# Genome-wide association study reveals sex-specific genetic architecture of facial attractiveness

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## Facial attractiveness phenotype in WLS

The Wisconsin Longitudinal Study (WLS) is a longitudinal study of a 1/3 random sample of over ten thousand Wisconsin high school graduates in 1957. Facial attractiveness in WLS was measured based on each individual's 1957 high school year book photo by 12 coders (six females and six males) selected from the same cohort in 2004 and 2008. An 11-point rating scale was used to quantify attractiveness. End-points of rating were labeled as "not at all attractive" and "extremely attractive" for 1 and 11, respectively.

**Table 1. Demographic information of study samples.**

| | Round of coding | | Year of birth | | | | Sex | |
|---|---|---|---|---|---|---|---|---|
| | coded in 2004 | coded in 2008 | 1937 | 1938 | 1939 | 1940 | male | female |
| **Discovery** | 1,422 | 2,723 | 53 | 639 | 3,247 | 206 | 1,922 | 2,223 |
| **Replication** | 149 | 306 | 14 | 70 | 352 | 19 | 243 | 212 |

## GWAS of facial attractiveness

We conducted a GWAS for facial attractiveness on individuals of European ancestry in WLS. A total of 3,928 individuals were included in the discovery stage. 455 additional individuals whose European ancestry was confirmed by genetic data and were used in the replication stage. Six analyses were performed: FC-AS, FC-FS, FC-MS, MC-AS, MC-FS, and MC-MS (i.e. male/female coder - male/female/all samples).

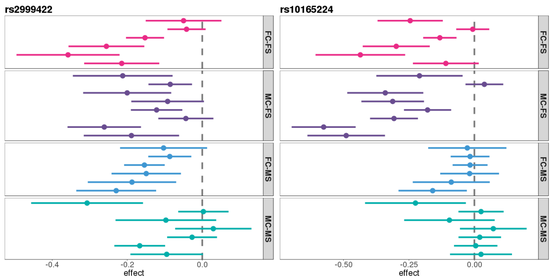
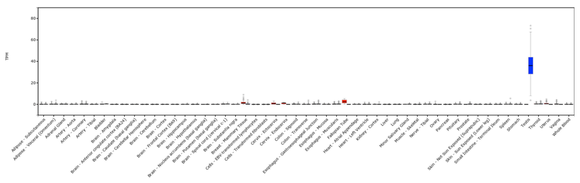



**Figure 3. Association signals for leading SNPs across coders.** Each interval shows association with attractiveness score given by one coder. Error bars denote standard error of effect estimates. Only coders who rated more than 500 male or female samples were included in the analysis.

## Relevant tissue types

A few genes at the leading association loci for facial attractiveness are specifically expressed in reproductive organs. We also performed heritability enrichment analysis. Testis was the top tissue for FC-AS (enrichment=3.9, p=0.04) and ovary was the most enriched tissue for MC-AS (enrichment=4.5, p=0.032), MC-FS (enrichment=5.7, p=0.040), and FC-FS (enrichment=3.0, p=0.005).

**Figure 4. Multi-tissue gene expression profile of *ANTXRL* in GTEx.**



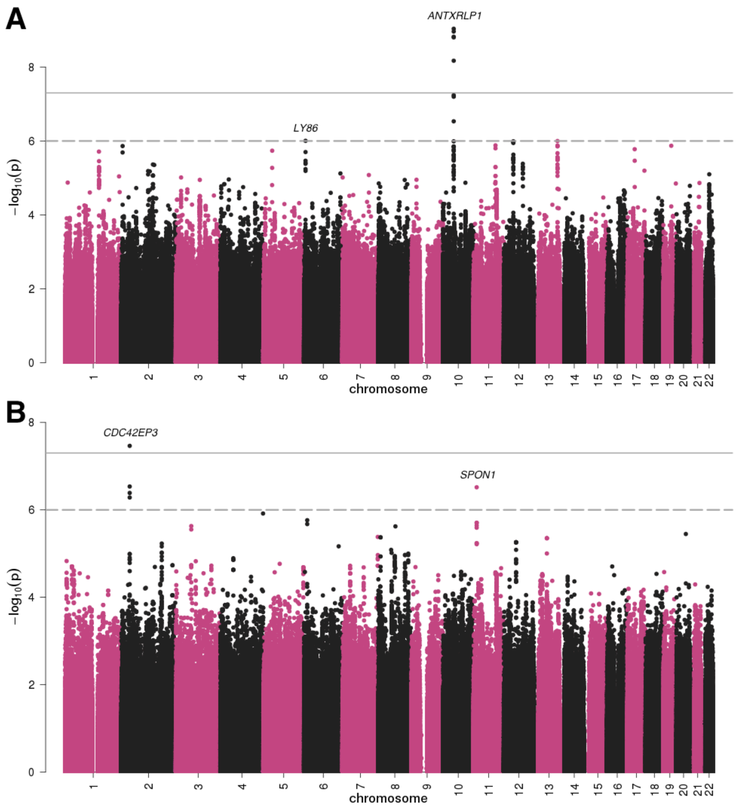



**Figure 1. Manhattan plots for (A) FC-AS and (B) MC-FS analyses.** The horizontal lines denote the genome-wide significance cutoff of 5.0e-8 and a suggestive cutoff of 1.0e-6.

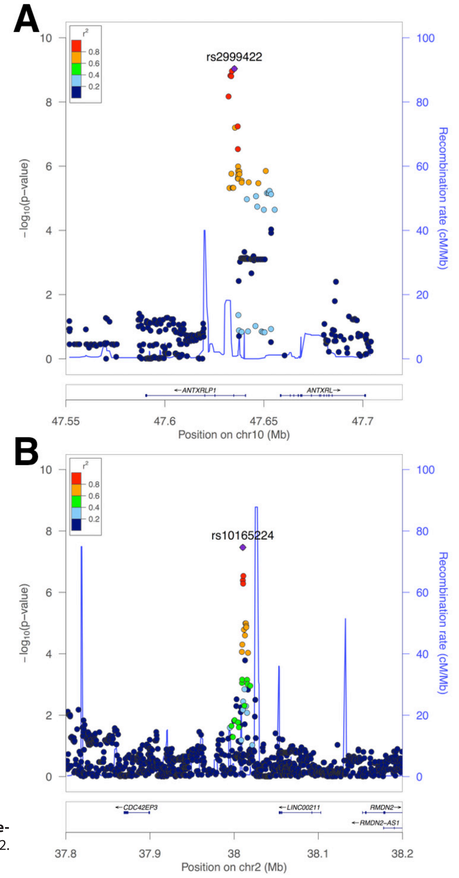



**Figure 2. Associations at two genome-wide significant loci. (A)** FC-AS at 10q11.22. **(B)** MC-FS at 2p22.2.

**Table 2. Genome-wide significant loci associated with facial attractiveness.**

| Trait | Locus | SNP[a] | Genes | Pos (hg19) | Alleles[b] | EAF[c] | $Beta_{dis}$ | $SE_{dis}$ | $P_{dis}$ | $Beta_{rep}$ | $SE_{rep}$ | $P_{rep}$ | $Beta_{meta}$ | $SE_{meta}$ | $P_{meta}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FC-AS | 10q11.22 | rs2999422 | *ANTXRLP1* | 47635107 | G/T | 0.43 | -0.19 | 0.03 | 9.2e-10 | -0.09 | 0.09 | 0.29 | -0.18 | 0.03 | 6.5e-10 |
| MC-FS | 2p22.2 | rs10165224 | *CDC42EP3, LINC00211* | 38010266 | G/A | 0.20 | -0.30 | 0.05 | 3.4e-08 | -0.16 | 0.17 | 0.33 | -0.29 | 0.05 | 2.3e-08 |

[a] The most significant SNP at each locus is listed; [b] Reference/effect allele; [c] Effect allele frequency

## Selection signatures of facial attractiveness

Further, we investigated the relationship between minor allele frequencies (MAF) and minor allele effects on facial attractiveness. We grouped SNPs with MAF between 0.05 and 0.5 into 10 equally-sized bins based on MAF quantiles. Minor alleles with low frequencies tend to have negative effects on male facial attractiveness. The mean minor allele effect on FC-MS from SNPs in the lowest 10% MAF quantile was -0.005, implying very strong statistical evidence for its deviation from zero (p=7.3e-313; two-sided t-test). SNPs in the highest 10% MAF quantile, however, did not show significantly negative associations (mean=-4.1e-5, p=0.493). This hinted at selection pressure on genetic variants associated with negative male attractiveness. The selection signature in females was not as clear.

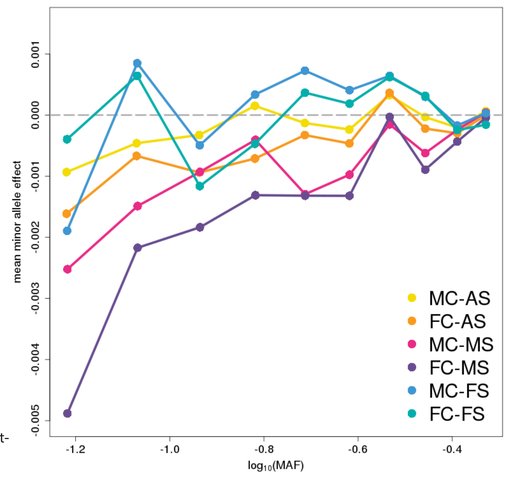
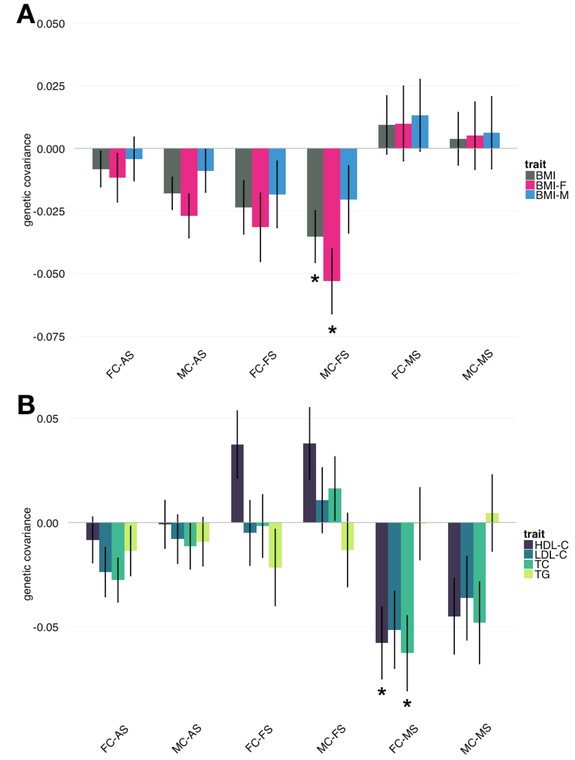



**Figure 5. Selection signatures of facial attractiveness.** SNPs with MAF between 0.05 and 0.5 were grouped into 10 equally-sized bins based on MAF quantiles. For SNPs in each bin, average MAF was calculated shown on the x-axis, while the average minor allele effects are shown on the y-axis.

## Genetic correlation with BMI and blood lipid

We estimated genetic covariance between facial attractiveness and 50 complex traits with publicly accessible GWAS summary statistics which covered a spectrum of social, psychiatric, anthropometric, metabolic, and reproductive phenotypes. Female BMI (BMI-F) and MC-FS, showed strong and negative correlation and achieved Bonferroni-corrected significance (covariance=-0.053, p=4.7e-5). Additionally, three other pairs of traits showed genetic covariance with Benjamini-Hochberg false discovery rate (fdr) below 0.1.

**Figure 6. Genetic covariance between facial attractiveness and (A) BMI traits, (B) lipid traits.** Intervals show the standard error of covariance estimates. Genetic covariance with fdr < 0.1 are marked by asterisks.




## Conclusion

1. Sex-stratified GWAS identified distinct associations.
2. Tissues involved in reproduction and hormonal regulation are highlighted.
3. SNPs associated with low male attractiveness are under purifying selection.
4. Female attractiveness is genetically correlated with BMI, while male attractiveness correlates with blood lipid.

## Reference

Hu, B., et al., Genome-wide association study reveals sex-specific genetic architecture of facial attractiveness. *bioRxiv*, 2018: p. 339226.

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