SUPPLEMENT TO “GENOME WIDE ASSOCIATION STUDY IDENTIFIES GENETIC ASSOCIATIONS WITH PERCEIVED AGE.”

V. Roberts, B. Main, N.J. Timpson, S. Haworth

Contents

Supplementary Table 1
Supplementary Table 9
Supplementary Text 1
Supplementary Text 2
Supplementary Figure 1
Supplementary Figure 2
Supplementary Figure 3a
Supplementary Figure 3b
Supplementary Figure 3c
Supplementary Figure 3d
Supplementary Figure 3e
Supplementary Figure 3f
Supplementary Figure 3g
Supplementary Figure 3h
Supplementary Figure 3i

References
**Supplementary Table 1: Demographic characteristics of the final sample**

|              | N (% of group) Older than their age | N (% of group) about their age | N (% of group) younger than their age | Total N (% of study) |
|--------------|------------------------------------|-------------------------------|---------------------------------------|----------------------|
| **Age**      |                                    |                               |                                       |                      |
| <45          | 1,861 (3.5)                        | 14,626 (27.6)                 | 36,457 (68.9)                         | 52,944 (12.5)        |
| 45 >= Age < 55| 3,262 (2.7)                       | 29,651 (24.1)                 | 89,966 (73.2)                         | 122,879 (29.0)       |
| 55 >= Age < 65| 2,952 (1.6)                       | 44,629 (24.0)                 | 138,483 (74.4)                        | 186,064 (43.9)       |
| 65 >= Age    | 555 (0.9)                          | 14,394 (23.2)                 | 47,156 (75.9)                         | 62,105 (14.5)        |
| **Male sex** |                                    |                               |                                       |                      |
| Male sex     | 6713 (3.5)                         | 54,831 (28.2)                 | 132,847 (68.3)                        | 194,391 (45.8)       |
| Female sex   | 1917 (0.8)                         | 48469 (21.1)                  | 179215 (78.1)                         | 229,601 (54.2)       |
| **Total N (% of study)** | 8,630 (2.0) | 103,300 (24.4) | 312,062 (73.6) | 423,992 (100.0) |
Supplementary Table 9: Previously reported single variant association signals for related traits

| RSID          | Chr | Pos          | Reported trait                              | P value       | Publication            |
|---------------|-----|--------------|---------------------------------------------|---------------|------------------------|
| rs12203592    | 6   | 396321       | Odds of increased pigmented spot severity   | 1.9x10^{-27}  | (Jacobs et al., 2015)  |
| rs35063026    | 16  | 89736157     |                                             | 9.4x10^{-15}  |                        |
| rs6059655     | 20  | 32665748     |                                             | 2.6x10^{-9}   |                        |
| rs12203592    | 6   | 396321       | Odds of increased skin ageing               | 8.8x10^{-13}  |                        |
| rs1805007     | 16  | 89986117     |                                             | 1.2x10^{-10}  |                        |
| rs4268748     | 16  | 90026512     |                                             | 1.2x10^{-15}  |                        |
| rs185146      | 5   | 33952106     |                                             | 4.1x10^{-9}   | (Law et al., 2017)     |
| rs4911414     | 20  | 32729444     | Odds of increased tanning ability           | 3.8x10^{-9}   |                        |
| rs12913832    | 15  | 28365618     |                                             | 1.4x10^{-22}  |                        |
| rs12203592    | 6   | 396321       |                                             | 3.3x10^{-23}  |                        |
| rs1805007     | 16  | 89986117     |                                             | 1.1x10^{-65}  |                        |
| rs1805008     | 16  | 89986144     |                                             | 1.3x10^{-13}  |                        |
| rs1805007     | 16  | 89986117     |                                             | 1.5x10^{-19}  |                        |
| rs1126809     | 11  | 89017961     | Odds of increased tanning ability           | 5.0x10^{-21}  | (Zhang et al., 2013)   |
| rs1308048     | 1   | 66888542     |                                             | 2.1x10^{-14}  |                        |
| rs12078075    | 1   | 2.05E+08     |                                             | 4.0x10^{-9}   |                        |
| rs9818780     | 3   | 1.56E+08     |                                             | 3.4x10^{-8}   |                        |
| rs16891982    | 5   | 33951693     |                                             | 2.0x10^{-17}  |                        |
| rs251464      | 5   | 1.49E+08     |                                             | 2.2x10^{-9}   |                        |
| rs12203592    | 6   | 396321       |                                             | 1.1x10^{-58}  |                        |
| rs117132860   | 7   | 17134708     |                                             | 7.6x10^{-23}  |                        |
| rs2737212     | 8   | 1.17E+08     |                                             | 4.3x10^{-25}  |                        |
| rs1326797     | 9   | 12716762     |                                             | 1.2x10^{-17}  |                        |
| rs10810650    | 9   | 16873551     |                                             | 2.4x10^{-59}  |                        |
| rs35563099    | 10  | 1.2E+08      |                                             | 6.6x10^{-24}  |                        |
| rs72917317    | 11  | 68817441     |                                             | 1.0x10^{-29}  |                        |
| rs1126809     | 11  | 89017961     |                                             | 2.4x10^{-17}  |                        |
| rs9561570     | 13  | 95156198     |                                             | 1.4x10^{-9}   |                        |
| rs1046793     | 13  | 1.14E+08     |                                             | 2.0x10^{-18}  |                        |
| rs746586      | 14  | 92775967     |                                             | 7.0x10^{-13}  |                        |
| rs12913832    | 15  | 28365618     |                                             | 6.3x10^{-18}  |                        |
| rs369230      | 16  | 89645437     | Odds for category of tanning response       | 1.0x10^{-52}  |                        |
| rs6059655     | 20  | 32665748     |                                             | 1.4x10^{-31}  |                        |
| rs11703668    | 22  | 45630335     | Odds for category of tanning response       | 1.0x10^{-16}  | (Visconti et al., 2018)|

RSID: Reference SNP cluster ID, Chr: Chromosome, Pos: Position, P value: reported P value in the original publication.
Supplementary Text 1: Estimation of effective sample size.

The number of participants who self-reported each category of the outcome are reported in the main text. As there is an uneven split in the 3 categories the effective sample size will be smaller than the total number of participants. To help understand the impact of this imbalance on statistical power, we estimated the effective sample size of the experiment as follows.

First, we note that in a conventional case control study, the number of cases is given by $N_{\text{full cases}} \times 1 + N_{\text{controls}} \times 0$. Because we considered people who looked about their age to have an intermediate phenotype between a full case and full control, we coded them as 0.5. We therefore reasoned that the effective number of cases could be given as $N_{\text{full cases}} \times 1 + N_{\text{half cases}} \times 0.5 + N_{\text{controls}} \times 0$.

We used the same approach to estimate the effective number of controls, and finally the effective sample size $N_{\text{eff}} = 4/(1/N_{\text{cases}} + 1/N_{\text{ctrls}})$ (Willer et al., 2010).

Using this approach, we estimate there were 60,280 effective controls and 363,712 effective cases, giving an overall effective sample size of 206,839 participants.
Supplementary Text 2: Simulations exploring the potential impact of measurement error

Methods

Simulations were undertaken using the ‘simulateGP’ package (https://github.com/explodecomputer/simulateGP) in the statistical language R (version 3.5.3, 2019 release). First, 100 genotypes were simulated with minor allele frequency of 0.3 for 423,992 participants. Of these genotypes, 50 had a causal effect on the simulated phenotype, and 50 had no effect. Participant age was simulated from a rectangular distribution between ages 30 and 71. Next, an underlying continuously distributed phenotype was generated representing liability for youthful appearance, affected by both participant age (explaining 50% of variation in the phenotype), the 50 causally related SNPs (explaining collectively 10% of variation in the phenotype) and randomly distributed unmeasured environmental and genetic factors (explaining 40% of variation in the phenotype). Next, underlying liability was altered with the addition of between 0% and 90% random error in 10% increments, i.e. up to 90% of variation in the latent liability variable was now due to additional random noise. At each threshold of noise, the latent phenotype was used to derive a new categorical phenotype with 8,630/103,300/312,062 participants in the respective categories. Next, each derived categorical phenotype was regressed on each causal and non-casual genotype using a linear regression model incorporating adjustment for age. The resulting estimates of genetic effect were flipped where necessary, so the estimates were always positively signed, and then converted to a log odds ratio using the same Taylor expansion series used in the main analysis.
Results

With increasing measurement error, the estimates of genetic effect at truly associated variants are biased towards the null, with an approximately log-linear relationship between odds ratio and percentage of measurement error. With finite statistical power, this means the association with some variants which was detectable in the baseline model is no longer detectable, and the type II error rate of the experiment therefore increases with increasing measurement error. Conversely, the type I error rate is not inflated by this form of measurement error (Supplementary Figure 2).
**Supplementary Figure 1:** Quantile-Quantile plot of p values from S-PrediXcan analysis.
Supplementary Figure 2: Attenuation of apparent genetic effect with increasing measurement error. At each level of measurement error (x axis) there are 100 dots, each representing the association on a log-odds ratio scale between a single simulated genetic variant and self-reported simulated perceived age. The true effect of each SNP is shown in the baseline model (x=0). Variants which have a detectable non-null effect in the true model are colored in cyan, and variants which have a null association in the true model are colored in orange. With increasing measurement error there is a log-linear attenuation in effect sizes away from the true effect (represented by x=0) towards the null for variants with a true effect (cyan regression line), meaning the true associations are no longer detectable for some variants. With increasing measurement error there is no inflation in effect sizes at truly null variants (orange regression line).
Supplementary Figure 3a: Regional association plot of the C9orf66-DOCK8 locus

Supplementary Figure 3b: Regional association plot of the GSDMC locus
Supplementary Figure 3c: Regional association plot of the \textit{CHCHD6} locus

Supplementary Figure 3d: Regional association plot of the \textit{AC074093.1} locus
Supplementary Figure 3e: Regional association plot of the EFEMP1 locus

Supplementary Figure 3f: Regional association plot of the LOC100270679 locus
Supplementary Figure 3g: Regional association plot of the AKAP12 locus

Supplementary Figure 3h: Regional association plot of the PAX3 locus
Supplementary Figure 3i: Regional association plot of the LOXI locus
References

Jacobs LC, Hamer MA, Gunn DA, Deelen J, Lall JS, van Heemst D, et al. A Genome-Wide Association Study Identifies the Skin Color Genes IRF4, MC1R, ASIP, and BNC2 Influencing Facial Pigmented Spots. Journal of Investigative Dermatology 2015;135(7):1735-42.

Law MH, Medland SE, Zhu G, Yazar S, Viñuela A, Wallace L, et al. Genome-Wide Association Shows that Pigmentation Genes Play a Role in Skin Aging. Journal of Investigative Dermatology 2017;137(9):1887-94.

Visconti A, Duffy DL, Liu F, Zhu G, Wu W, Chen Y, et al. Genome-wide association study in 176,678 Europeans reveals genetic loci for tanning response to sun exposure. Nature Communications 2018;9:1684.

Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26(17):2190-1.

Zhang M, Song F, Liang L, Nan H, Zhang J, Liu H, et al. Genome-wide association studies identify several new loci associated with pigmentation traits and skin cancer risk in European Americans. Human Molecular Genetics 2013;22(14):2948-59.