



**University of Dundee**

**Genome-wide association meta-analyses combining multiple risk phenotypes provide insights into the genetic architecture of cutaneous melanoma susceptibility**

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## **Supplementary Note**

**Genome-wide association meta-analyses combining multiple risk phenotypes provides insights into the genetic architecture of cutaneous melanoma susceptibility**

## Inclusion of self-report cases

Before combining the two self-report sets and the clinically confirmed GWAS data, we used LDSC<sup>1</sup> to investigate the genetic correlation ( $R_g$ ) between self-reported CM cases and the confirmed-only cases from the meta-analysis GWAS data (**Supplementary Note, Supplementary Table 2**). Correlations with clinically confirmed CM GWAS results were high, with the self-report 23andMe, Inc. and UK Biobank (UKBB) GWAS yielding  $R_g$  of 1.00 (SE = 0.13) and 0.65 (SE = 0.15), respectively (**Supplementary Table 2**). While the  $R_g$  for the UKBB self-reported cases may be lower as all UKBB self-reported cases that could be confirmed by cancer registries were moved into the UKBB confirmed set, LDSC estimates can be imprecise when the effective sample size is less than 5,000 (**Online Methods, Supplementary Table 1**).

Moreover, the confidence intervals between the UKBB self-report and 23andMe overlapped substantially (UKBB self-report  $R_g=0.65$ , 95% CI=0.36-0.95; 23andMe  $R_g=1.00$  95% CI=0.74-1.00). This suggests that the UK Biobank self-report GWAS does not differ in terms of genetic architecture from the other CM GWAS.

Looking specifically at the lead SNPs identified in the confirmed only meta-analysis (**Supplementary Table 6**), the correlation of  $\log(\text{OR})$  beta estimates (weighted by their inverse variance) from the confirmed only meta-analysis and from the UKBB self-report set is high,  $r^2 = 0.62$  (**Extended Data Figure 6**). As a further sensitivity analysis, we excluded the UKBB self-report set from the meta-analysis, retaining all confirmed sets and 23andMe. Three loci found in the total (all confirmed sets plus 23andMe and UKBB self-report) no longer reached genome-wide significance. Heterogeneity was low across these loci ( $I^2 \leq 10\%$ ), both with and without the UKBB self-report set, suggesting its presence was improving power without driving the discovery of these loci nor leading to heterogeneity. For each of these three lead SNPs the estimate within UKBB self-report was consistent with the wider meta-analysis (**Supplementary Table 18**). For example, rs6908626 in the UKBB self-report had a  $\log(\text{OR}) = 0.151$ , and a 95% CI = 0.047 - 0.255. In the meta-analysis without UKBB self-report the  $\log(\text{OR}) = 0.078$ , 95% CI = 0.049 - 0.107, with overlapping confidence intervals. The consistency of UKBB self-report GWAS at these three loci is further supported by the reported forest plots for these SNPs in **Supplementary Figure 2**. These show that  $\log(\text{OR})$  estimates from UKBB self-report set are consistent with, and overlap, those of other confirmed case sets.

Thus, although the  $R_g$  between UKBB self-report and the confirmed meta-GWAS is not 1 (which may be for a range of reasons e.g., LD score regression power), the inclusion of the UKBB self-report GWAS boosts the power to identify new melanoma GWAS loci without introducing bias.

## Replication of previously reported melanoma GWAS loci

Our analysis directly confirms 19 of the 21 loci reaching genome-wide significance in a previous CM GWAS<sup>2-9</sup> (**Table 1**). The previously reported peak variant for the locus in intron 8 of *FTO* rs16953002 did not formally replicate ( $P_{\text{meta}_r} = 1.2 \times 10^{-6}$ ,  $I^2 = 35\%$ ,  $P_{\text{meta}} = 3.8 \times 10^{-8}$ ) nor did any SNPs in LD, with the most strongly associated SNP at this region being rs62034121. However, rs16953002 and rs62034121 are in LD ( $r^2_{\text{EUR}} = 0.96$ ), and these variants are genome-wide significant in the meta-analysis of confirmed-only CM cases, and the combined CM plus nevus analysis (see below and **Online Methods**). A recent melanoma GWAS<sup>9</sup> reported rs187843643 near *BASP1* as a melanoma locus; while we included the contributing GWAS study in our analysis, this locus was no longer genome-wide significant in the meta-analysis ( $I^2 = 35\%$ ,  $P_{\text{meta}_r} = 0.3$ ,  $P_{\text{meta}} = 0.00071$ ).

The previously reported CM susceptibility variant centromeric to *AGR3* (rs1636744) on chromosome 7 is still significantly associated with CM, but is no longer the regional peak. While a SNP in LD ( $r^2_{\text{EUR}} = 0.91$ ) with rs1636744, rs73069846, is an independent risk variant for CM (**Supplementary Table 3**) the peak variant for this locus is now rs117132860 ( $r^2_{\text{EUR}} < 0.03$  with previously reported variants) located near the *AHR* gene (**Table 1, Supplementary Table 3**;  $P_{\text{meta}} = 3.8 \times 10^{-21}$ ). This region exhibits a complex LD structure and more focused investigations are needed to disentangle the CM association(s) in this region. Similarly, the peak variant near *IRF4* is rs12215602 and not the previously reported rs12203592, for which substantial heterogeneity was observed ( $I^2 = 81\%$ ,  $P_{\text{meta}_R} = 0.1$ ,  $P_{\text{meta}} = 1.9 \times 10^{-13}$ ).

The total CM meta-analysis also confirmed 6 regions previously identified only by combining nevus count and CM GWAS data<sup>10</sup> (**Table 2**). While in our CM meta-analysis the peak variant for another region near *MFSD12* and *FZRI*, rs12984831, is independent from the previously-reported peak at rs34466956 ( $r^2_{\text{EUR}} = 0.001$ ), rs34466956 is also significantly associated in our combined analysis of CM and nevus count described below ( $P_{\text{CM+nevus}} = 2.5 \times 10^{-9}$ ; **Supplementary Table 7**).

### Meta-analysis of pathologically confirmed-only melanoma GWAS

The meta-analysis for pathologically confirmed-only CM cases (N=30,134; **Supplementary Table 1**) identified a total of 46 loci associated with CM susceptibility (**Supplementary Table 6, Extended Data Figures 2-3**). Three loci were significant in the confirmed-only CM and not the total CM analysis. The first, on chromosome 4, rs2301293 (confirmed  $P_{\text{meta}} = 3.2 \times 10^{-9}$ , OR=0.89,  $I^2 = 0\%$ ) while not significant in the total CM meta-analysis, showed negligible difference in its estimate ( $P_{\text{meta}} = 5.8 \times 10^{-8}$ ,  $I^2 = 11\%$ , OR=0.91). The second locus near *DOCK8* is identified by the combination of CM and nevus count (**Table 1**, rs478882 and rs520015  $r^2_{\text{EUR}} = 0.96$ )<sup>10</sup>. The third locus is the previously-reported region on chromosome 16 containing *FTO* with SNP rs62034139 meeting our significance requirements ( $P_{\text{meta}_R} = 3.7 \times 10^{-8}$ ,  $I^2 = 36.8$ ).

### A role for multiple pathways in the development of CM

While interpretation of the variants and genes associated with new CM loci require further laboratory analyses to confirm biological relationships, they nonetheless offer clues suggesting multiple pathways are involved in CM risk. For example, a region on chromosome 17 spanning the 3' UTR of *TP53* implicates the tumor suppressor *TP53*, with peak SNP rs78378222 (**Table 2**) also associated with nevus count (**Supplementary Table 9**). The rs78378222 *TP53* variant has no high-LD ( $r^2_{\text{EUR}} > 0.6$ ) proxy variants, and rs78378222 itself has been shown to disrupt the polyadenylation signal sequence from AATAAA to AATACA, impairing proper 3' termination and polyadenylation of the *TP53* transcript and resulting in reduced mRNA expression levels<sup>11</sup>. Associations with rs78378222 have been observed for basal cell carcinoma (BCC)<sup>11,12</sup> and glioma<sup>13,14</sup>. We also identified an independent additional CM associated variant at the *TP53* locus, rs1641548 (**Supplementary Table 3**; OR=1.08,  $P_{\text{meta}} = 1.1 \times 10^{-9}$ ), which has not been reported as associated with other traits.

Two new CM loci hint at a potential role for immunity in the etiology of melanoma. Specifically, rs28986343 in the HLA region was found to be associated with CM (OR=1.15,  $P_{\text{meta}} = 1.6 \times 10^{-8}$ ; **Table 2**). Interestingly, two variants in the *HLA* region, rs9275642 and rs1050529, have previously been associated with BCC<sup>12</sup>; the CM variant rs28986343 is independent of both of these BCC variants ( $r^2_{\text{EUR}} < 0.03$ ). In addition, the rs6908626 variant on chromosome 6 (**Table 2**) is in strong LD ( $r^2_{\text{EUR}} = 0.97$ ) with SNPs (e.g., rs72928038) associated with autoimmune disorders including vitiligo<sup>15</sup>, suggesting a potential role of this locus in immunity. While we did not observe significant

eQTLs or TWAS results for this locus in skin-related tissues, rs6908626 is near *BACH2*, a gene that plays a critical role in immune regulation<sup>16</sup>, as well as *CASP8AP2*, a component of the death-inducing signaling complex involved in Fas-mediated apoptosis<sup>17</sup>. Evidence at this stage for an immune-related germline genetic pathway is suggestive, but deserves further study.

Consistent with prior studies implicating genes and loci associated with telomere maintenance in both melanoma families<sup>18-20</sup> as well as in population-based studies of sporadic melanoma<sup>21-23</sup>, we identified four telomere length-associated variants as novel genome-wide significant CM loci (**Table 1-2, Supplementary Table 5**). Three loci previously reported as marginal CM associations<sup>23</sup> were found here to be genome-wide significant (rs3950296 near *TERC*, OR=1.08,  $P_{\text{meta}}=4.5\times 10^{-11}$ ; rs143190905 near *RTEL1*, OR=1.15,  $P_{\text{meta}}=6.5\times 10^{-13}$ ; rs4731207 near *POT1*, OR=0.93,  $P_{\text{meta}}=2.2\times 10^{-15}$ ), and one additional novel association was observed for rs2967383 near *MPHOSPH6* (OR=1.07,  $P_{\text{meta}}=2.2\times 10^{-9}$ ). Of these, allelic gene expression is supported by TWAS findings for *MPHOSPH6* in both sun-exposed and non-sun-exposed skin, as well as additionally for *OBFC1* at another known genome-wide significant locus in transformed dermal fibroblasts. Lastly, in addition to a previously-identified signal at the telomerase reverse transcriptase (*TERT*) multi-cancer risk locus on chromosome 5 (rs13178866,  $P_{\text{meta}}=1.1\times 10^{-43}$ ), conditional and joint analysis using GCTA identified two independent genome-wide significant CM associations at this locus (rs7705526,  $P_{\text{meta}}=2.0\times 10^{-14}$ ; rs2853667,  $P_{\text{meta}}=7.7\times 10^{-9}$ ).

We identified multiple loci that potentially implicate genes established to regulate the development and differentiation of cells of melanocytic lineage as also having a role in CM. A new locus on chromosome band 1p31.3 with lead SNP rs670318 is located approximately 50kb from a key regulator of neural crest development, *FOXD3*. While eQTL analysis did not identify associations between this variant and expression of any nearby genes in melanocytes or other skin tissues, *FOXD3* is known to be downregulated during melanocyte development and is poorly expressed in differentiated cultured melanocytes. Melanocyte TWAS identified the expression of *NOTCH2*, a gene that plays a role in the maintenance and differentiation of melanocytes<sup>24</sup>, as significantly associated with CM. Higher melanocyte-specific expression of *NOTCH2* is associated with the CM risk allele.

TWAS analysis using melanocyte-specific expression (**Supplementary Table 10**) of the chromosome 16 locus with lead SNP rs4420522 (**Table 2**, OR=0.93,  $P_{\text{meta}}=8.3\times 10^{-14}$ ) implicates the following target genes: *CDHI*, *ZFP90*, *FTLP14*, and *TANGO6*. Among these, *CDHI* has a well-characterized role in progression of melanoma and other cancer types. *CDHI*, a calcium-dependent protein that regulates cell adhesion and motility, is considered the major adhesion molecule between melanocytes and keratinocytes<sup>25</sup>, with expression of *CDHI* frequently lost during progression from radial to vertical melanoma growth<sup>26</sup>. The risk allele of the lead CM SNP, rs4420522, is associated with higher levels of melanocyte *CDHI* expression and is also in strong LD ( $r^2_{\text{EUR}}=0.93$ ) with rs9929218, which is a GWAS hit for colorectal cancer<sup>27</sup>.

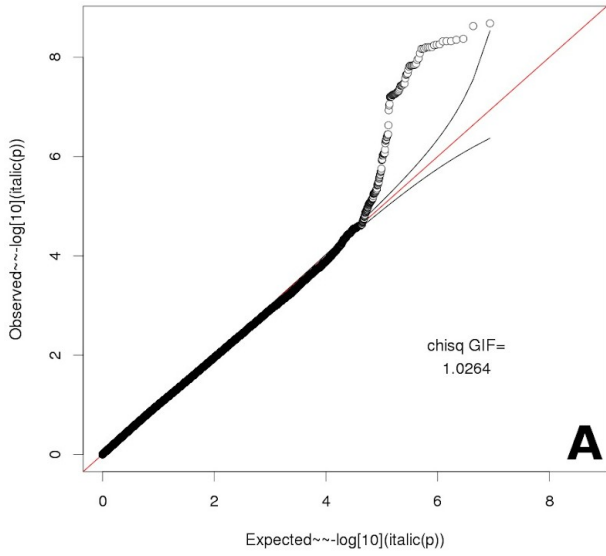
#### eQTL colocalization analyses

In order to annotate CM GWAS loci for candidate susceptibility genes for pathway analyses as well as future functional studies, we turned to eQTL colocalization analyses in addition to the TWAS data. Colocalization analyses of genome-wide significant CM GWAS loci and eQTLs from four skin-related tissues using eCAVIAR<sup>28</sup> nominated 35 genes from 19 CM GWAS loci with a colocalization posterior probability (CLPP) cutoff of 1% (**Supplementary Table 15**). Considering only melanocyte eQTLs, 11 genes with colocalizing eQTLs were identified at 9 loci. We then combined the 105 unique genes nominated by colocalization and TWAS analyses as a set of candidate susceptibility genes for pathway enrichment analysis using the Ingenuity Pathway Analysis (IPA) tool. Among significantly enriched canonical pathways were those relevant to

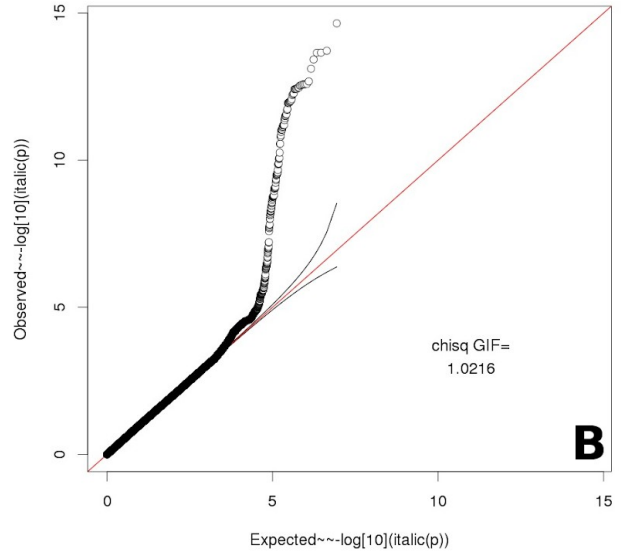
melanin biosynthesis, melanocyte development, as well as epithelial adherens junction signaling (**Supplementary Table 16**). Amongst the top upstream regulators of candidate melanoma susceptibility genes was *TFEB*, a member of the microphthalmia family of basic helix-loop-helix–leucine-zipper (bHLH-Zip) transcription factors (**Supplementary Table 17**;  $P = 4.6 \times 10^{-4}$ ).

## Supplementary Figures

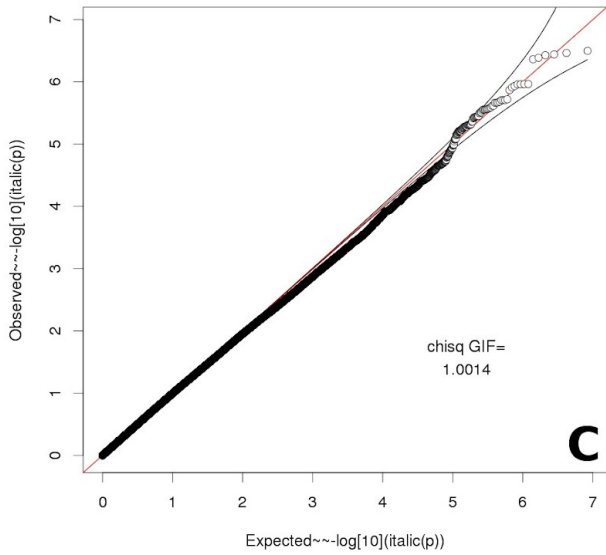
QQ plot with 95% CIs



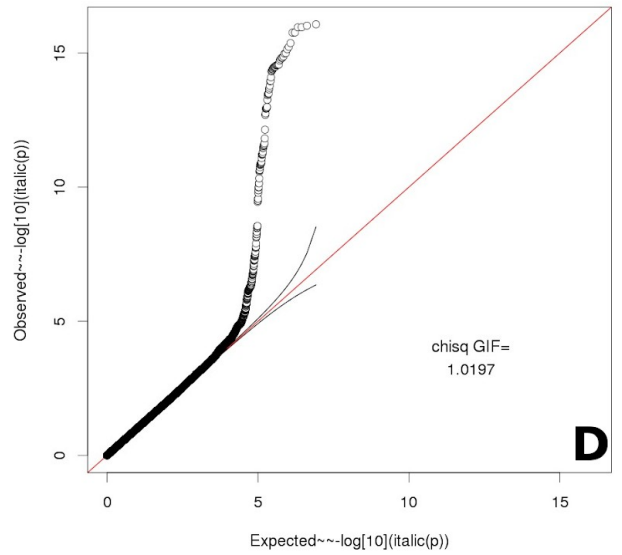
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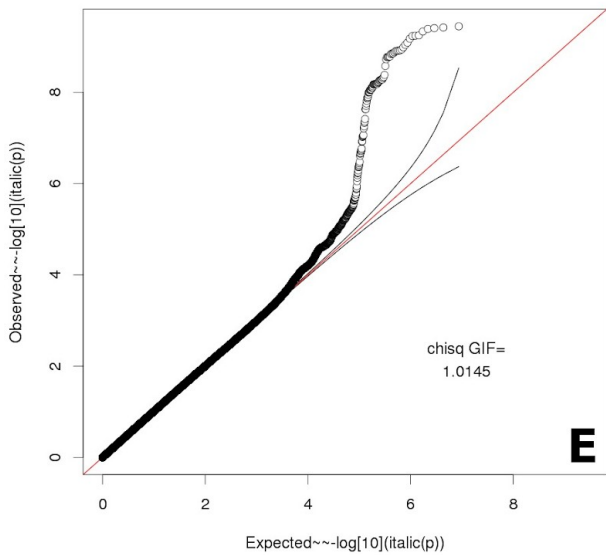
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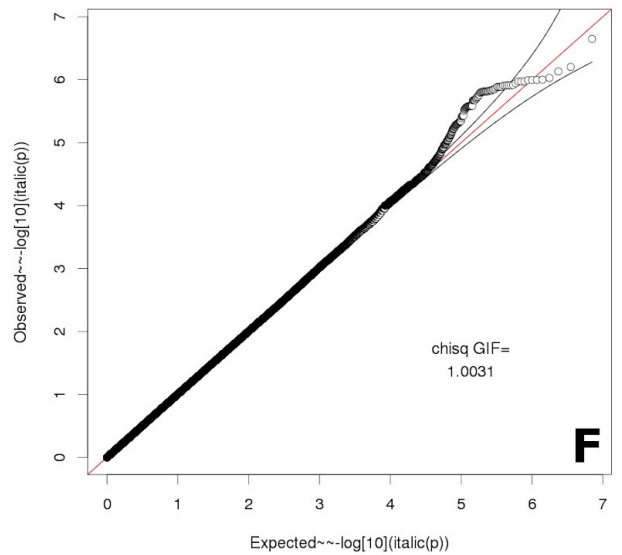
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QQ plot with 95% CIs

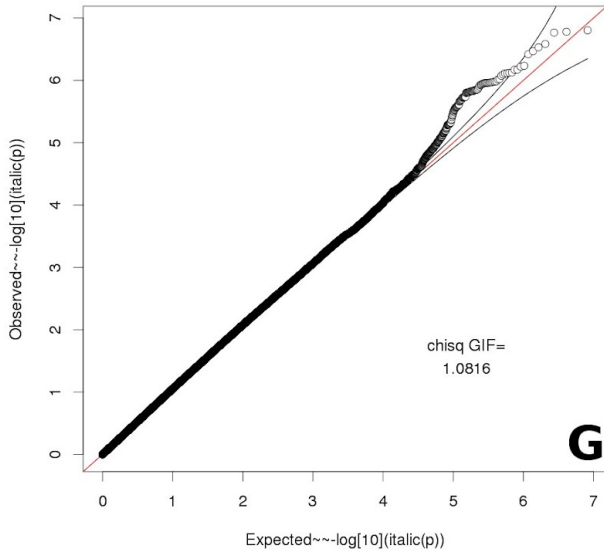


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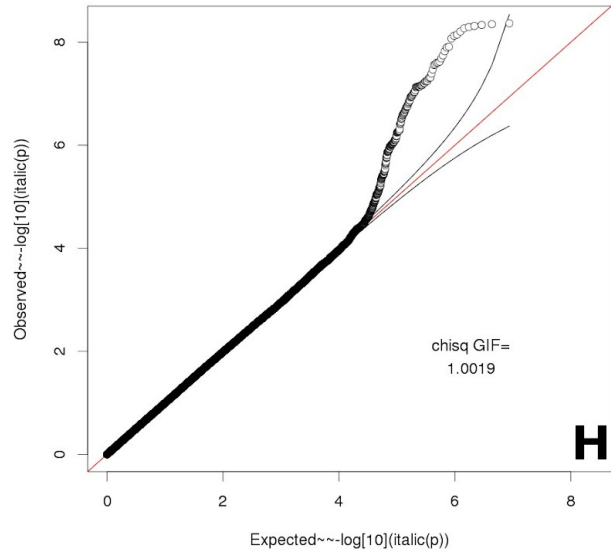




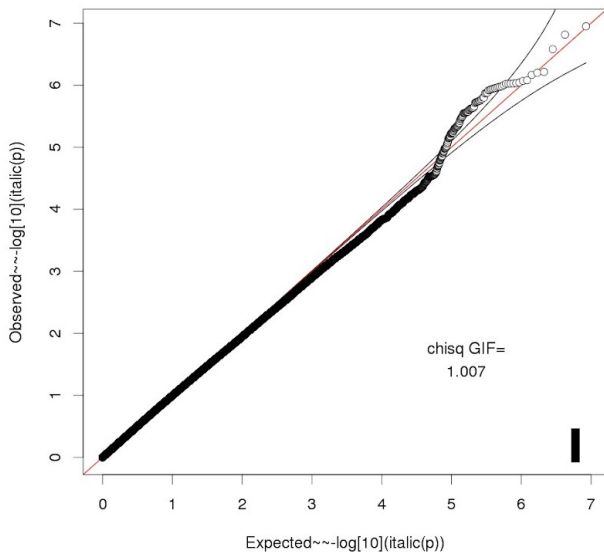
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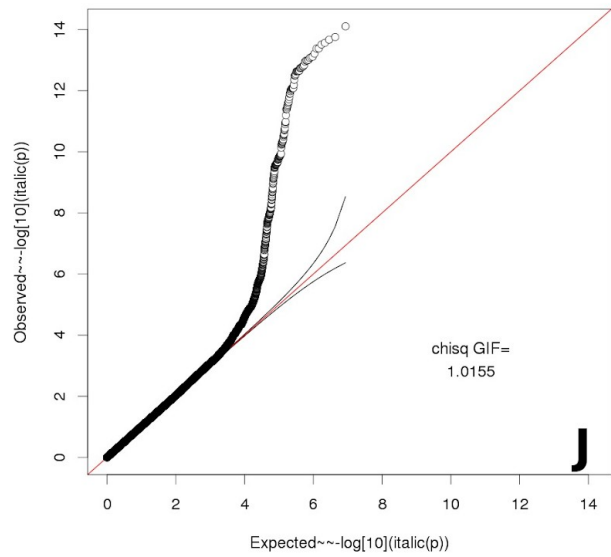
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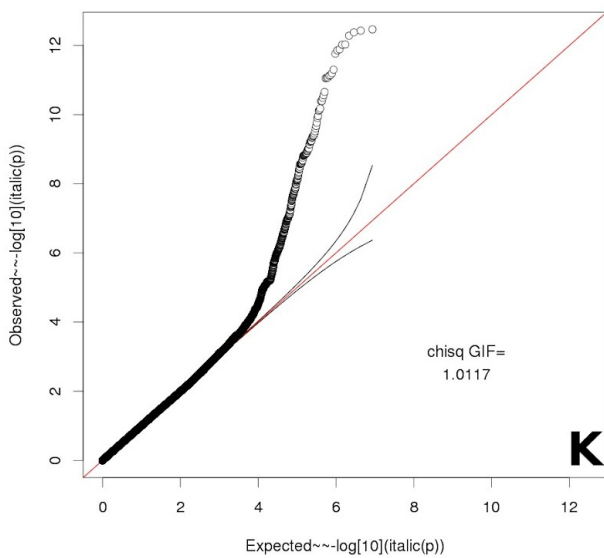
QQ plot with 95% CIs



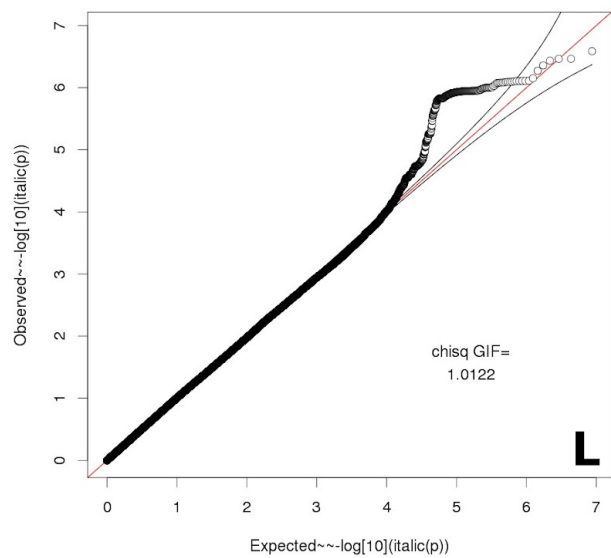
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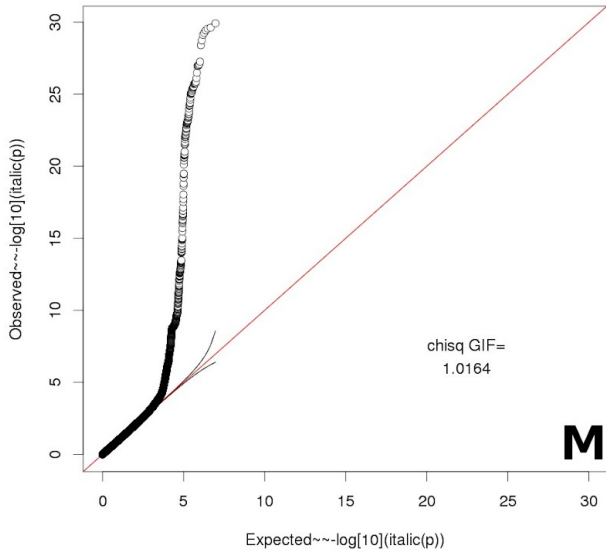
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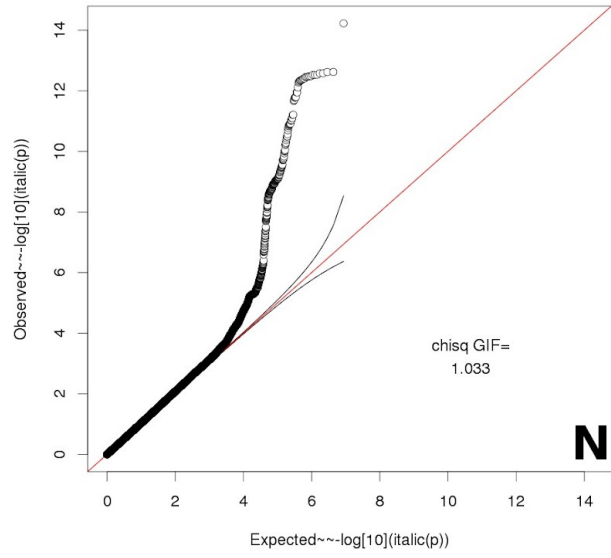
QQ plot with 95% CIs



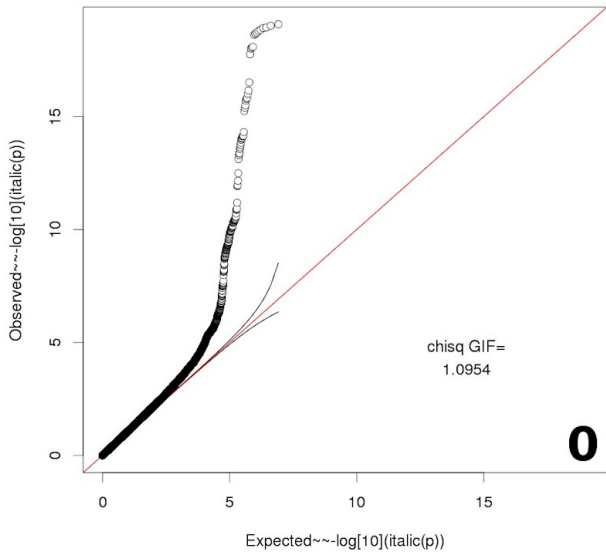
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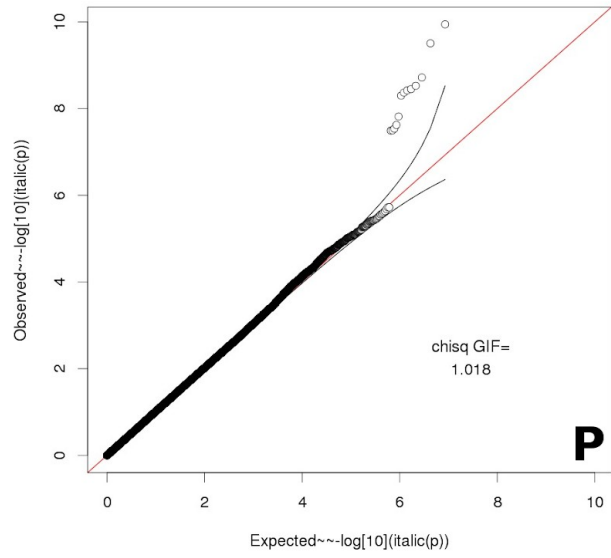
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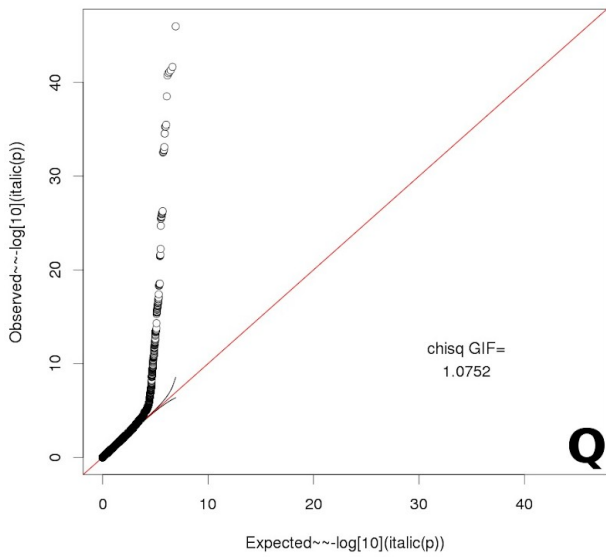
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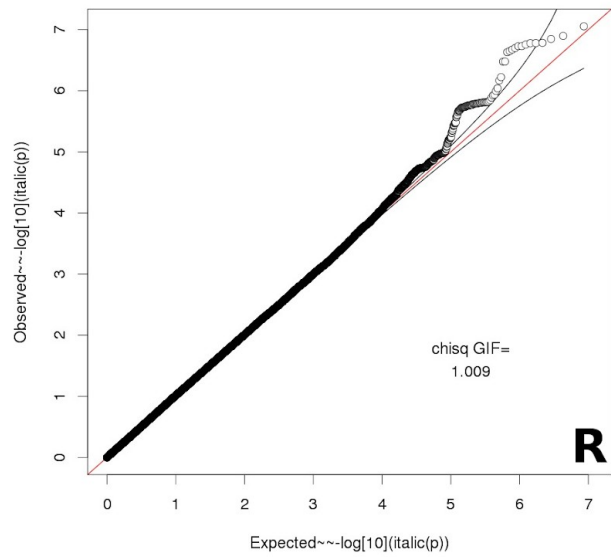
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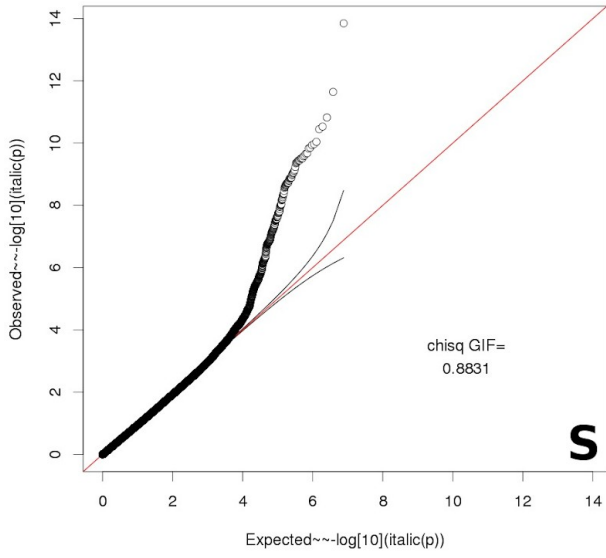
QQ plot with 95% CIs



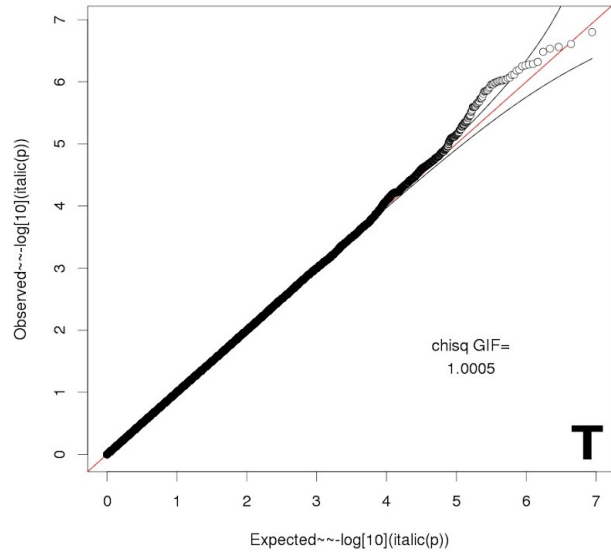
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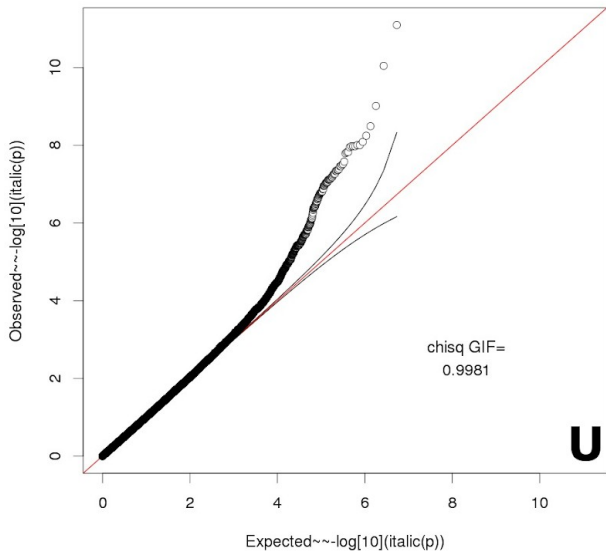
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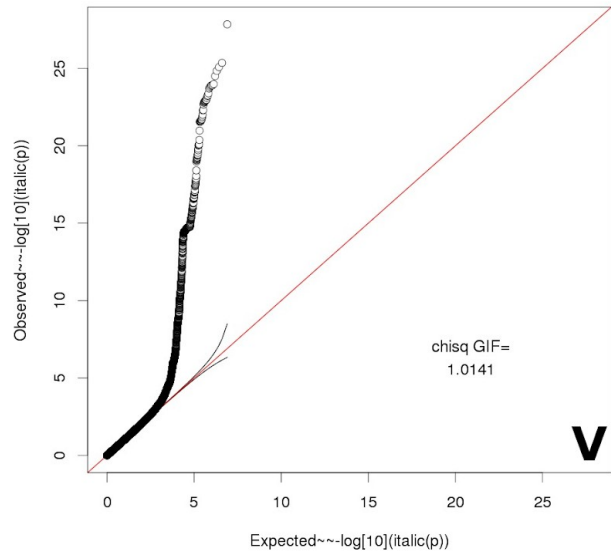
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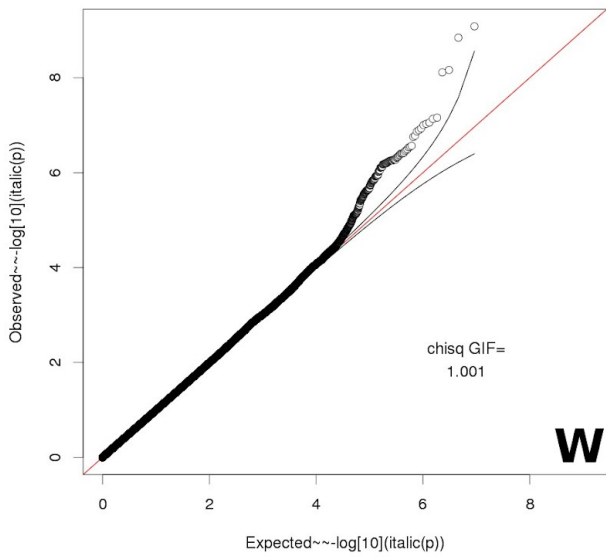
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QQ plot with 95% CIs



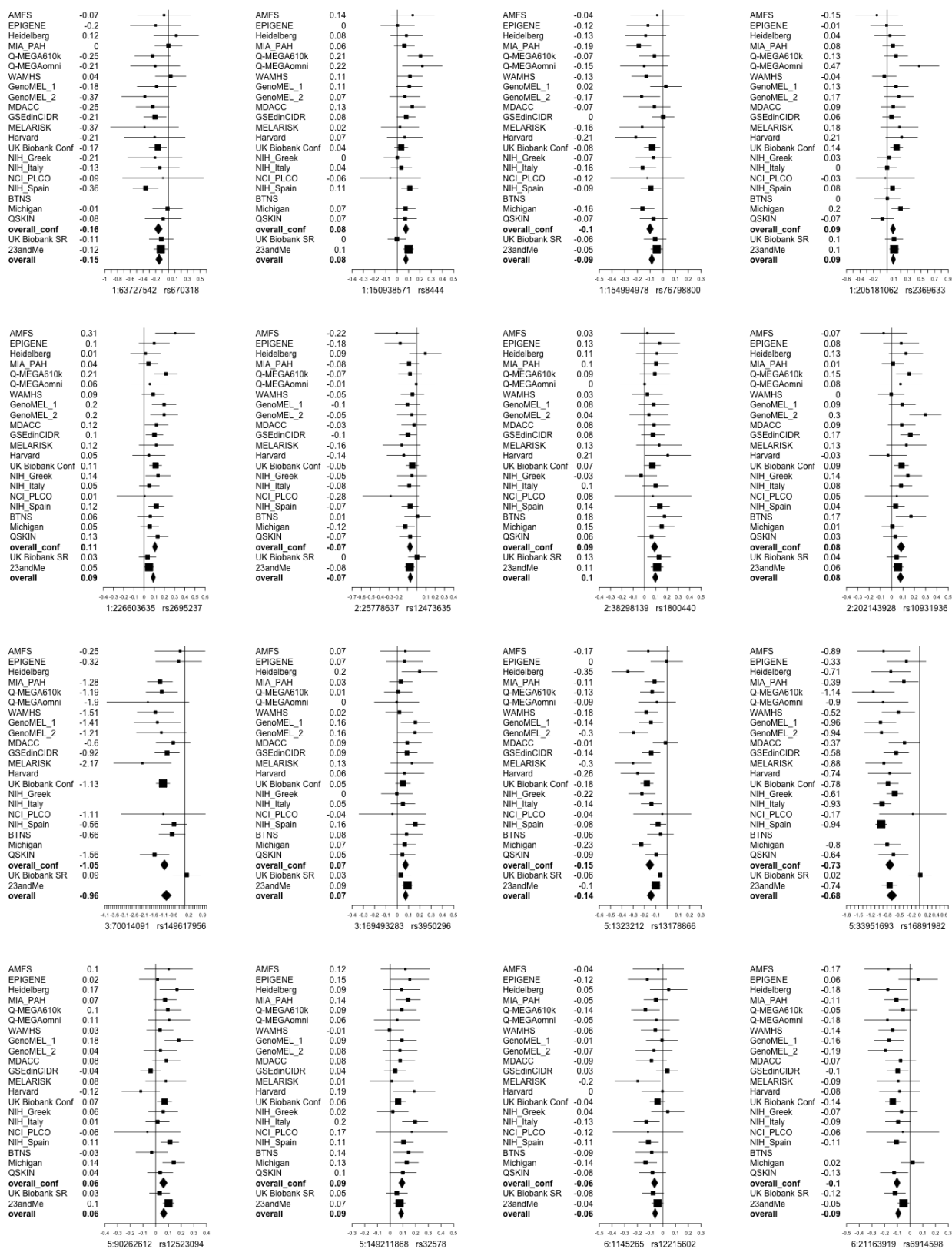
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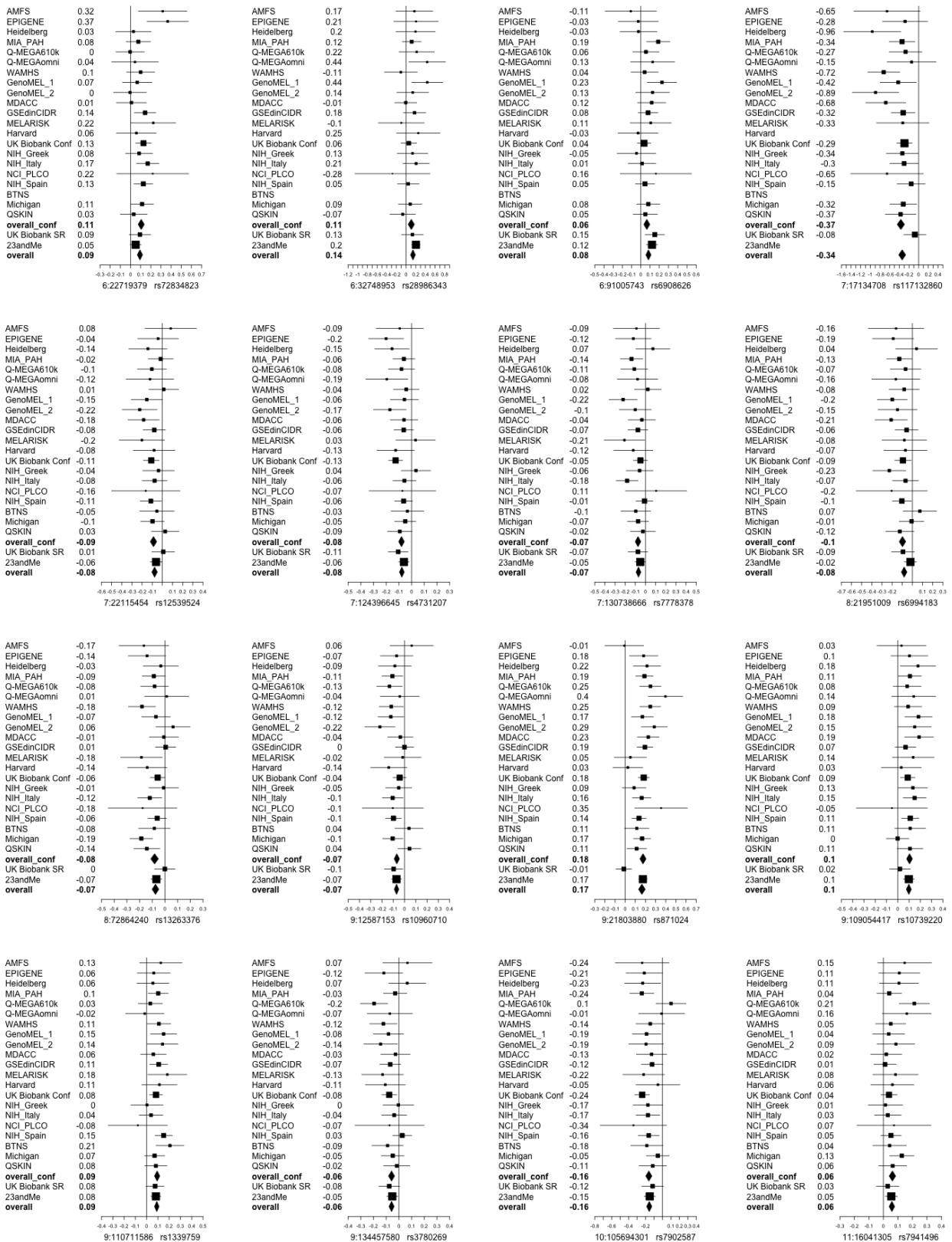


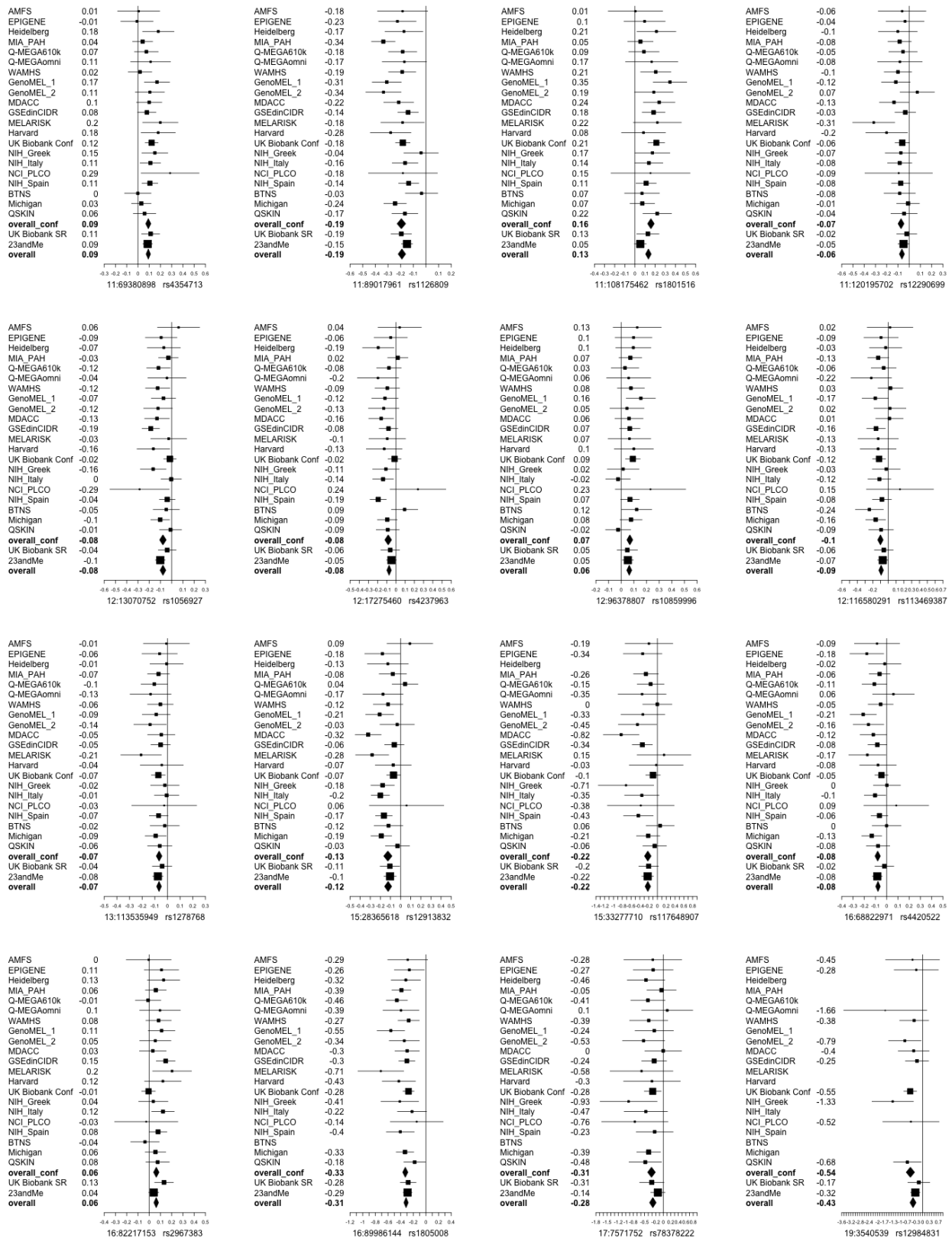
## Supplementary Figure 1: Quantile-Quantile plots.

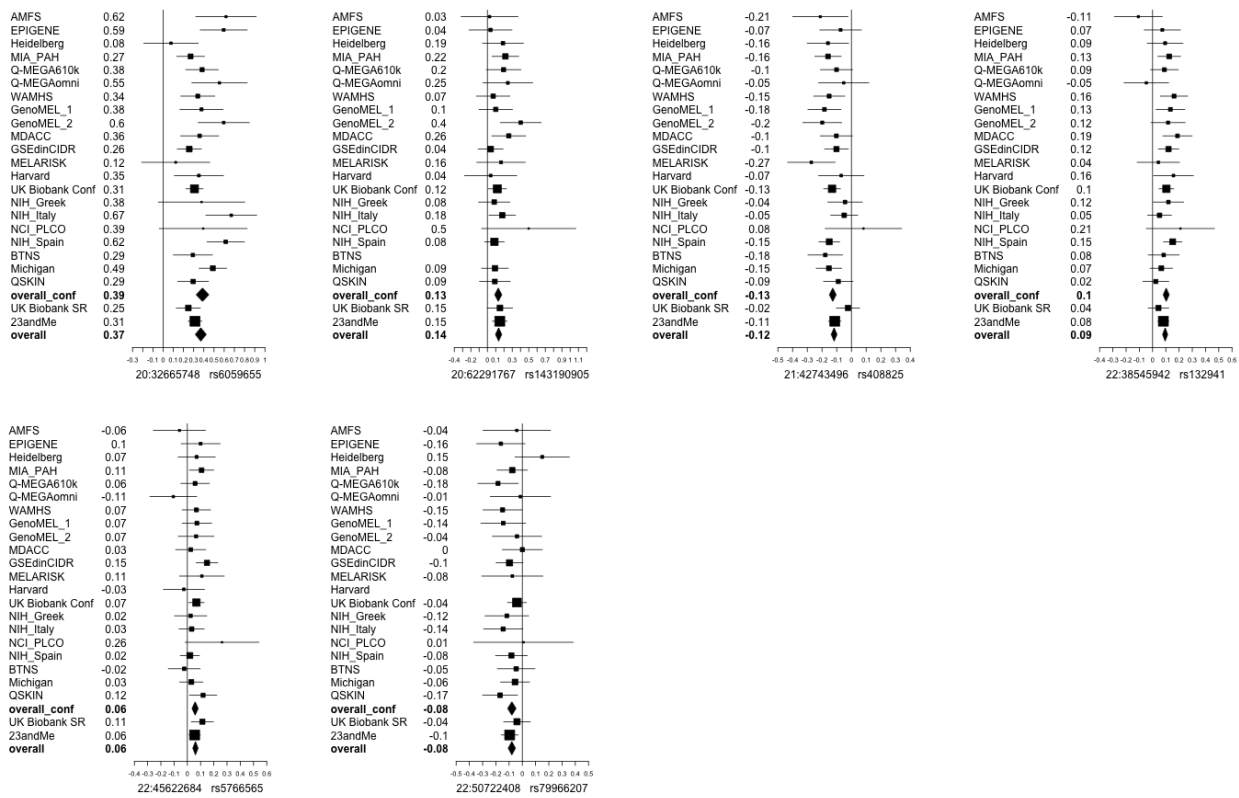
Quantile-quantile plots of negative log<sub>10</sub> two-sided P-value derived from a logistic regression GWAS for all post QC imputed SNPs with a MAF > 0.005. The sample size for each GWAS is listed in **Supplementary Table 1** and analysis methods for each GWAS are in the **Online**

**Methods.** A: AMFS; B: CIDR\_WAMHS; C: EPIGENE; D: GenoMEL\_P1; E: GenoMEL\_P2; F: HARVARD; G: HEIDELBERG; H: MDACC; I: MELARISK; J: MIA\_PAH; K: QMEGA\_610k; L: QMEGA\_omni; M: UKBB500K\_pathconf; N: GSEdinCIDRchr; O: italy; P: greek; Q: spain; R: PLCO; S: MICHIGAN; T: QSkin; U: BNMS; V: 23andMe; W: UKBB500K\_selfrep.





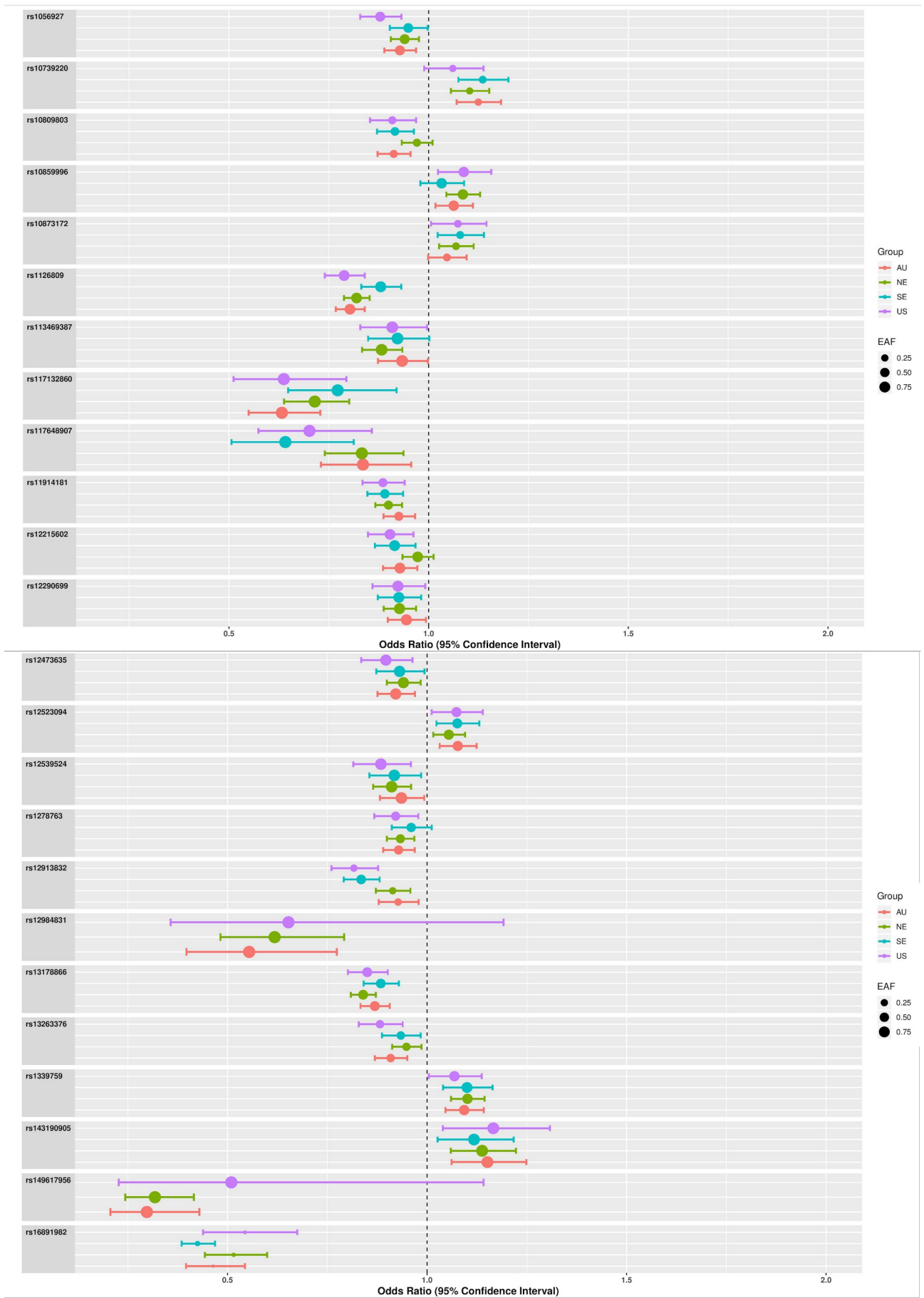


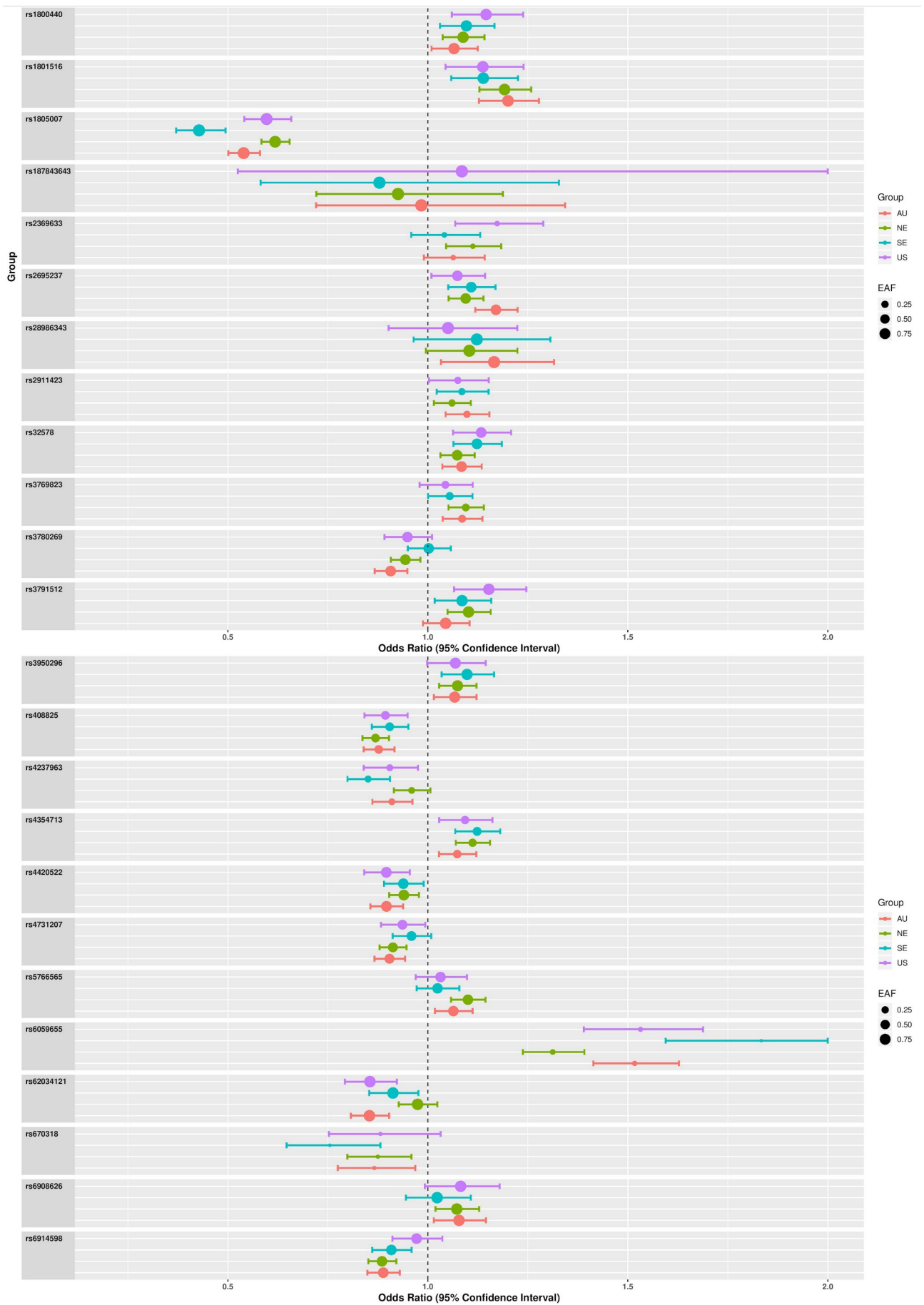


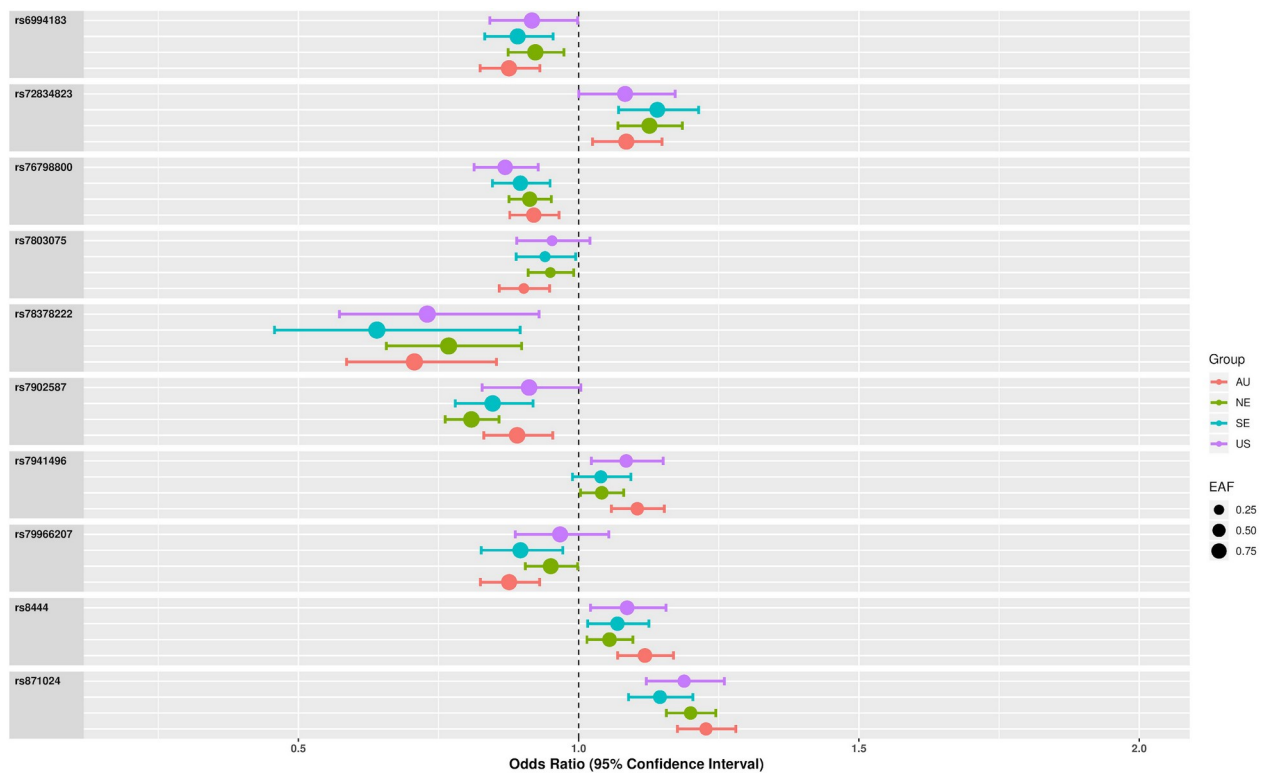
**Supplementary Figure 2: Effect size estimates across contributing GWAS.**

Forest plots showing results across the studies for the most significant SNP at each of the 54 genome-wide significant loci. Results shown for meta-analysis with only clinically-confirmed cases (“overall\_conf”) and including self-reported cases (“overall”). Estimated log(OR) and 95% confidence intervals are plotted. The results for each study were calculated using the sample sizes listed in **Supplementary Table 1**.









**Supplementary Figure 3: Effect size and minor allele frequency by geographic region.**

Forest plots showing the effect size estimates, 95% confidence intervals and allele frequency for each independent genome-wide significant SNP grouped by geographic region (AU: Australia, 7398 cases and 13413 controls; NE: Northern European, 13498 cases and 26808 controls; SE: Southern European, 6445 cases and 7819 controls; US: United States, 3710 cases and 32825 controls). Allele frequency is indicated by point size.

## Supplementary Table Legends

### Supplementary Table 1. Summary of GWAS sets.

**Type** is clinically confirmed cutaneous melanoma (CM) or self-report. **Population** is the broad population of origin for samples. **European** is multiple European countries; **US** United States, **UK** United Kingdom; **European-derived** is combined populations drawn from Australian and European countries. MIA\_PAH includes Australian case and control samples supplemented with additional UK controls. The Brisbane Nevus Morphology Study (**BNMS**) includes a combined set of Australian and German cases and controls. Principal component analysis was used to ensure homogeneity within GWAS; see GWAS descriptions for details. **Study** is the GWAS name. In addition to **case** and **control** number, the **effective case and control** number to better display discovery power was calculated as

$$2/\sigma^2, \text{ where } \sigma^2 = \sqrt{\left(\frac{1}{Case_N} + \frac{1}{Control_N}\right)}$$

**GWAS Array** is the array used for genotyping. When arrays were combined SNPs were filtered to the minimum overlapping set (see Methods). The Harvard, BNMS, and 23andMe GWAS were imputed to 1000 genomes phase 1 v3; all other data sets were imputed to HRC v1.1 using the Michigan Imputation Server. The genomic inflation (**Lambda**) and LD Score Regression (**LDSC Intercept** and its standard error (**SE**))<sup>1</sup> are both reported as the intercept better reflects test statistic inflation while lambda is also influenced by true polygenic signal and sample size.

The field “**In previous meta-analyses?**” indicates if a GWAS was included in<sup>8</sup>. \*This GWAS was included in the previous meta-analysis, but has now been supplemented with additional cases and controls such that 39% of cases and 92% of controls are new.

**Supplementary Table 2. Inflation, LD Score intercept and genetic correlation between confirmed and self-report sets.**

**Dataset** is the **confirmed** meta-analysis, the total confirmed plus self-report (**Confirmed plus SR**), the UK Biobank self-report GWAS (**UK Biobank SR**), and the **23andMe** self-report set. Array heritability ( $h^2$ ), genomic inflation factor (**Lambda**), **LDSC intercept** and its **SE**, and the ratio between them are reported <sup>1</sup>. The genetic correlation ( $R_g$ ) and its **SE** as calculated by LDSC indicate a high degree of genetic overlap between self-report and confirmed GWAS datasets.

**Supplementary Table 3. Annotation and detailed results for independent SNPs associated with CM in the total confirmed plus self-report meta-analysis.**

**Locus:** Independent SNP within 1 MB are combined into a single locus. **SNP:** Independent SNP number. **CHR** and **BP** are provided as per hg 19 positions. **rsID:** dbSNP142 rs number.

We list the **Nearest gene** and **Nearest protein coding genes** as reported by the open targets genetics platform<sup>29</sup>. Where loci overlap, we summarise the TWAS results using melanocyte-specific expression (**Online Methods, Supplementary Table 11**) or gene expression from the skin representing sun-exposed skin, non-sun-exposed skin, and transformed skin fibroblasts from GTEx (**Online Methods, Supplementary Table 12**). If known we list the functional gene target based on presence of a missense protein change, or if identified by a previous publication the gene name and PUBMED ID.

**CHR:BP:REFALT** is a positional ID made by combining HRC position, ref and alt allele. Effect allele (**EA**) and non-effect allele (**NEA**) as well as the freq of the effect allele (**EA freq**) are provided. For the two inverse variance weighted meta-analysis of log(OR) effect-sizes (derived from the logistic regression GWAS reported in **Supplementary Table 1**) performed using PLINK v1.9<sup>30</sup> - the total (confirmed and self-report combined), and the confirmed cases only - we report summary data including number of contributing GWAS (**N**), Fixed effects two-sided P-value and OR (**Pmeta**, **OR**) and random effects (**Pmeta\_r**, **OR random**), and measures of heterogeneity (**Q** and **I<sup>2</sup>**). Finally, we report the per study OR for the EA allele for each study. To account for multiple testing only SNPs reaching genome-wide significance ( $P < 5 \times 10^{-8}$ ) are reported; see **Online Methods** for additional filters on significant loci.

#### Supplementary Table 4. SNPs independently associated with CM in the total analysis set.

The total inverse-variance weighted CM meta-analysis includes all confirmed and self-report cases, with a sample size of 36,760 melanoma cases and 375,188 controls.

**Locus:** Independent SNP within 1 MB are combined into a single locus. **SNP:** Independent SNP number. **CHR** and **BP** are provided as per hg 19 positions. **rsID:** dbSNP142 rs number. **CHR:BP:REFALT** is a positional ID made by combining HRC position, ref and alt allele. Effect allele (**EA**) and non-effect allele (**NEA**) as well as the freq of the effect allele (**EA freq**) are provided. **BETA** is the log of the fixed effects OR for the total (confirmed plus self-report) meta-analysis and its standard error (**SE**) and P-value (**Pmeta**).

Conditionally independent SNPs were determined using a stepwise model selection as implemented in GCTA<sup>31,32</sup> (**Online Methods**) with the resultant adjust **joint conditional BETA**, **SE** and **P-value** reported. Finally, we report the linkage disequilibrium  $r$  as estimated in the reference population for SNP  $i$  and SNP  $i + 1$  (**Ld\_r**). This can be informative when the joint conditional P is more significant than the single SNP analysis (e.g., where two adjacent SNPs are in negative LD).

To limit the chance of false positive claims of novel SNP/loci, we further filtered the list of 75 conditionally independent variants to those (i) genome-wide significant ( $P < 5 \times 10^{-8}$ ) in single SNP and joint conditional analysis, and (ii) as recommended<sup>33</sup> where there was evidence of heterogeneity between studies ( $I^2 > 31\%$ ) the random effect P-value also needed to be  $< 5 \times 10^{-8}$ . The **Independent SNP** field reports this; if a variant passes all filters its number is recorded; otherwise the reason for filtering is noted; **het** indicates the SNP has  $I^2 > 31\%$  and the random effects is not significant; **cojo** indicates the variant is only significant in the cojo analysis and not  $p < 5 \times 10^{-8}$  in the initial single SNP GWAS so is not counted as a secondary SNP at this locus.

<sup>a</sup>While the lead SNP selected by joint analysis rs12523094 has meta-analysis  $I^2 > 31$  and a random effects p-value  $< 5 \times 10^{-8}$  there are SNPs in LD that pass this filter. E.g., rs12173258 has the strongest p-value and is passes filters ( $P_{\text{meta}} = 1.1 \times 10^{-11}$  and  $I^2 = 29.6$ ) and this locus was retained.

<sup>b</sup>The HLA region is excluded from LD reference panel used for conditional analysis (See **Online Methods**) and the lead SNP is reported. <sup>c</sup>All SNPs at this locus near the *FTO* gene, including the lead SNP, have  $I^2 > 31$  and a random effects p-value  $< 5 \times 10^{-8}$ , and as such is not counted as an independent CM risk locus in this analysis.

### Supplementary Table 5. Independent CM SNPs and their association with risk phenotypes.

**Locus:** Independent SNPs within 1 MB are combined into a single locus. **SNP:** Independent SNP number. **CHR** and **BP** are provided as per hg 19 positions. **rsID:** dbSNP142 rs number. Nearest, or if known likely functional **gene** target, is provided. The meta-analysis P-value for the confirmed only sets (**Pmeta confirmed**) and total including self-report (**Pmeta confirmed SR**) are listed for each variant, as is their association P-value from a series of GWAS of melanoma risk phenotypes from the UK Biobank (**Online Methods**); Ease of tanning (**P Ease**), Number of Childhood sunburns (**P Childhood Sunburns**), **Skin Colour**, non-red hair colour (**Hair Colour**) as well as red hair yes/no (**Red Hair**). Each SNP's association with leukocyte telomere length (P Telomere Length) taken from a GWAS of 37,684 individuals<sup>34</sup> and the same nevus count GWAS meta-analysis used for the joint analyses of CM and nevus count and pigmentation (N = 65,597, Methods). Two-sided P-values from logistic (binary traits) or linear (quantitative) regression GWAS are reported for the listed traits.

For a number of SNPs, telomere GWAS results were not available for the lead CM SNP; where possible a proxy SNP (**Telomere SNP**) was identified using an expanding LD window in PLINK v1.9 using the same LD reference panel as the GCTA conditional analysis (**Online Methods**). The LD window to search for proxies started at 2mb and 100 SNPs wide, with a minimum LD  $r^2_{\text{EUR}} > 0.9$ , with the threshold relaxed until a SNP was identified; if no SNP was found with a window of 1000 SNPs, 4 Mb and LD  $r^2_{\text{EUR}} > 0.5$  the search was stopped. LD  $r^2$  between the **Telomere SNP** and the lead SNP is listed ( $r^2$ )

<sup>a</sup>For two SNPs, rs7705526 and rs143190905 data for telomere association was not available for the lead SNP nor a proxy with LD  $r^2_{\text{EUR}} > 0.5$ . For these two SNPs the p-value is derived from a separate telomere GWAS<sup>35</sup> identified via the open targets genetic platform. <sup>b</sup>SNP is not in the Nevus GWAS meta-analysis data, nor is there a proxy SNP within a window of 1000 SNPs, 4 Mb and LD  $r^2_{\text{EUR}} > 0.5$ . <sup>c</sup>P value for a proxy SNP for rs116927526 is reported; rs193247693 LD  $r^2_{\text{EUR}}$  0.70



**Supplementary Table 6. SNPs independently associated with CM in the confirmed cases only analysis set.**

**Locus:** Independent SNPs from the confirmed cases meta-analysis within 1 MB are combined into a single locus. **SNP:** Independent SNP number. **SNP formally significant and independent** discounts SNPs that, while selected in the joint conditional analysis (**Online Methods**), are not significant in the single SNP GWAS (e.g.  $P_{\text{meta}} > 5 \times 10^{-8}$  or  $P_{\text{meta}_r} > 5 \times 10^{-8}$  where heterogeneity  $I^2 > 31$ ). See footnotes below for further detail.

**CHR** and **BP** are provided as per hg 19 positions. **rsID:** dbSNP142 rs number. **CHR:BP:REFALT** is a positional ID made by combining HRC position, ref and alt allele. Effect allele (**EA**) and non-effect allele (**NEA**) as well as the freq of the effect allele (**EA freq**) are provided. **BETA** is the log of the fixed effects OR for the confirmed cases only meta-analysis and its standard error (**SE**) and P-value (**Pmeta**). Conditionally independent SNPs were determined using a stepwise model selection as implemented in GCTA (**Online Methods**) with the resultant adjust **joint conditional BETA**, **SE** and **P**-value reported. Finally, we report the linkage disequilibrium  $r$  as estimated in the reference population for SNP  $i$  and SNP  $i + 1$  (**Ld\_r**). This can be informative when the joint conditional  $P$  is more significant than the single SNP analysis (e.g. where two adjacent SNPs are in negative LD).

For reference we append the relevant summary data including number of contributing GWAS (**N**), Fixed effects P-value and OR (**Pmeta**, **OR**) and random effects (**Pmeta\_r**, **OR random**), and measures of heterogeneity (**Q** and **I2**) from the confirmed cases only meta-analysis results performed using PLINK v1.9<sup>30</sup>.

We also report the per study OR for the EA allele for each study.

Results are compared to the “**Total Meta-analysis lead SNP**” with the overlapping locus number from **Supplementary Table 3** provided.

<sup>a</sup>While the lead SNP in this locus selected by conditional analysis has fixed  $P > 5 \times 10^{-8}$ ,  $I^2$  heterogeneity measure  $> 31\%$  and a random meta-analysis P-value  $> 5 \times 10^{-8}$ , other SNPs exist that qualify, e.g. chromosome 2 rs3769823  $r^2_{\text{EUR}} = 0.75$  with lead SNP rs10931936; chromosome 5 rs12173258  $r^2_{\text{EUR}} = 0.82$  with lead SNP rs11747245; chromosome 8 rs1481853 ( $r^2_{\text{EUR}} = 0.99$  with lead SNP rs13263376); chromosome 12 rs4257028 ( $r^2_{\text{EUR}} = 0.99$  with lead SNP rs4763456); chromosome 16 rs16953002 ( $r^2_{\text{EUR}} = 0.85$  with lead SNP rs62034139); chromosome 16 rs2967361 ( $r^2_{\text{EUR}} = 0.85$  with lead SNP rs2911423). <sup>b</sup>While the lead SNP in the total meta-analysis is rs2301293, that SNP is  $P > 5e-8$  in the total meta-analysis and not formally a CM locus. <sup>c</sup> $I^2$  heterogeneity measure  $> 31\%$  and a random meta-analysis P-value  $> 5 \times 10^{-8}$ . <sup>d</sup>Indicates the variant is only significant in the cojo analysis and not  $p=5 \times 10^{-8}$  in the initial single SNP GWAS, so is not counted as a secondary SNP at this locus.

**Supplementary Table 7. Results from total confirmed plus self-report meta-analysis for SNPs with meta-analysis  $P < 5 \times 10^{-8}$ .**

Fixed or random effects meta-analysis results are displayed with respect to  $I^2 < 31\%$  (**Online Methods**). The meta-analysis was an inverse-variance weighted meta-analysis of log(OR) effect-sizes derived from the logistic regression GWAS for all GWAS listed in **Supplementary Table 1** (36,760 melanoma cases and 375,188 controls). All p-values are two-sided.

**Supplementary Table 8. Sample sizes for sub phenotype GWAS analysis.**

Numbers of cases and controls available across contributing GWAS data for the histology, age and sex stratified GWAS analyses.

## Supplementary Table 9. Combined analysis of CM and Nevus count GWAS meta-analyses.

Total sample size for the total CM meta-analysis includes all confirmed and self-report cases, with a total sample size of 36,760 melanoma cases and 375,188 controls. The Nevus GWAS meta-analysis included 65,597 participants. Two-sided P-values from each meta-analysis were combined using Stouffer's method (see Methods).

LD calculations performed in PLINK using a reference panel of 10,000 white British UK Biobank individuals as implemented in the FUMA platform was used to identify independent SNPs with  $P < 5 \times 10^{-8}$ ; independent SNPs within 1 Mb were considered to be single loci (**Online Methods**). The lead SNP for each locus is reported. Bolding indicates that the locus is significant at a Bonferroni corrected P-value threshold of  $P \leq 1.25 \times 10^{-8}$ . Chromosome (**CHR**), base pair (**BP**) and **rsID** are provided for the peak variant for each locus using hg19 positions. Effect allele (**EA**) and non-effect allele (**NEA**) as well as the freq of the effect allele (**EA freq**) are provided. We list the **Nearest gene** and **Nearest protein coding genes** as reported by the open targets genetics platform<sup>29</sup>. If the lead SNP is an eQTL for skin tissues in GTEx we list the gene (**GTEx skin eQTL gene**); if the p-value is not significant following Bonferroni correction ( $> 0.05$  divided by the number of genes) the actual P-value is also reported. If known we list the functional gene target based on presence of a missense protein change, or if identified by a previous publication the gene name and PUBMED ID.

If the locus overlaps with a locus identified in the total confirmed plus self-report CM meta-analysis (**Table 1, Table 2, Supplementary Table 3**) its number is noted here, as is the peak CM rsID if appropriate, and the LD  $r^2_{\text{EUR}}$  between the two SNPs (**Overlapping CM locus, rsID and LD r2 between lead SNPs**).

If the locus overlaps with a recent combined analysis of CM and nevus count GWAS meta-analysis<sup>10</sup> this is noted (otherwise novel ones are indicated by new), and the peak SNP there is provided, as is the LD  $r^2_{\text{EUR}}$  between the new peak and that SNP, as well as the likely model for this locus (CM alone, Nevus alone, or pleiotropic for CM and nevus count (**Overlapping 2018 Nevus+CM locus; rsID, LD r2 between lead SNPs, and 2018 Model**)).

The **Model** field indicates which GWAS-PW model has a PPA  $> 0.5$  (**Online Methods**); model 3, pleiotropic for CM and Nevus count (CM+Nevus) or Model 1 (CM alone). No loci were associated with model 2, Nevus count alone. Where appropriate we also indicate if this locus is pleiotropically associated with pigmentation (**Online Methods, Supplementary Table 10**).

We summarise the Stouffer's method meta-analysis and GWAS-PW approach (Online methods). For the peak locus SNP in field **rsID** we provide the Z score and its variance (**V**) for the total CM GWAS meta-analysis (**CM**), the Nevus GWAS meta-analysis (**Nevus**). The P-value from Stouffer meta-analysis of both (**CM + Nevus P**). GWAS-PW assigns SNPs to **LD blocks**, and the hg19 start and end bp for each is provided as well as the maximum Z score for CM or Nevus for SNPs within each block. The PPA for GWAS-PW models for the association signal at each block being CM alone, Nevus alone, or CM + Nevus are provided. GWAS-PW also reports a 4th model, where the signal is co-located but independent. This is unlikely for nevus count and melanoma, where nevus count is a direct risk for melanoma<sup>10</sup> and as such all model 4 PPAs were dropped and scores for the remaining 3 models reweighted to sum to 1. As all PPA values for model 4 were all  $< 0.01$  barring locus 41, peak SNP rs9651783 on chromosome 11 which reach 0.03, again supporting that colocalization is an unlikely model for CM and nevus count, this made little difference to the final model PPA.



## Supplementary Table 10. Combined analysis of CM and hair colour GWAS.

Total sample size for the total CM meta-analysis includes all confirmed and self-report cases, with a total sample size of 36,760 melanoma cases and 375,188 controls. The hair colour GWAS included 352,662 UK Biobank participants. Two-sided P-values from each meta-analysis were combined using Stouffer's method (see Methods).

The independent locus, as defined by LD calculations implemented in FUMA platform (**Online Methods**), that is novel to previous reports and has a GWAS-PW model 3, pleiotropy, PPA > 0.5 is reported (**CM + Hair colour Locus; Supplementary Methods**). Bolding indicates that the locus is significant at a Bonferroni corrected P-value threshold of  $P \leq 1.25 \times 10^{-8}$ . Chromosome (**CHR**), base pair (**BP**) and **rsID** are provided for the peak variant for each locus using hg19 positions. Effect allele (**EA**) and non-effect allele (**NEA**) as well as the freq of the effect allele (**EA freq**) are provided. [For the peak locus SNP in field **rsID** we provide the **nearest gene** and **nearest protein coding gene**]. If the lead SNP is an eQTL for skin tissues in GTEx we list the gene (**GTEx skin eQTL gene**); if the p-value is not significant following Bonferroni correction ( $> 0.05$  divided by the number of genes), the actual P-value is also reported. If known, we list the functional gene target based on the presence of a missense protein change, or if identified by a previous publication, the gene name and PUBMED ID.

If the Locus overlaps with a locus identified in the total confirmed plus self-report CM meta-analysis (**Table 1, Table 2, Supplementary Table 3**) its number is noted here (**CM Locus**), as is the peak **CM rsID** if appropriate, and the LD  $r^2_{EUR}$  (**LD\_r2**) between the two SNPs.

The **Model** field indicates which GWAS-PW model has a PPA > 0.5 (**Online Methods**); model 3, pleiotropic for CM and Pigmentation (CM+Pigment) or Model 1 (CM alone). Where appropriate we also indicate if this locus is pleiotropically associated with nevus count (**Online Methods, Supplementary Table 9**).

For the peak locus SNP in field **rsID** we provide the Z score (**Z**) and its variance (**V**) for the total CM GWAS meta-analysis (**CM**), the Hair colour GWAS (**Hair**), and the P-value from Stouffer meta-analysis of both (**CM + Hair P**). GWAS-PW assigns SNPs to **LD blocks** (50 SNPs wide) and provides the maximum absolute Z score for CM or Hair colour for SNPs within each block. The PPA for GWAS-PW models for the association signal at each block (**PPA**) being CM alone, hair colour alone, or CM + hair colour are provided.

**Supplementary Table 11. Top melanoma TWAS genes using melanocyte eQTL data as a reference.**

For genes whose expression in melanocytes is predicted to be significantly associated with CM by TWAS (**Online Methods**; melanocyte eQTL dataset from 106 individuals), the transcript gene name (**Gene**) along with its hg19 chromosome (**CHR**), transcription start (**Start**) and end (**End**) positions are reported. We also provide the peak CM SNP's rsID (**CM rsID**) and Z score for association with CM in the total (confirmed plus self-report) meta-analysis (**CM Z**). In addition, we report the rsID of the most significant eQTL variant in the locus from the 1000 genomes reference panel for the named transcript (**eQTL Top Variant**), that variant's eQTL Z score (**eQTL Z**), and that variant's total GWAS meta-analysis Z-score (**CM Z for eQTL variant**). The number of variants included in the TWAS models for each locus is reported (**Number of variants**), as is the weighted number of variants (**Number of Weight**). For each transcript the best performing TWAS **Model**, and its **TWAS Z** and **TWAS P** are provided (See **Online Methods** for the statistical tests). We also provide **TWAS P cutoff** that we applied based on the multiple testing corrections described in **Online Methods**. To assist interpretation, we note if the significant gene maps to a previously or newly identified **CM locus**, and if so, report the peak SNP and locus number from **Supplementary Table 3** or is otherwise **new** to CM. As done for independent SNPs identified in the total and confirmed CM meta-analysis, TWAS genes identified within 1 Mb of each other were combined in a single locus. Finally, we report if this same transcript was significantly associated with CM in Zhang and colleagues' work<sup>36</sup>, which applied melanocyte TWAS to the phase 1 CM data (**Reported by Zhang**; Y=yes, N=no).

### Supplementary Table 12. Top melanoma TWAS genes using skin eQTL data as a reference.

For genes whose expression in three skin tissues (sun-exposed, not-sun-exposed, and fibroblasts) within GTEx (V7) is predicted to be significantly associated with CM by TWAS (**Online Methods**), the transcript gene name (**Gene**) along with its hg19 chromosome (**CHR**), transcription start (**Start**) and end (**End**) positions are reported. We also provide the peak CM SNP's rsID (**CM rsID**) and Z score for association with CM in the total (confirmed plus self-report) meta-analysis (**CM Z**). In addition we report the rsID of the most significant eQTL variant in the locus from the 1000 genomes reference panel for the named transcript (**eQTL Top Variant**), that variant's eQTL Z score (**eQTL Z**), and that variant's total GWAS meta-analysis Z-score (**CM Z for eQTL variant**). The number of variants included in the TWAS models for this locus are reported (**Number of Variants**), as is the weighted number of variants (**Number of Weight**). For each transcript the best performing TWAS **Model**, and its **TWAS Z** and **TWAS P** are provided (See **Online Methods** for the statistical tests). We also provide **TWAS P cutoff** that we applied based on the multiple testing corrections described in **Online Methods**. To assist interpretation, we note if the significant gene maps to a previously or newly identified **CM locus**, and if so, report the peak SNP and locus number from **Supplementary Table 3** or is otherwise **new** to CM. As done for independent SNPs identified in the total and confirmed CM meta-analysis, TWAS identified genes within 1 Mb of each other were combined in a single locus.



**Supplementary Table 13. Top melanoma TWAS genes using all tissues eQTL data as a reference.**

For genes whose expression in 45 GTEx (V7) tissues (excluding 3 skin tissues shown in **Supplementary Table 12**) is predicted to be significantly associated with CM by TWAS (**Online Methods**), the transcript gene name (**Gene**) along with its hg19 chromosome (**CHR**), transcription start (**Start**) and end (**End**) positions are reported. We also provide the peak CM SNP's rsID (**CM rsID**) and Z score for association with CM in the total (confirmed plus self-report) meta-analysis (**CM Z**). In addition, we report the rsID of the most significant eQTL variant in the locus from the 1000 genomes reference panel for the named transcript (**eQTL Top Variant**), that variant's eQTL Z score (**eQTL Z**), and that variant's total GWAS meta-analysis Z-score (**CM Z for eQTL variant**). The number of variants included in the TWAS models for this locus are reported (**Number of Variants**), as is the weighted number of variants (**Number of Weight**). For each transcript the best performing TWAS **Model**, and its **TWAS Z** and **TWAS P** are provided (See **Online Methods** for the statistical tests). **TWAS P cutoff** was set for each tissue based on the number of genes passing a heritability cutoff and being tested within each tissue type (0.05/number of genes). P-values of genes that pass a Bonferroni-corrected cross-tissue wide P-value cutoff (based on the total number of tested genes in 45 tissues, N=211,941) are bolded. To assist interpretation, we note if the significant gene maps to a previously identified **CM locus**, and report the applicable peak SNP and locus number from **Supplementary Table 3**.

#### **Supplementary Table 14: Tabulation of loci associated across primary and secondary analyses**

Sample size: The Total CM inverse variance weighted meta-analysis of logistic regression GWAS included 36,760 melanoma cases and 375,188 controls. The nevus GWAS meta-analysis included 65,597 participants. The hair colour GWAS included 352,662 UK Biobank participants. Two-sided P-values from the CM meta-analysis, and either the nevus or hair colour GWAS, were combined using Stouffer's method (see **Online Methods**). For TWAS, summary statistics from Total CM GWAS meta-analysis and eQTL datasets of different sample sizes were used (GTEx v7 datasets; n = 106 for melanocytes; See **Online Methods** for the statistical tests).

Loci derived from the Total CM meta-analysis were significant at multiple testing corrected threshold of  $P < 5 \times 10^{-8}$ ; the significance threshold for the additional, secondary analyses were further correct to  $P < 1.25 \times 10^{-8}$  (see **Online Methods**).

Each **Locus** is numbered in order (see **Online Methods** for how loci are defined), and the positions (**CHR, BP**) and **rsID** for the lead SNP are reported for the SNP with the strongest total CM associations signal (totalCM, TWAS results) or for the loci derived from the joint analysis, the SNP with the strongest joint p-value. **Gene** prioritises the functional target if known, followed by melanocyte or skin tissue TWAS data, or finally the closest protein coding gene (**Supplementary Table 3, 11, and 12**). For each of the named analyses we indicate with a "1" if the loci passes the significance threshold for that analysis (**Supplementary Tables 3,9,10,11,12**).

**Supplementary Table 15. Colocalization of melanoma GWAS signal and eQTLs from melanocytes and skin tissues.**

eCAVIAR<sup>28</sup> was used for testing colocalization of melanocyte and GTEx skin tissue eQTLs (listed in **eQTL dataset**) for the reported gene (listed in **Gene** column), and the melanoma GWAS signal (here we report the **CM GWAS locus**, lead independent **SNP**). Fifty SNPs upstream of and downstream from the GWAS lead SNP in each locus were chosen to quantify the probability of the variant to be causal in both the GWAS and eQTL studies.

We report the colocalization posterior probability (**CLPP**), which is the probability that the same variant is causal in both GWAS and eQTL (See **Online Methods** for the statistical tests). A cutoff of  $CLPP > 0.01$  was applied to the resulting list of SNPs, and SNPs were further filtered using an LD  $r^2$  cutoff of  $> 0.9$  with the GWAS lead SNP (1000 Genomes, EUR population), as well as to those with a significant eQTL P-value ( $< 0.05/\text{number of eGenes tested for each eQTL dataset}$ ). We report the SNP with the highest CLPP score for each gene, as well as its LD **r2 with the lead GWAS SNP**, and **eQTL P-value**. Finally, we indicate if the gene is also significantly associated with CM by TWAS in melanocyte or skin tissues (**Supplementary Tables 11-12**).

**Supplementary Table 16. Enriched canonical pathways in genes identified through TWAS and colocalization from melanocyte or skin tissues.**

All significant TWAS genes from melanocyte (**Supplementary Table 11**) plus skin tissues (**Supplementary Table 12**), as well as all colocalized genes identified by eCAVIAR applied to melanocyte and 3 skin tissue datasets (**Supplementary Table 15**) were queried as a gene list in IPA analysis (Qiagen, version 46901286). Significantly enriched canonical pathways are displayed ( $-\log(\mathbf{P}\text{-value}) > 1.3$ , right-tailed Fisher's Exact Test).

**Supplementary Table 17. Top 5 enriched upstream regulators in genes identified through TWAS and colocalization from melanocyte or skin tissues.**

All significant TWAS genes from melanocyte (**Supplementary Table 11**) plus skin tissues (**Supplementary Table 12**), as well as all colocalized genes identified by eCAVIAR applied to melanocyte and all 3 skin tissue datasets (**Supplementary Table 15**) were queried as a gene list in IPA analysis (Qiagen, version 46901286). The top 5 enriched **Upstream Regulators** are listed (**P-value of overlap** < 0.05, right-tailed Fisher's Exact Test; **Molecule Type** and **Target molecules in dataset** are also reported).

**Supplementary Table 18: Results for UKBB self-report set for three loci no longer significant following their removal from the total meta-analysis**

For each locus that is no longer significant following the exclusion of the UKBB self-report set we report the position and rsID for the lead SNP. For each SNP we report the results for the total inverse-variance weighted meta-analysis of log(OR) effect-sizes, which includes all pathology-confirmed GWAS together with 23andMe and UKBB self-report cases (36,760 melanoma cases and 375,188 controls). We also report results for the meta-analysis without UKBB self-report cases (34,958 cases and 367,980 controls), and for logistic regression results for the UKBB self-report GWAS itself (1,802 self-report CM cases and 7,208 controls). For each GWAS we tabulate the respective log(OR) (**BETA**), standard error (**SE**) and P-value (**P**). All tests were two-sided and were significant at a multiple testing corrected threshold of  $P < 5 \times 10^{-8}$ .

## Supplementary Methods

### GWAS descriptions

#### Q-MEGA

1,617 CM cases were drawn from population-based studies undertaken in Queensland were combined as The Queensland study of Melanoma: Environment and Genetic Associations (Q-MEGA) study<sup>37</sup>. CM cases were histologically confirmed using the Queensland Cancer Registry<sup>37</sup>. All contributing studies were approved by the Human Research Ethics Committees of QIMR Berghofer, University of Sydney, University of Melbourne and cancer registries of NSW, Victoria and Queensland. Informed consent was obtained from all participants.

Samples were genotyped in two phase using the Illumina HumanHap610 and Omni1-Quad arrays (San Diego, CA, USA), and to ensure maximum SNPs were retained each phase was cleaned, imputed and analysed as QMEGA\_610k and QMEGA\_omni respectively.

**Q-MEGA\_610k:** 926 Q-MEGA cases were combined with 1,799 unrelated controls genotyped on the Illumina HumanHap610 from the Brisbane Adolescent Twin Study<sup>38,39</sup>. 20% of the samples were a singleton from twin pairs or sibling sets, with the remainder drawn from parents of twins. Controls were further supplemented by 2,155 endometriosis patients genotyped using the Illumina HumanHap670 array (San Diego, CA, USA)<sup>40</sup>. Controls who self reported melanoma in themselves or a family member were excluded. Following cleaning (see **Online Methods**) there were 912 cases and 3,777 controls and 487,089 autosomal SNPs. Ethical approval is as per the overall Q-MEGA study above.

**Q-MEGA\_omni:** 691 Q-MEGA CM samples were with 553 healthy cancer-free controls from the Study of Digestive Health (SDH)<sup>41</sup>. After QC (**Online Methods**) there were 656 cases, 538 controls and 767,979 SNPs available for imputation. Ethical approval is as per the overall Q-MEGA study above.

#### AMFS

549 cases with histopathologically confirmed invasive CM, and 431 city, age and sex-matched controls from Melbourne, Brisbane, and Sydney, Australia were drawn from the Australian Melanoma Family Study (AMFS)<sup>42</sup>. The outlined study was approved by the Human Research Ethics Committees of the University of Sydney, University of Melbourne and cancer registries of NSW, Victoria and Queensland. Informed consent was obtained from all participants. AMFS samples were genotyped using Illumina Omni1-Quad (San Diego, CA, USA). After QC (see online methods) there were 535 cases, 427 controls and 791,961 SNPs.

#### WAMHS

DNA samples were available from 1,289 CM cases from the Western Australian Melanoma Health Study (WAMHS)<sup>43</sup>. The WAMHS population based study was collected from Perth, Australia based on histopathology confirmed invasive, cutaneous melanoma cases in the Western Australian Cancer Registry.

WAMHS CM cases were genotyped using Infinium HumanOmniExpressExome, and were combined with two control sets on matching arrays. The first was 960 Australian individuals (including healthy individuals, and a subset with ulcerative colitis) genotyped on the Infinium

HumanOmniExpressExome arrays from the Inflammatory Bowel disease (IBD) Clinical and Research Programme at the Royal Brisbane & Women's Hospital Brisbane, Queensland <sup>44</sup>. The second was 1,298 advanced glaucoma cases from the ANZRAG; Australian & New Zealand Registry of Advanced Glaucoma; 651 were genotyped on Omni1M and 647 on the HumanOmniExpress arrays from Illumina (San Diego, CA, USA). Controls were not screened for melanoma. Following GWAS cleaning (**Online methods**), including filtering to a common set of SNPs that passed QC across all arrays, 1,237 melanoma cases, 1,980 controls, and 567,914 SNPs were available for imputation.

This work was undertaken with ethics approval from The University of Western Australia and the Department of Health Western Australia, with ANZRAG inclusion approved by the Southern Adelaide Clinical Human Research Ethics Committee. Informed consent was obtained from all participants.

### **UK Biobank**

A full description of the UK Biobank dataset and the quality control and imputation approaches applied are described elsewhere <sup>45</sup>. Briefly, UK Biobank is a volunteer cohort of approximately 500,000 persons recruited between 2006 and 2010. Besides answering a broad range of questions, participants gave permission for their health records to be accessed and for linkage to national cancer registries which record pathologically and clinically diagnosed cancers; for melanoma essentially all diagnoses have pathological verification. The Cancer Registry records were searched for diagnoses made under ICD9 (172.x) or ICD10 (C43.x). Overall, 3,659 cases were identified with one or more diagnoses with the date of first diagnosis ranging from 1968 to 2015 at the time of this analysis; about 40% of diagnoses were incident (following recruitment) while the remainder were made prior to recruitment into UK Biobank. UK Biobank participants also self-reported cancer diagnoses at recruitment; overall 1,651 participants had a confirmed diagnosis of melanoma without a self-report of melanoma (the majority of these confirmed diagnoses being after recruitment, the time at which self-reports were made), 1,873 reported melanoma but did not have a confirmed diagnosis and 2,008 had both a self-report of melanoma and a confirmed diagnosis.

Within UK Biobank, biological samples were available for genetic analysis from 488,000 participants. The majority of participants were genotyped using a purpose designed UK Biobank Applied Biosystems Axiom array assessing 826,000 SNPs and indels. The quality control and imputation approaches applied are described elsewhere <sup>45</sup>. UK Biobank provides a lists of participants whose genetic results should be excluded on the basis of poor performance or close relatedness; these persons were excluded in our analysis. Non-European outliers were identified using the same approach that UK Biobank apply to their "Caucasian" definition: the 'aberrant' routine in R <sup>46</sup> was applied to PCs 1&2, 3&4 and 5&6, but anyone declaring themselves to be White was included in this analysis (where UK Biobank automatically exclude "Irish" and "any other white background"); the lambda parameter used was 100.

Following the application of QC and restriction by ancestry as described above, we included 3,499 individuals with confirmed melanoma from the cancer registry and a further 1,802 individuals with self-reported melanoma without cancer registry confirmation. The confirmed and self-reported cases were analysed separately, in a case-control analysis using four times as many controls as cases, randomly selected from UK Biobank.

Analysis was conducted in PLINK2 correcting for population stratification by including PCs 1-15 as covariates.



## Michigan

The Michigan Genomics Initiative (MGI) is a repository of patient electronic health and genetic data at Michigan Medicine<sup>47</sup>. MGI participants are recruited primarily through pre-surgical encounters at Michigan Medicine and consent to linking of genetic and clinical data for research purposes. Blood derived DNA was genotyped on Illumina Infinium CoreExome-24 bead arrays (San Diego, CA, USA). Genotype data was imputed to the Haplotype Reference Consortium using the Michigan Imputation Server, providing > 17 million imputed variants after standard quality control and filtering (minimac imputation  $R^2 > 0.3$ ). We restricted our analysis to samples of European descent based on Principal Component Analysis using the Human Genome Diversity Panel as references<sup>48</sup>. The CM phenotype was derived from ICD-9 codes extracted from patient electronic health records using the PheWAS R package<sup>49</sup>. We identified 1,198 CM cases samples required to have at least two inclusion ICD-9 codes for melanoma and 26,211 controls with zero inclusion or exclusion codes. The association analysis consisted of a Firth bias-reduced logistic regression controlling for sex, age and 10 principal components. The Firth test corrects for imbalance in case-control ratio<sup>50</sup> and was performed using the epacts software (<https://github.com/statgen/EPACTS>). All participants signed an informed consent form and the local Institutional Review Board approved the study.

## GSXP1 & P2

GenoMEL Phase 1 and 2 are updated relative to previous reports<sup>5,8</sup> with CM samples from the Leeds melanoma cohort now included in the GSEdinCIDR dataset. For a more detailed description see<sup>3,5</sup>, but briefly phase 1 includes cases with histologically confirmed CM from 7 collections centres from 5 European countries genotyped on the Illumina HumanHap300 BeadChip and HumanCNV370k arrays (San Diego, CA, USA). Controls were collected by the same groups as cases and were melanoma-free. After QC there were 1,075 cases and 2,163 controls. Phase 2 samples includes cases and controls from 9 centres (4 new to phase 1) from 8 European countries plus Israel, totalling 925 cases and 1,128 controls, with genotyping performed on the Illumina HumanHap610 array. All participants signed an informed consent form and the local Institutional Review Board approved the study.

## GSEdinCIDR - Leeds/Cambridge/Scotland

Cases are from two sources. 2,949 are from several studies from Leeds and 1,379 from the Cambridge SEARCH study. Both were genotyped on the Illumina Infinium HumanOmniExpressExome (San Diego, CA, USA) array.

The Leeds data are predominantly from the Leeds melanoma cohort, a population-based melanoma study recruited population-based incident melanoma cases diagnosed between September 2000 and December 2012 from a geographically defined area of Yorkshire and the Northern region of the UK<sup>3,51-53</sup>. Cases were identified by clinicians, pathology registers and via the Northern and Yorkshire Cancer Registry and Information Service to ensure overall ascertainment. For all but 18 months of the study period, recruitment was restricted to patients with Breslow thickness of at least 0.75mm. All controls and the first 960 cases recruited were examined by trained interviewers who performed a standardized examination of the skin, recording nevi by anatomical site and size.

CM cases were identified and recruited from the Eastern Cancer Registry and Information Centre (Eastern England) by the SEARCH study, University of Cambridge<sup>54,55</sup>. CM cases were aged 18-70 at diagnosis. 5,304 of the controls are from Generation Scotland, sampled to preferentially select those individuals reporting English ancestry. 476 of the controls are from the Leeds Melanoma Cohort, selected to be matched by age and GP surgery to the cases. The Leeds controls were

selected to be melanoma-free while the Generation Scotland controls are simply population samples.

In Leeds participants consented to studies approved by the Northern and Yorkshire Research Ethics Committee. Approval for the SEARCH study was obtained from the Eastern Multicentre Research Ethics Committee, UK. Informed consent was obtained from all participants.

## **MDACC**

The MDACC dataset consists of 931 white (non-Hispanic) individuals with cutaneous melanoma who were recruited together with 1,026 cancer-free controls (friends or acquaintances of patients reporting to other clinics at M.D. Anderson). Controls were frequency matched on age and sex. The GWAS CM dataset also includes an additional 873 individuals presenting for treatment for cutaneous melanoma at M.D. Anderson. All samples were collected between March 1998 and August 2008. Samples were genotyped using the Illumina HumanOmni1-Quad\_v1-0\_B array (San Diego, CA, USA) and called using the BeadStudio algorithm. A more detailed description of the QC procedures applied to these data can be found elsewhere <sup>4</sup> The study protocols were approved by the Institutional Review Board at MD Anderson, and informed consent was obtained from all participants.

## **Harvard**

410 pathologically confirmed invasive CM cases and 2,920 melanoma free controls were drawn from US non-Hispanic Caucasian participants of two cohorts; the Nurses' Health Study and the Health Professionals Follow-up Study who were genotyped on Illumina HumanHap660 arrays (San Diego, CA, USA) <sup>56</sup>). Cohort recruitment required informed consent, and ethical oversight and approval was via the Institutional Review Board at Brigham and Women's Hospital and the Harvard School of Public Health. Following QC, imputation to 1000 genomes phase 1 Integrated Release Version 3 Haplotypes (2010-11 data freeze, 2012-03-14 haplotypes) was conducted using MACH <sup>57,58</sup>. Only SNPs with a MAF > 0.01 were carried forward for analysis using logistic regression; age, sex, family history of melanoma and the first 5 principal components were included as covariates.

## **EPIGENE**

787 CM cases genotyped on the Illumina CoreExome array (San Diego, CA, USA) were available from the EPIGENE cohort, which recruited histopathologically confirmed invasive CM cases (with informed consent) from southern Queensland, Australia <sup>59</sup>. CM cases were aged 18-79 at the time of diagnosis, and were diagnosed between April 1<sup>st</sup> 2007 and September 30, 2010.

These were combined with 983 healthy controls from the Brisbane Adolescent Twin Study <sup>38,39</sup> genotyped on the Illumina CoreExome array (San Diego, CA, USA); control samples were selected to be unrelated (PLINK IBD PI\_HAT < 0.1875) to each other, to EPIGENE samples, and to controls used in the QMEGA\_610k GWAS. Following QC as performed for the other GWAS sets (Methods) there were 773 CM cases and 910 controls. Genotyped data was imputed to the HRC as outlined in the **Online Methods**. The study protocol was approved by the HREC of QIMR Berghofer Medical Research Institute, Brisbane, Australia.

## **MIA\_PAH**

Clinically confirmed CM cases were drawn from participants three cohorts genotyped on the Illumina Oncoarray (San Diego, CA, USA). Germline DNA samples and data from the Melanoma Institute of Australia (MIA) cohort (1,745 cases) were obtained from the MIA Biospecimen Bank (protocol HREC/10/RPAH/530), which is based on an Institute-wide prospective protocol of

registration and clinical data collection from all melanoma cases (MIA Melanoma Research Database, protocol HREC/11/RPAH/444). Study protocols for the MIA, as well as overall ethical oversight, was managed by the Sydney Local Health District (SLHD) Ethics Review Committee (RPAH Zone), Camperdown, New South Wales, Australia. All MIA cases were confirmed by histopathology. A further N = 236 were recruited from the Princess Alexandra Hospital and Brisbane treatment centres (PAH). Ethical approval for the PAH dataset was through the Metro South Hospital and Health Service, Human Research Ethics Committee, Woolloongabba, Queensland, Australia. All patients with melanoma recruited into the PAH study were diagnosed with locally invasive primary cutaneous melanoma and referred to the Multidisciplinary Melanoma Clinic at the Princess Alexandra Hospital and related clinics. Patients who proceeded to a sentinel lymph node biopsy procedure between 1994 and 2007 were considered for inclusion. Patient demographics, date of diagnosis and clinicopathological characteristics of the primary melanoma for each patient were prospectively recorded in a hospital database through the PAH surgical clinic. Consenting patients were sent a saliva kit for DNA collection. The third set of samples was participants in the Q-MEGA cohort not previously genotyped an unrelated ( $IBD < 0.15$ ) with participants in the Q-MEGA omni and Q-MEGA 610k GWAS (N = 60).

Controls were cancer free women genotyped on the Illumina Oncoarray (San Diego, CA, USA)<sup>60</sup> drawn from the population based controls of the Australian Ovarian Cancer Study (N = 1,134)<sup>61,62</sup>, combined with N = 1,794 UK cancer free controls (all female) from the SEARCH study<sup>63</sup>. PCA was used to confirm cancer free controls were homogenous with the Australian cases and controls.

GWAS samples were cleaned as per other datasets (Online Methods). In addition to the standard genotype QC (**Online Methods**) the Oncoarray genotype data was first cleaned and aligned as per Oncoarray Consortium protocols to remove poorly performing assays specific to that array<sup>60</sup>. After QC and cleaning there were 1,933 CM cases (N = 1,641 from the MIA set, 232 from the PAH set, and 60 from Q-MEGA). 2,841 controls were available after cleaning (AOC N = 1,113, SEARCH = 1,778).

### **MELARISK, France**

Additional clinically confirmed CM cases and controls were available from two French cohorts contributing to GenoMEL Phase 1 and 2; MELARISK (535 cases)<sup>64</sup> and the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) study (856 controls - population samples not screened for melanoma)<sup>65 34</sup>. The project was approved by the Human Research Ethics Committees of PARIS SAINT-LOUIS, PARIS NECKER and Ile de France II for the MELARISK study and from the Human Research Ethics Committee of PARIS Cochin for the SU.VI.MAX study. Informed consent was collected for all individuals taking part. Following genotyping on IHuman660W-Quad array (San Diego, CA, USA) at the Centre National de Genotypage (CNG, Evry, France), QC as per the Online Methods were applied. Post QC, 511 melanoma cases and 815 controls were available for GWAS.

### **Essen-Heidelberg, Germany**

Histologically confirmed CM cases (N = 1,218) were genotyped using the Illumina HumanCytoSNP-12v1-0\_D arrays (San Diego, CA, USA). These were combined with healthy controls (N = 1,223) from Germany genotyped on the Illumina HumanOmniExpress12\_v1\_C array (San Diego, CA, USA). The combined genotyped data was thinned to the 220,000 SNPs overlapping across the arrays before applying the standard cleaning and quality control (Online Methods). Participation required informed consent, and the study was approved and overseen by the Human Research Ethics Committee of University Hospital Essen.

## QSkin

Data for 17,695 individuals genotyped using the Illumina Global Screening Array (San Diego, CA, USA) was available from the QSkin cohort<sup>66</sup>. Following excluding participants with > 5% genotype missingness ( $n = 322$ ), were related to another participant at PLINK IBD PI\_HAT > 0.1875 ( $N = 400$ ), or were more than 6 sd on PC1 and PC2 compared to a European reference population constructed using 1000 genomes data ( $N = 378$ ; some individuals overlap across exclusions), 16,708 participants were available. Genotyped SNPs were cleaned for GenTrain score < 0.6, Hardy-Weinberg P-value <  $1 \times 10^{-6}$ , or a minor allele frequency (MAF) < 1%, leaving 496,695 SNPs for imputation. Imputation was performed using the University of Michigan Imputation Server as per the other GWAS datasets (Online Methods). Cleaned, imputed data were split into a CM GWAS set ( $N = 1,285$  with histopathologically confirmed CM and 2,493 controls without melanoma) and a distinct Nevus GWAS dataset ( $N = 12,930$ ). The CM GWAS was performed using logistic regression in PLINK v1.9 with the first 10 principal components fitted as covariates. The QSkin nevus phenotype was a self reported 4 point scale (None, some, a few, many based on a reference picture; see [https://qskin.qimrberghofer.edu.au/page/About/Baseline\\_survey](https://qskin.qimrberghofer.edu.au/page/About/Baseline_survey)). Following rank normalisation in R, this was analysed using PLINK v1.9 as a quantitative phenotype with the orthogonal transformation of age, age<sup>2</sup>, sex, sex  $\times$  age, and sex  $\times$  age<sup>2</sup> and the first 10 principal components fitted as covariates. Ethical approval and oversight of the QSkin project was managed by the Human Research Ethics Committee of QIMR Berghofer Medical Research Institute, Brisbane, Australia.

## Brisbane Nevus Morphology Study

The ethical aspects of this research project have been given approval by the Human Research Ethics Committee of Princess Alexandra Hospital and The University of Queensland. Patients and controls for this study were all enrolled in the larger Brisbane Naevus Morphology Study, (BNMS) study run by University of Queensland Dermatology Research Centre. Recruitment of patients was via referral with patient consent from treating doctor (including private and public hospital clinics) or some patients had heard about the trial from friends or family and self referred. Controls were people with no history of melanoma who volunteered for the BNMS, often due to knowledge of it via friends, family, or who were being seen in the dermatology clinic and were offered participation. Once identified, participants are contacted by research assistants and asked if they would like to come for an in-person consultation and more information, and if they elect to proceed, to complete the consent process.

Patients are asked to provide a saliva sample using a self-collection kit (Oragene-DNA self-collection, DNA Genotec, Ottawa, ON, Canada). A minimum of 2.5ug of DNA was provided to UQ Centre for Clinical Genomics (UQCCG) at the Translational Research Institute (TRI) for high throughput microarray processing. The concentration range for the submitted samples was 100 to 300ng/ul, aliquoted in 96-well semi-skirted PCR Plates (Axygen Scientific) and sealed with Clear Self-Adhesive Topseal (PerkinElmer). These samples were genotyped on the Illumina Infinium Microarray on HumanCoreExome-24.

To account for the family structure in the BNMS sample, dosage data was analysed using the Genome-Wide Efficient Mixed Model Association (GEMMA) algorithm<sup>67</sup>. The ordinary least squares beta output from GEMMA regression was converted to a log odds ratio using a simplified formula adapted from the first term of the formula provided by<sup>68</sup> of  $B/(C(1-C))$ , where B is the ordinary least squares beta and C the proportion of cases.

## 23andMe

Self-reported CM cases were defined as having answered yes, or reported melanoma for at least one of the following question asked to 23andMe, Inc. participants 1) "Have you ever been diagnosed by a doctor with melanoma?"; 2) "What type(s) of cancer were you diagnosed with? Please check all that apply."; 3) "What type(s) of skin cancer did you have? Please check all that apply."; 4) "Have you ever been diagnosed with melanoma?"; 5) "Have you ever been diagnosed with or treated for any of the following conditions?" with the list including "Melanoma". Cancer free controls were drawn from those who answered No, or not reporting melanoma, to any of the above questions, and without responding yes to any of these questions. Further, controls answered No to at least one general cancer questions, and Yes to none 1) "Have you ever been diagnosed with cancer, including skin cancer or cancerous moles?"; 2) "Has a doctor ever told you that you have a type of cancer?"; 3) "Have you ever been diagnosed or treated with any of the following conditions? Cancer, any type".

DNA samples were genotyped using one of four genotyping platforms; two variants of the *Illumina HumanHap550+ BeadChip* (V1, V2), a custom *Illumina OmniExpress+ BeadChip* (V3) with improved overlap with the V2 array, and a custom array (V4) designed for 23andMe, Inc. from Illumina that overlaps with the V2 and V3 arrays and improved coverage of lower frequency SNPs. Samples were filtered on < 98.5% call rate, < 97% European ancestry when compared to 1000 genomes reference panels, or more closely related by IBD than first cousins. Genotyped SNPs were filtered for being non-polymorphic; failing parent offspring tests; HWE  $P < 1 \times 10^{-20}$ ; genotype missingness  $\geq 10\%$  or exhibiting batch effects across the 4 GWAS arrays used. SNPs were imputed by genotyping batch (V1-V4), with 945446 SNPs passing QC across the batches. Following imputation to the September 2013 release of 1000 Genomes Phase1 reference panel using Minimac2, there were 12833621 SNPs in total with 9,829,439 exceeding imputation quality threshold (INFO)  $> 0.5$ . Variants in the HLA region, including imputed HLA alleles for *HLA-A*, *B*, *C*, *DPB1*, *DQA1*, *DQB1*, and *DRB1* loci at four-digit resolution, were imputed using HIBAG6. Imputed HLA alleles were otherwise analysed as dosage data as per the rest of the imputed genotype data. Logistic regression using genotype dosages was performed with Age, sex and PC0-4 (first 5 Pcs) as covariates.

MelaNostrum Consortium:

Ethical approval was obtained from the National Cancer Institute, NIH and from each center listed below:

Athens – Andreas Sygros Hospital Study

The Athens sample is a case-control study that collected melanoma cases from Andreas Sygros Hospital and the Medical Oncology Center of Laiko Hospital. These are large referral centers for melanoma and skin cancer that receives the majority of melanoma cases in Athens and central Greece<sup>69</sup>. Melanoma cases were defined as individuals with a histologically confirmed diagnosis of invasive melanoma between 2000 to 2014. Melanoma-free controls were collected from blood donors of an Athens blood donation center or individuals with minor skin diseases and no history of skin malignancy who attended the hospital outpatient service or who were hospital personnel. All participants were older than 18 years. Demographic variables, pigmentation traits (eye, hair, and skin color), skin phototype, tanning ability, and information from clinical examination were obtained through a questionnaire that was filled out by all participants under the supervision of a certified dermatologist who performed the clinical examination. The questionnaire and clinical examination was conducted for both melanoma cases and controls. The participation rate was approximately 95% for patients and 90% for controls. The study protocol was approved by the Scientific and Ethics Committee of Andreas Sygros Hospital, and all participating individuals gave written informed consent before study participation.

#### Athens – Hellenic Cooperative Oncology Group (HeCOG)

Melanoma cases from this study were previously enrolled in Trial 13A/98, a prospective, multicenter, randomized phase III trial conducted at 13 institutions by the Hellenic Cooperative Oncology Group (HeCOG)<sup>70</sup>. The trial enrolled patients with histologically confirmed primary cutaneous melanoma between 1998 and 2004. Eligible cases were also required to be  $\geq 18$  years of age with an ECOG performance status  $\leq 1$ , adequate organ function and no significant medical or psychiatric comorbidity. Cases were excluded if they had received prior adjuvant chemotherapy, radiotherapy or immunotherapy. Melanoma-free controls were randomly selected healthy unrelated Greek individuals. All participants gave informed consent to participate in the trial. This study was approved by the ethics committees of the Hellenic Cooperative Oncology Group, University Authorities and “G. Gennimatas” Hospital.

#### Barcelona – Melanoma: Image, Genetics and Immunology Study

The Melanoma Unit of from IDIBAPS (Barcelona, Spain), Hospital Clínic of Barcelona, and CIBERER (Instituto de Salud Carlos III, Spain) started recruiting familial and sporadic melanoma cases and controls in 1992. The collection consists of a series of case-series, case-control and cohort studies from Barcelona, Spain<sup>71-80</sup>. Since 1999, data has been collected on clinical information, follow-up, and biological species. Melanoma cases were defined as individuals with clinically diagnosed melanoma based on histopathological evaluation. Controls were cancer-free individuals, some of which were non-affected family members recruited for familial melanoma studies. In the case-control melanoma studies, the controls used have no personal or family history of melanoma. Matching was performed based on age and gender for some included studies. All participants signed an informed consent form and the local Institutional Review Board approved the study.

#### Cyprus

The Cypriot cohort consisted of 32 histologically confirmed unrelated cases of malignant melanoma and 201 healthy controls. The control samples were cancer-free volunteers participating in the MASTOS study<sup>81</sup>. All subjects were above 18 years. All participants signed an informed consent form and the local Institutional Review Board approved the study.

#### Cesena

The Cesena study is a case-control study conducted at M. Bufalini Hospital, Cesena, Italy<sup>82-87</sup>. Cases are cutaneous melanoma cases with histopathological confirmation which included hematoxylin and eosin staining, HMB-45, S100, and Melan-A (MART-1) makers. Healthy control subjects were recruited from patient’s spouses or friends from in-patients or out-patients at the dermatologic department mainly with diagnoses of streptodermitis, subcutaneous abscesses, lipomas, mild contact dermatitis, hair or nail diseases. Controls were melanoma free at time of recruitment and matched to cases on age, gender and region of birth. All participants donated a sample of peripheral blood for molecular analysis and were examined by a single physician who reported data on pigmentation, nevi and other skin characteristics. All participants provided written informed consent and responded to an interview-based questionnaire on melanoma risk factors and the study was approved by the local Institutional Review Board.

#### Genoa – The Genoa Study

The Genoa study is a hospital based case-control study conducted at the Genetics of Rare Cancers Unit at the San Martino University Hospital in Genoa, Italy and IRCCS AOU San Martino-IST Research Hospital<sup>88-91</sup>. Cases were cutaneous melanoma patients recruited over the past 15 years referred for clinical genetic testing. Cases were either sporadic or affected by multiple primary melanoma or were probands from melanoma families. All cases were 18 years of age or older with a histologically confirmed in situ or invasive cutaneous melanoma. Controls were healthy volunteers or spouses 18 years old or older who were recruited in the same period as the cases and

matched by gender, age and place of residence. Participants donated a sample of peripheral blood for molecular analyses as well as filled out a detailed questionnaire on hair, eye and skin color, sun exposure, and history of melanoma. A trained interviewer also assessed presence of freckles and nevi. All participants provided written informed consent and the study was approved by the Ethics Committees of the participating Institutions.

#### L'Aquila

The Department of Dermatology of the University of L'Aquila, Italy recruited familial and sporadic melanoma cases and controls for study participation<sup>85,92-94</sup>. Familial melanoma cases were defined as patients from melanoma families with at least 2 first- or second-degree relatives or with at least 3 documented cases of melanoma irrespective of the degree of relatedness. Sporadic melanoma cases were defined as patients consecutively presenting with histopathologically confirmed sporadic primary cutaneous melanoma of any stage either as a first diagnosis or during the periodic follow-up. Controls were individuals free of melanoma at time of study entry. Only controls related to sporadic melanoma patients were recruited. Control individuals were matched to cases by gender, age (within 1 year), ethnicity and residential area and were consecutively recruited in the same period from patients with allergic disorders, skin infections, psoriasis, ulcers or autoimmune diseases referred to the same department. All sporadic and familial melanoma patients and control individuals were of Italian origin. Basic demographic information and phenotypic characteristics of patients were collected through a standardized questionnaire. Skin examination was performed by a dermatologist who evaluated skin type, hair color, eye color, number of melanocytic nevi and presence or absence of clinically atypical nevi. All participants signed an informed consent form and the local Institutional Review Board approved the study.

#### Milano

The Milano study is a case-control study conducted at the Fondazione IRCCS Istituto Nazionale Tumori in Milan, Italy. Melanoma cases were defined as patients hospitalized for surgical treatment of melanoma at the Melanoma and Sarcoma Surgery Unit. All cases of melanoma were confirmed by histopathology. Controls were melanoma free at study entry and recruited from healthy blood donors from the Immunohematology and Transfusion Medicine Unit. No matching of controls to cases was performed. Phototype information was obtained by a self-administered questionnaire. Atypical nevi and phototypes were defined by a single clinician. All participants signed an informed consent form and the local Institutional Review Board approved the study.

#### Padua

The Padua study is comprised of melanoma-prone families with at least 2 melanoma cases referred to the Veneto Institute of Oncology (IOV) in Padua, Italy<sup>95,96</sup>. All cases of melanoma were confirmed by pathology reports. Family history and phenotypic features were obtained from personal interviews using a standardized questionnaire. Self-reported hair/eye/skin colour was recorded using reference colour classes. Presence/absence of freckles and nevus count were defined according to physical examination by a trained dermatologist. Control participants were healthy individuals without personal or family history of melanoma who were donors at the Blood Collection Center, Hospital Transfusion Centre of Padua. All melanoma patients and control individuals were of Caucasian origin and living in Veneto, a region in the North-East Italy. Written informed consent was obtained by all participants enrolled in the study and the project was approved by the institutional local ethical committee.

#### Roma

The Roma study is a series of familial and sporadic melanoma cases recruited from the Institute of Dermatology, Catholic University Rome, Italy since 2014. Familial melanoma cases were defined as patients from melanoma families with at least 2 first- or second-degree relatives or with at least 3 documented cases of melanoma irrespective of the degree of relatedness. Sporadic cases were

defined as patients consecutively presenting with histopathologically confirmed sporadic primary cutaneous melanoma of any stage either as a first diagnosis or during the periodic follow-up. All cases were confirmed by histopathological review of melanoma tissue slides. No controls were recruited that were related to sporadic melanoma patients. A standardized questionnaire was administered by physicians trained in data gathering to collect demographic information and phenotypic characteristics. Skin examination was performed by a dermatologist who evaluated skin type, hair color, eye color, number of melanocytic nevi and presence or absence of clinically atypical nevi. All participants signed an informed consent form and the local Institutional Review Board approved the study.

### Valencia

The Valencia study consists of sporadic cases, familial cases and melanoma-free controls<sup>97</sup>. The sporadic cases consisted of Spanish cutaneous melanoma patients recruited at the Department of Dermatology, Instituto Valenciano de Oncología, a referral skin cancer center for the provinces of Valencia, Alicante and Castellon, with a catchment population of approximately 5 million people. All cases are histopathologically confirmed melanoma cases by an expert pathologist devoted to skin cancer pathology and were treated at the center. Clinical and pathological data from the patients were prospectively collected since January 2000 through the review of medical history, personal interview and clinical examination by expert dermatologists. Controls are disease free and ethnically matched blood donors recruited at the Transfusion Center of Valencia between September 2008 and January 2009. All the epidemiological and phenotypic characteristics of skin were obtained from a structured questionnaire performed at the time of blood sampling. All participants signed an informed consent form and the local Institutional Review Board approved the study.



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## **Essen-Heidelberg**

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## **Western Australian Melanoma Health Study (WAMHS)**

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