# **Supplementary Methods for Funkhouser *et al.* 2020**

Table of Contents

[Supplementary Methods for Funkhouser et al. 2020 1](#_Toc33434071)

[Genotype data 1](#_Toc33434072)

[Phenotype data 1](#_Toc33434073)

[LBR hyperparameters 2](#_Toc33434074)

[Defining local, LD-based windows 4](#_Toc33434075)

[Single marker regression 4](#_Toc33434076)

[Simulations 5](#_Toc33434077)

## **Genotype data**

Individuals from the UK Biobank 36 were genotyped using the custom UK Biobank Axiom Array (<http://www.ukbiobank.ac.uk/scientists-3/uk-biobank-axiom-array/>) containing ~800,000 SNPs. SNP quality control proceeded with the Caucasian cohort (N = 409,700); SNPs with a minor allele frequency < 0.01 and missing call rate > 0.05 were removed. SNPs from sex chromosomes and the mitochondrial chromosome were not considered in this study, resulting in 607,497 autosomal SNPs. Individuals with coefficient of relatedness of 0.03 or greater were removed from analysis, resulting in 258,928 distantly related genotyped individuals for use in this study.

## **Phenotype data**

All phenotypic data was collected using baseline measurements of UK Biobank participants. For height, the description “Standing height” from the UK Biobank was used. Individuals with heights (cm) less than 147 or more than 210 were removed from analysis. For BMD, the descriptions “Heel bone mineral density (BMD)”, “Heel bone mineral density (BMD) (left)”, and “Heel bone mineral density (BMD) (right)” were used in conjunction; for individuals with missing “Heel bone mineral density (BMD)” records, either the (left), the (right), or if available, the average between (left) and (right) was used. For BMI, the description “Body mass index (BMI)” was used and for WHR, the ratio of "Waist circumference” to “Hip circumference” was used. Prior to model fitting, all traits were pre-corrected for sex, age, batch, genotyping center, and the first 5 principle components derived from genomic data. The adjusted phenotypes consisted of least-squares residuals from a model that included the effects listed above. For each trait, sample sizes and within-sex summary statistics are provided in S1 Table.

## **LBR hyperparameters**

Hyperparameters used in the LBR model (eq. 1) were error variances for each sex, the proportion of nonzero effects for each SNP effect component, and the variances of nonzero effects for each SNP effect component $\left\{σ\_{m}^{2}, σ\_{f}^{2},π\_{0},π\_{m},π\_{f},σ\_{b\_{0}}^{2},σ\_{b\_{m}}^{2},σ\_{b\_{f}}^{2}\right\}$. Variances (of either SNP effect components or sex-specific errors) were given a scaled-inverse Chi-square prior, parameterized by a degree of freedom parameter *df* (set to 5) and scaling parameter *S*. *S* is set according to built-in rules of the BGLR package using a prior model R-squared of 0.03 for main effects and 0.01 for the sex-interaction terms. More detail on how the scale parameter *S* is calculated can be found in Perez and de los Campos, 2014 27. $π\_{k}$ was given a beta prior with shape parameters $α= $2 and $β= $2. An example of how to implement LBR (eq. 1) using BGLR with the above hyperparameter specifications is provided at <https://github.com/funkhou9/LBR-sex-interactions>.

**Inference using post-processing of posterior samples**

BGLR uses Markov chain Monte Carlo (MCMC) to sample from the posterior distribution of sex-specific effects. For each MCMC sample we derived male and female effects using $β\_{m\_{j(s)}}=b\_{0\_{j(s)}}+b\_{m\_{j(s)}} $and $β\_{f\_{j(s)}}=b\_{0\_{j(s)}}+b\_{f\_{j(s)}}$, where *s =* 1,…, 4,350 indexes MCMC samples. Here, results were obtained using three separate MCMC chains. Each chain was obtained using 3,400 MCMC samples; the first 500 samples were discarded as burn-in and the remaining samples where thinned by an interval of 2, leading to 1,450 samples per chain.

Estimates of sex-specific SNP effects ($\hat{β}\_{m\_{j}}$ and $\hat{β}\_{f\_{j}}$) were obtained from their posterior means. We estimated the posterior probability of a female-specific non-zero SNP effect using $PPF\_{SNP\_{j}}=max\left[Pr\left(β\_{f\_{j}}>0 | D\right), Pr\left(β\_{f\_{j}}<0 | D\right)\right]$, where $D$ represents the observed data. This was done by counting the proportion of $β\_{f\_{j}} $samples above zero and below zero. This was repeated for inferring the male-specific SNP effect. The posterior probability of sex-difference at individual SNP-effects was estimated using $PPDiff\_{SNP\_{j}}=max\left[Pr\left(β\_{m\_{j}}>β\_{f\_{j}} | D\right), Pr\left(β\_{m\_{j}}<β\_{f\_{j}} | D\right)\right]$ where again these probabilities were estimated using the corresponding frequencies from the posterior distribution samples.

For each MCMC sample we also aggregated SNP effects within window *j\** using $u\_{m\_{j^{\*}(s)}}=X\_{j^{\*}}β\_{m\_{j^{\*}(s)}}$ and $u\_{f\_{j^{\*}(s)}}=X\_{j^{\*}}β\_{f\_{j^{\*}(s)}}$. For this calculation we used a common genotype matrix $X\_{j^{\*}}$ consisting of all *N* male and female genotypes to avoid differences in additive genetic values arising from allele frequency differences between males and females occurring by random sampling. Samples of sex-specific window variances were obtained using the sample variance: $\hat{σ}\_{g\_{m\_{j^{\*}(s)}}}^{2}=\left(N-1 \right)^{-1}$ $\sum\_{i=1}^{N}\left(u\_{m\_{i}\_{j^{\*}\left(s\right)}}-\overbar{u}\_{m\_{j^{\*}\left(s\right)}}\right)^{2}$ and $\hat{σ}\_{g\_{f\_{j^{\*}(s)}}}^{2}=\left(N-1 \right)^{-1}$ $\sum\_{i=1}^{N}\left(u\_{f\_{i}\_{j^{\*}\left(s\right)}}-\overbar{u}\_{f\_{j^{\*}\left(s\right)}}\right)^{2}$. Estimates of sex-specific window variances were obtained from their posterior means. Inferring sex-specific window variances was done by estimating $PPM\_{σ\_{g\_{j^{\*}}}^{2}}=Pr\left(σ\_{g}^{2}\_{m\_{j^{\*}}}>0 | D\right)$ and $PPF\_{σ\_{g\_{j^{\*}}}^{2}}=Pr\left(σ\_{g}^{2}\_{f\_{j^{\*}}}>0 | D\right)$ and inferring a G×S interaction at window *j\** was done by estimating:

$$PPDiff\_{σ\_{g\_{j\*}}^{2}}=max\left[\begin{array}{c}Pr\left(σ\_{g}^{2}\_{m\_{j^{\*}}}-σ\_{g}^{2}\_{f\_{j^{\*}}}>t\_{j^{\*}} | D\right), \\Pr\left(σ\_{g}^{2}\_{m\_{j^{\*}}}-σ\_{g}^{2}\_{f\_{j^{\*}}}<t\_{j^{\*}} | D\right)\end{array}\right],$$

where $t\_{j^{\*}}$ was used to exert judgment about how different sex-specific window variances must be to declare a meaningful G×S interaction. Here, $t\_{j^{\*}}$ was one-tenth of the mean of all posterior samples of $σ\_{g}^{2}\_{m\_{j^{\*}}}$ and $σ\_{g}^{2}\_{f\_{j^{\*}}}$. Functions to process posterior samples to estimate and infer non-null sex-specific effects and G×S interactions is provided at <https://github.com/funkhou9/LBR-sex-interactions>.

## **Defining local, LD-based windows**

 To define SNPs contained within window *j\*,* a region of LD centered on SNP *j,* we collected all SNP $j^{'}$ immediately surrounding SNP *j* for which $Cor\left(x\_{j}, x\_{j^{'}}\right)^{2}\geq 0.1$. We allowed up to two consecutive SNPs in which $Cor\left(x\_{j}, x\_{j^{'}}\right)^{2}<0.1$ to allow for potential mapping errors or other unexplained instances where LD with SNP *j* dips only briefly. The function getWindows(), which provides windows given a genotype matrix ***X***, is provided in <https://github.com/funkhou9/LBR-sex-interactions>.

## **Single marker regression**

 We also performed single-marker regression analyses using following model:

$$\left[\genfrac{}{}{0pt}{}{y\_{m}}{y\_{f}}\right]=\left[\genfrac{}{}{0pt}{}{1μ\_{m}}{1μ\_{f}}\right]+\left[\genfrac{}{}{0pt}{}{x\_{m\_{j}}}{x\_{f\_{j}}}\right]β\_{j}+\left[\genfrac{}{}{0pt}{}{x\_{m\_{j}}}{0}\right]β\_{j\_{G×S}}+\left[\genfrac{}{}{0pt}{}{ε\_{m}}{ε\_{f}}\right].$$

As with the LBR model (eq. 1), we assume sex-specific errors are distributed normally with zero mean and sex-specific variances. SNP effects and interactions were estimated using weighted least squares. To test for a G×S interaction at SNP *j*, a t-test is used: ${\hat{β}\_{j\_{GxS}}}/{SE\left(\hat{β}\_{j\_{GxS}}\right)}∼t\_{N-3}$. The *p-*value from such a test is referred to as *pvalue-*diff. To test for any association (either among males, females, or both), we used an F-test, comparing a restricted model: $\left[\genfrac{}{}{0pt}{}{y\_{m}}{y\_{f}}\right]=\left[\genfrac{}{}{0pt}{}{1μ\_{m}}{1μ\_{f}}\right]+\left[\genfrac{}{}{0pt}{}{ε\_{m}}{ε\_{f}}\right]$ against the unrestricted model: $\left[\genfrac{}{}{0pt}{}{y\_{m}}{y\_{f}}\right]=\left[\genfrac{}{}{0pt}{}{1μ\_{m}}{1μ\_{f}}\right]+\left[\genfrac{}{}{0pt}{}{x\_{m\_{j}}}{x\_{f\_{j}}}\right]β\_{j}+\left[\genfrac{}{}{0pt}{}{x\_{m\_{j}}}{0}\right]β\_{j\_{G×S}}+\left[\genfrac{}{}{0pt}{}{ε\_{m}}{ε\_{f}}\right]$.

## **Simulations**

Simulated traits were developed using 60,000 genotyped SNPs (the first 6,000 SNPs from the first ten chromosomes) from 119,190 males and 139,738 females. Using these SNP genotypes, each trait was simulated as follows:

1. A total of 150 causal variants (CVs) were randomly sampled from 60,000 SNPs.
	* Let $Z\_{m}=\left\{z\_{m}\_{ik}\right\}\_{i=1,k=1}^{N\_{m}=119,190 ,q=150}$and$Z\_{f}=\left\{z\_{f}\_{ik}\right\}\_{i=1,k=1}^{N\_{f}=139,738,q=150}$denote matrices of male and female genotypes at sampled CVs.
2. Additive CV effect sizes were randomly sampled from the gamma distribution. 90 CVs (those with homogenous effects) were sampled from $Gamma\left(k=10, θ= 1\right)$ and were made negative with a probability of 0.5. Of the 60 CVs with differing sex-specific effects, 30 had nonzero effects in both sexes but with deferring magnitudes: at random one sex’s effects were sampled from $Gamma\left(k=5, θ= 1\right)$ and the other from $Gamma\left(k=20, θ= 1\right)$. For the remaining 30 CVs, at random one sex’s effects were exactly zero while the other sex’s effects were sampled from $Gamma\left(k=10, θ= 1\right)$.
	* Let $γ\_{m}=\left\{γ\_{m\_{k}}\right\}\_{k=1}^{q=150}$and $γ\_{f}=\left\{γ\_{f\_{k}}\right\}\_{k=1}^{q=150}$denote vectors of male-specific and female-specific CV effects, respectively, for all 150 CVs.
3. Error variances for males $σ\_{δ\_{m}}^{2}$ and females $σ\_{δ\_{f}}^{2}$ were adjusted such that the proportion of phenotypic variance explained by all QTL is 0.05 for both males and females (on the complete genome scale this corresponds to a heritability of about 0.5).
	* Let $δ\_{m}\_{i}∼N\left(0, σ\_{δ\_{m}}^{2}\right)$ and $δ\_{f}\_{i}∼N\left(0, σ\_{δ\_{f}}^{2}\right)$ denote residual error for the $i^{th}$ male and $i^{th}$ female.
4. Male traits $ϕ\_{m}=\left\{ϕ\_{m}\_{i}\right\}\_{i=1}^{N\_{m}=119,190 }$and female traits $ϕ\_{f}=\left\{ϕ\_{f}\_{i}\right\}\_{i=1}^{N\_{f}=139,738}$ were simulated from a linear combination of QTL genotypes plus a residual error:

$ϕ\_{m}=Z\_{m}γ\_{m}+δ\_{m}$ and $ϕ\_{f}=Z\_{f}γ\_{f}+δ\_{f}$

1. Steps 1-4 are repeated for 30 Monte Carlo replicates.