Exploring germline genetics of invasive and *in situ* cutaneous melanoma

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Introduction

Understanding whether germline genetic factors play a role in cutaneous melanoma (CM) invasion may inform future efforts towards tailored screening and management. While many single nucleotide polymorphisms (SNPs) that play a role in CM risk have been identified by genome-wide association studies (GWAS) (Landi et al. 2020), none have been identified that are specific to invasiveness of CM. Using data from the UK Biobank (UKBB) (Bycroft et al. 2018), the FinnGen cohort (Kurki et al. 2022), the QSkin Sun and Health Study (QSkin) (Olsen et al. 2012), and the Queensland Study of Melanoma: environmental and genetic associations (Q-MEGA) (Baxter et al. 2008) we explored if (a) propensity to develop invasive vs *in situ* CM is heritable (b) if there are specific genetic loci that associate with diagnosis of an invasive or *in situ* CM, (c) we can construct a polygenic risk score (PRS) that is associated with being diagnosed with an invasive vs an *in situ* CM.

Methods

Melanoma status was derived from cancer registry data by each cohort. **Table 1** shows the ratio of invasive, *in situ*, and skin-cancer-free controls for each cohort. Samples with both an invasive and *in situ* diagnosis were counted as invasive. Samples were filtered to include only those with European ancestry using principal component (PC) analysis. Genetic-relatedness matrices were calculated for each cohort to account for related samples. Logistic regression GWAS case-control and case-case (invasive vs *in situ*) were performed using SAIGE v.0.45 (Zhou et al. 2018) for QSkin and Q-MEGA, and REGENIE v.2.2.4 (Mbatchou et al. 2021) for UKBB. Summary statistics were downloaded from FinnGen (r.7). METAL v.1.0 (Willer et al. 2010) was used for GWAS meta-analysis. A PRS using clumping and thresholding and a binomial generalised mixed model was calculated in R v4.2.0. Age, sex, and PCs 1 to 10 were included as covariates in all GWAS and PRS calculations.

To avoid sample overlap, the PRS was generated using a GWAS meta-analysis that excluded half of Q-MEGA, with the excluded half then used as the target set.

TABLE 1

| Cohort	Invasive	*In situ*	Controls
QSkin	668	586	15,309
UKBB	5,792	1818	395,698
Q-MEGA	1,168	282	1,240
FinnGen	2,466	632	238,678

Results

Case-control GWAS: We meta-analyzed GWAS of invasive or *in situ* CM compared to controls. **Figure 1** shows 25 genome-wide significant (P < 5 × 10⁻⁸) loci associated with invasive CM (**blue**), and 6 loci for *in situ* CM (**red**). *IRF4* (rs12203592) on chromosome 6 and *KLF4* (rs10979147) on chromosome 9 are specific to *in situ*.
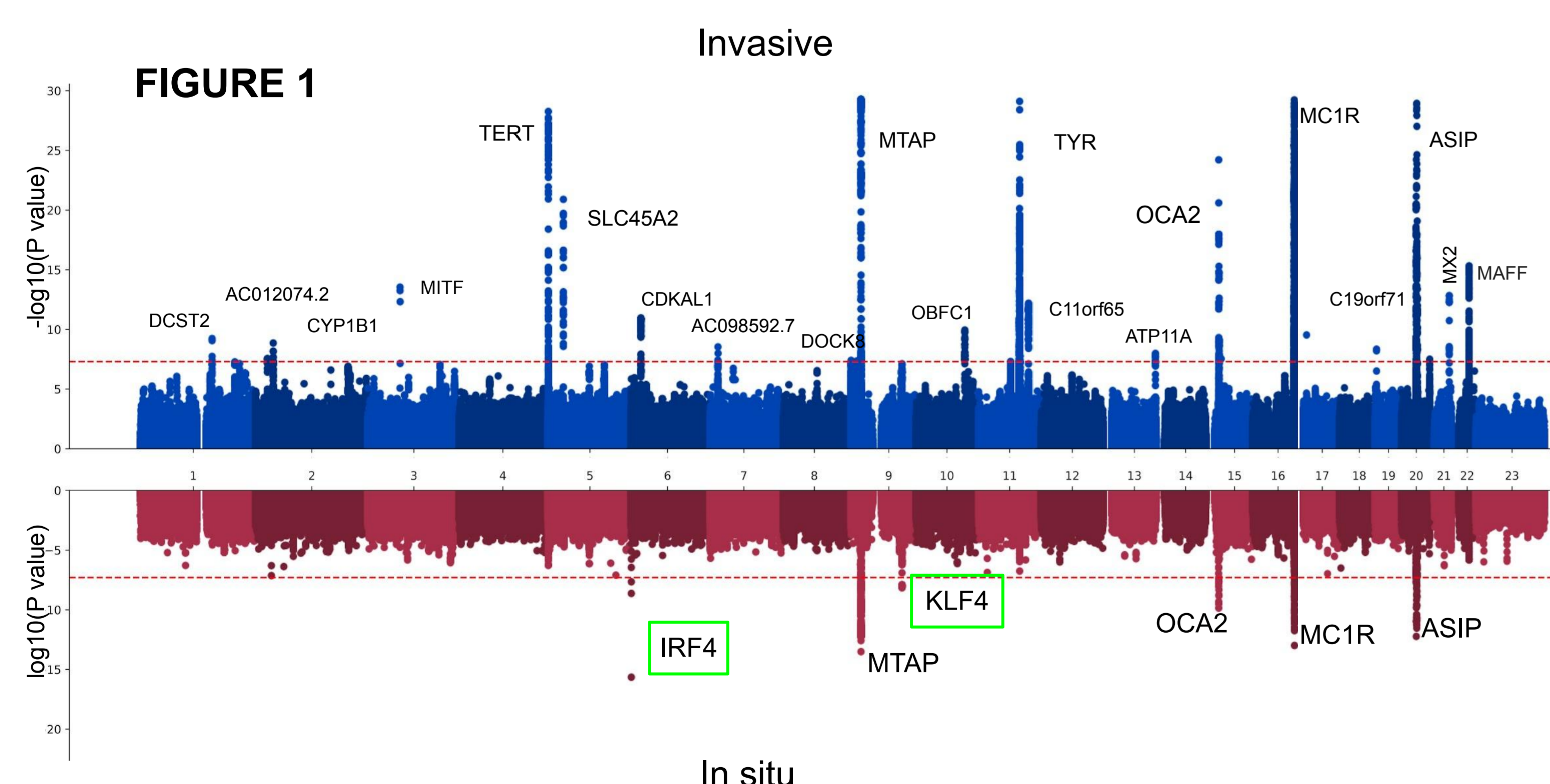

FIGURE 1

FIGURE 2

There was a strong correlation between the effect estimates from the lead SNPs from the invasive and *in situ* case-control GWAS (**Figure 2**). However, there are a some SNPs that show a larger effect in one GWAS than the other. The genetic correlation (rg) between the invasive and *in situ* case-control GWAS was 0.95 (95% CIs = 0.72 to 1.19).

FIGURE 3
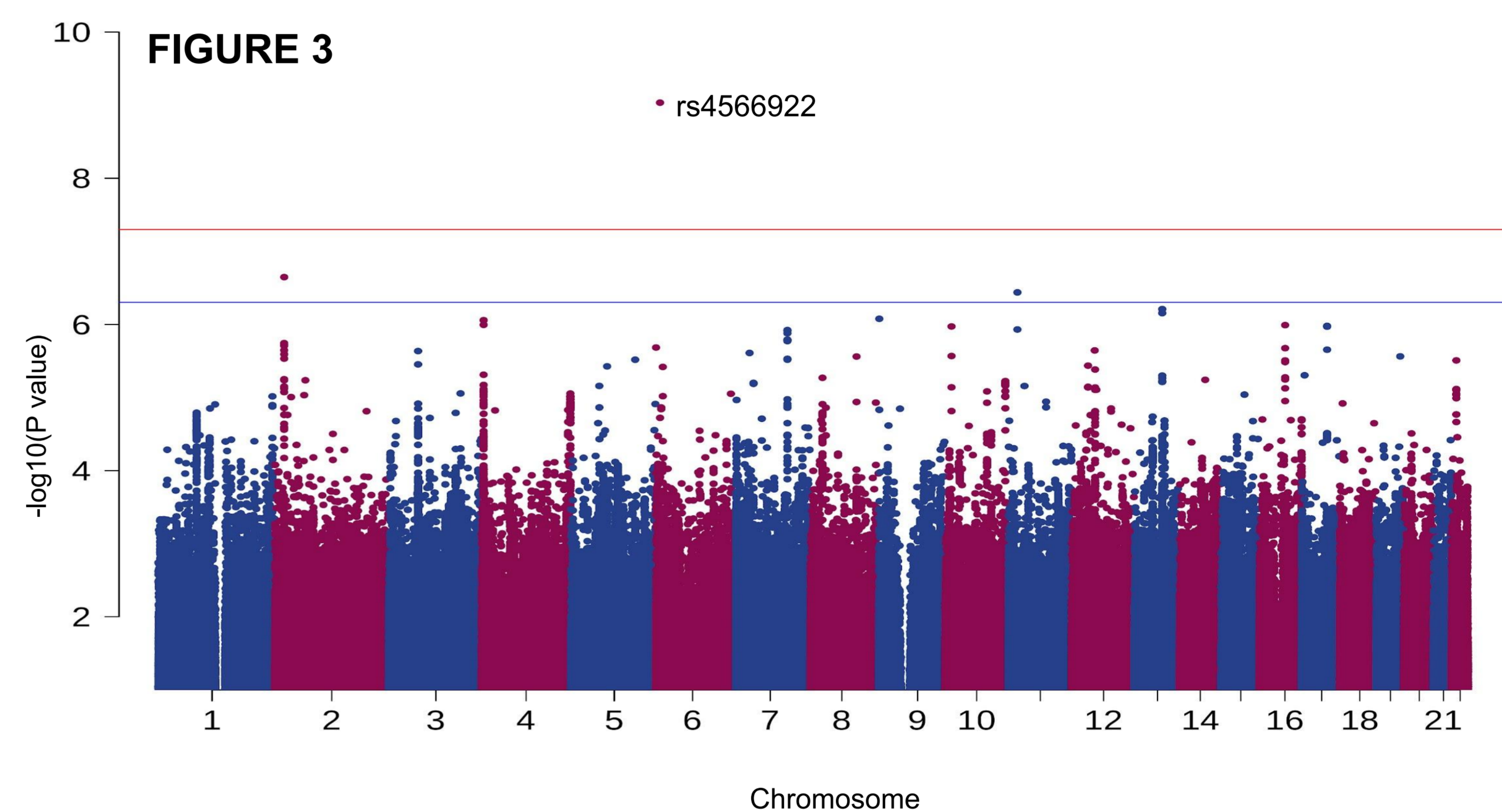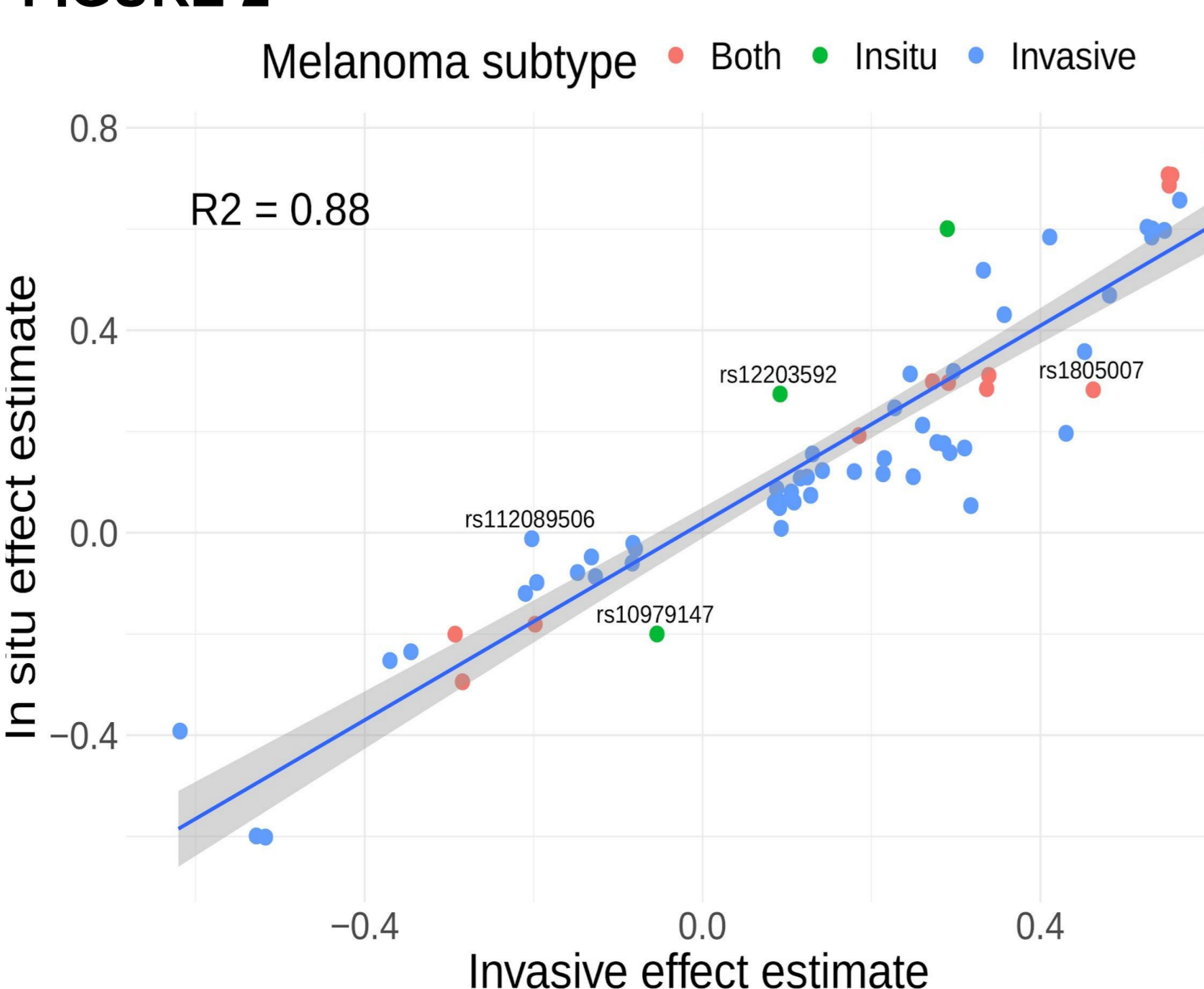
Case-case GWAS: A meta-analysis of GWAS of invasive vs *in situ* was performed to identify genetic effects influencing specifically invasive melanoma (**Figure 3).** This revealed one significant (P < 5 × 10⁻⁸) SNP on chr 6, rs4566922, near *SLC35B3*. SNP-based heritability of this GWAS was estimated at 14.8% (se = 13.6 P = 0.28).

A PRS was derived from the case-case GWAS of invasive and *in situ* CM after excluding a subset of the Q-MEGA cohort. Applying this PRS to the excluded Q-MEGA subset revealed that invasive cases had a significantly higher PRS (**Figure 4**), OR = 1.32, 95% CI = 1.1 to 1.6 per one standard deviation in PRS.

FIGURE 4
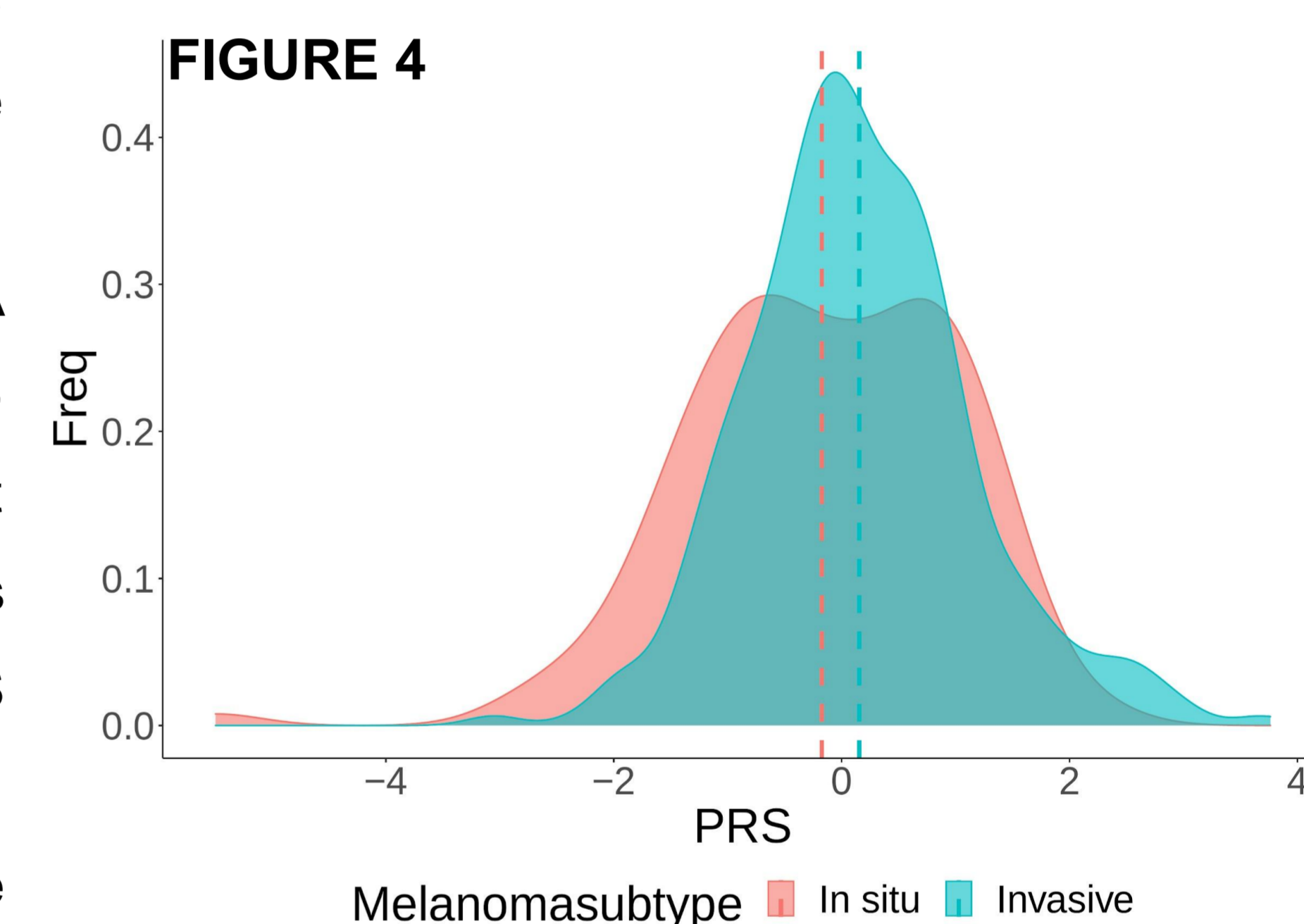
Discussion and Conclusion

Much of the genetic architecture of invasive and *in situ* CM is shared, with many overlapping genetic loci. However, rs12203592 *(IRF4)* and rs10979147 (*KLF4*) were more strongly associated with *in situ* CM with non overlapping effect estimates (rs12203592 *in situ* OR = 1.31, 95% CI 1.23 - 1.40, P = 2.2 × 10⁻¹⁶; invasive OR = 1.09, 95% CI 1.05 - 1.13, P = 1.4 × 10⁻⁵; rs10979147 *in situ* OR = 0.82, 95% CI 0.76 - 0.87, P = 7.0 × 10⁻⁹; invasive OR = 0.95, 0.91 - 0.98, P = 0.004). Both of these loci have been associated with CM risk and nevus count (Duffy et al. 2010, 2018, Landi et al. 2020). This may reflect dysplastic nevi being diagnosed as *in situ* CM and thus reflected in the stronger association at these SNPs. While requiring replication in an independent cohort, the case-case GWAS identified rs4566922. The nearest gene to this SNP is *SLC35B3*; however this gene is 450 kb away, and there is no evidence of a direct functional target for this SNP via resources such as Open Targets Genetics. Interestingly, a PRS for invasive vs *in situ* melanoma was significantly associated with invasiveness in an independent subset of the GWAS cohorts used, suggesting while the majority of genetic risks overlap, larger datasets may be able to identify additional genetic variants specific to invasiveness.

Affiliations & references via the QR code:

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