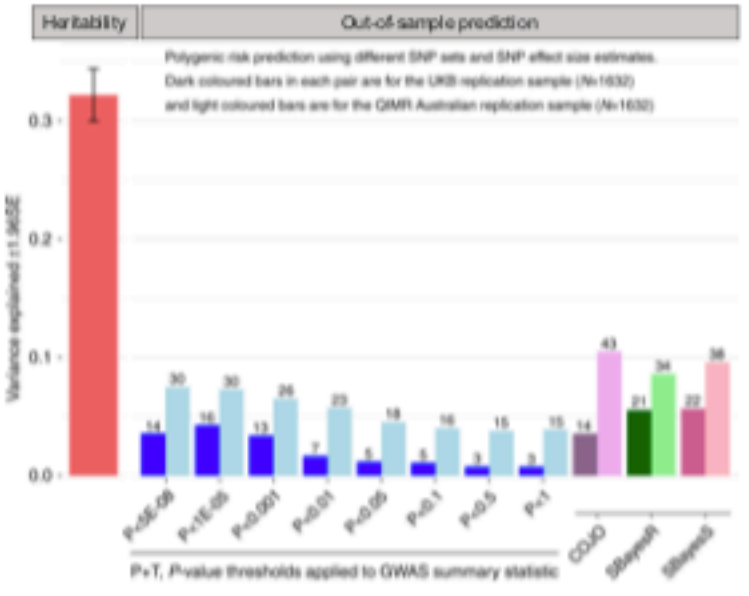
Genetic correlation (rg) estimates and respective standard errors (s.e.) were also obtained from the bivariate GREML analyses LDSC regression.

	Method	genetic correlation	s.e.
25OHD/BMI	GREML	-0.19	0.03
25OHD/BMI	LDSC	-0.17	0.03
25OHD/BMI (summer)	GREML	-0.18	0.03
Summer/winter	GREML	0.80	0.11
Summer/winter	LDSC	0.89	0.05
Summer/winter (BMI cov)	GREML	0.82	0.11



Out of sample prediction

In out-of-sample prediction into the QIMR and the UKB replication (UKBR) samples, polygenic risk scores (PRS) calculated by the standard P-value threshold method (P + T) were outperformed by using SNP effect estimates calculated from GWAS summary statistics using the SBayesR or SBayesS methods. Bars of the same colour used the same methodology (noting that SBayesR generates an estimate of SNP-based heritability as well as SNP effect sizes in prediction analysis). The numbers on top of the bars are −log10 P-value of the regression of 25OHD on 25OHD PRS. COJO conditional and joint, rg genetic correlation, s.e. standard error.



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