Deciphering Sex-Specific Genetic Architectures Using Local Bayesian Regressions

Scott A. Funkhouser,*† Ana I. Vazquez,‡ Juan P. Steibel,§ Catherine W. Ernst,* and Gustavo de los Campos*†

*Institute for Behavioral Genetics, The University of Colorado, Boulder, Colorado 80309, †Genetics Graduate Program, ‡Departments of Epidemiology and Biostatistics and Statistics and Probability, Institute for Quantitative Health Science and Engineering, and §Department of Animal Science, Michigan State University, East Lansing, Michigan, 48824

ORCID IDs: 0000-0001-7798-6830 (S.F.); 0000-0001-5692-7129 (G.d.l.C.)

ABSTRACT Many complex human traits exhibit differences between sexes. While numerous factors likely contribute to this phenomenon, growing evidence from genome-wide studies suggest a partial explanation: that males and females from the same population possess differing genetic architectures. Despite this, mapping gene-by-sex (G × S) interactions remains a challenge likely because the magnitude of such an interaction is typically and exceedingly small; traditional genome-wide association techniques may be underpowered to detect such events, due partly to the burden of multiple test correction. Here, we developed a local Bayesian regression (LBR) method to estimate sex-specific SNP marker effects after fully accounting for local linkage-disequilibrium (LD) patterns. This enabled us to infer sex-specific effects and G × S interactions either at the single SNP level, or by aggregating the effects of multiple SNPs to make inferences at the level of small LD-based regions. Using simulations in which there was imperfect LD between SNPs and causal variants, we showed that aggregating sex-specific marker effects with LBR provides improved power and resolution to detect G × S interactions over traditional single-SNP-based tests. When using LBR to analyze traits from the UK Biobank, we detected a relatively large G × S interaction impacting bone mineral density within ABO, and replicated many previously detected large-magnitude G × S interactions impacting waist-to-hip ratio. We also discovered many new G × S interactions impacting such traits as height and body mass index (BMI) within regions of the genome where both male- and female-specific effects explain a small proportion of phenotypic variance ($R^2 < 1 \times 10^{-4}$), but are enriched in known expression quantitative trait loci.

KEYWORDS Bayesian methods; gene-by-sex interactions; GWAS

SEX differences are widespread in nature, and observed readily among many human traits and diseases. For quantitative traits, sex may affect the distribution of phenotypes at various levels, including mean-differences between genetic males and genetic females (hereafter referred to as males and females, respectively) as well as differences in variance. Sex differences are likely due to myriad factors, including differential environmental exposures and unequal gene dosages for sex-linked genes, as well as sex-heterogeneity in the architecture of genetic effects at one or more autosomal loci [i.e., gene-by-sex (G × S) interactions]. In this way, sex provides two well-defined conditions in which allele frequencies and linkage disequilibrium (LD) patterns are equivalent, but nevertheless genetic effects of one or many autosomal loci may differ.

Evidence for different genetic architectures between sexes among human populations is largely supported by genome-wide parameters (Weiss et al. 2006; Zillikens et al. 2008; Yang et al. 2015; Rawlik et al. 2016) including unequal within-sex heritabilities ($h^2_{\text{male}} \neq h^2_{\text{female}}$) and between-sex genetic correlations $r_g <$ 1; the former suggests that the proportion of phenotypic variance explained by genetic factors varies between sexes, while the latter suggests genetic
effects are disproportional between sexes (Lynch 1998). Although many traits seem to have a between-sex genetic correlation that is evidentially $< 1$, genome-wide association (GWA) studies intended to map $G \times S$ interactions have struggled to pinpoint such loci (Liu et al. 2012; Hoffmann et al. 2017). Based on this dichotomy, $G \times S$ interactions presumably exist for many traits, but the magnitude of a typical $G \times S$ interaction is suspected to be exceedingly small, explaining why such events commonly elude detection, particularly after multiple test correction. However, just as numerous small effect causal loci accumulate to affect phenotypic variance, small $G \times S$ interactions may accumulate to influence both sex differences and phenotypic variance.

Most GWA studies utilize single-marker regression (SMR), in which the phenotype is regressed upon allele content one SNP at a time, thereby obtaining marginal SNP effect size estimates that do not fully account for LD patterns. In contrast, whole-genome regression methods, in which the phenotype is regressed upon all SNPs across the genome concurrently, fully account for multi-locus LD. These methods are increasingly being used as a one-stop solution to estimate conditional (with respect to other SNPs) effect sizes of SNP markers and to provide genome-wide estimates including genomic heritability (Meuwissen et al. 2001; Yang et al. 2010; de Los Campos et al. 2015a) and between-sex correlations (Zillikens et al. 2008; Yang et al. 2015; Rawlik et al. 2016). By estimating conditional SNP effect sizes, the goal across many studies is to select SNPs with nonzero effects and to build a model for predicting polygenic scores (de los Campos et al. 2013). Other works have directly illustrated the use of whole-genome regression methods for GWAS (Yi et al. 2003; Ayers and Cordell 2010; Guan and Stephens 2011; Zeng et al. 2012; Fernando et al. 2017). Whole-genome regressions are computationally challenging to use with biobank-level data; however, recent work suggests relatively accurate genomic prediction and SNP effect estimation can be achieved simply by accounting for local (as opposed to global) LD patterns (Vilhjálmsdóttir et al. 2015).

Building on the idea of utilizing conditional SNP marker effects, here we developed local Bayesian regressions (LBR) in which the phenotype is regressed upon multiple SNPs spanning multiple LD blocks (thereby accounting for local LD patterns) to study sex differences in complex traits from the UK Biobank. The LBR model uses random-effect SNP-by-sex interactions (de Los Campos et al. 2015b; Veturi et al. 2019) that decompose conditional SNP effects into three components: (i) one shared across sexes, (ii) a male-specific deviation from the shared component, and (iii) a female-specific deviation from the shared component. Using samples from the posterior distribution of conditional SNP effects, we developed methods to infer sex-specific effects and $G \times S$ interactions at the single SNP level and by aggregating SNP effects within small LD-based regions, offering multiple perspectives to study sex-specific genetic architectures.

In this study, we have utilized genotypes for 607,497 autosomal SNPs from $\sim$259,000 distant related Caucasians from the UK Biobank for assessing the performance of LBR in analyzing simulated and real complex traits including height, body mass index (BMI), waist-to-hip ratio (WHR), and heel bone mineral density (BMD). Using simulations, we showed that (i) for inferences of $G \times S$ interactions, LBR offers higher power with lower false discovery rate (FDR) than methods based on marginal effects (aka single-marker regression), and (ii) under imperfect LD between SNPs and causal variants (i.e., when causal variants are not genotyped), aggregating SNP effects within small LD-based regions offers higher power than methods based on testing individual SNPs.

The traits analyzed in this study span a range of genome-wide metrics and $G \times S$ plausibility, from height and BMI, for which previous studies indicate males and females possess very similar genetic architectures (Yang et al. 2015), to WHR, a trait with well-documented $G \times S$ interactions (Heid et al. 2010; Randall et al. 2013; Shungin et al. 2015; Winkler et al. 2015), and BMD, for which $G \times S$ interactions are thought to exist but have eluded detection (Karasis and Ferrari 2008). LBR provided evidence of $G \times S$ interactions impacting height, BMI, and BMD at regions of the genome where sex-specific genetic effects are relatively small; however, such regions are enriched in known eQTL. For WHR, LBR replicated many large-magnitude $G \times S$ interactions previously discovered using single-marker regression, but also located novel $G \times S$ interactions near such genes as the estrogen receptor ESRI.

Materials and Methods

Genotype and phenotype data

Genotyped SNPs from the custom UK Biobank Axiom Array (http://www.ukbiobank.ac.uk/scientists-3/uk-biobank-axiom-array/) were used in all analysis. Prior to analysis, all phenotypes were precorrected for sex, age, batch, genotyping center, and the first five genomic principal components. More information on genotypes and phenotypes can be found in the Supplemental Methods.

Overview of the LBR model, inference methods, and implementation

Here, we present brief details of the LBR model and implementation, with more details found in the Supplemental Methods. An example of how to fit LBR and perform post-processing of posterior samples of model parameters is available at: https://github.com/funkhou9/LBR-sex-interactions.

To study sex differences, we regressed male and female phenotypes ($y_m$ and $y_f$) on male and female genotypes ($X_m$ and $X_f$) using a SNP-by-sex interaction model of the form

$$
\begin{bmatrix}
   y_m \\
   y_f
\end{bmatrix} = \begin{bmatrix} 1 & \mu_m \\
   1 & \mu_f \end{bmatrix} + \begin{bmatrix} X_m \\
   X_f \end{bmatrix} \begin{bmatrix} b_0 \\
   b_m \end{bmatrix} + \begin{bmatrix} 0 \\
   1 \end{bmatrix} \epsilon_f + \begin{bmatrix} \epsilon_m \\
   \epsilon_f \end{bmatrix}.
\end{equation}

(1)

Above, $\mu_m$ and $\mu_f$ are male and female intercepts, $b_0 = \{b_0\}$ ($j = 1, \ldots, p$) is a vector of main effects, $b_m = \{b_m\}$ and $b_f = \{b_f\}$ are male and female interactions, respectively,
and $\varepsilon_m = \{\varepsilon_m\}$ and $\varepsilon_f = \{\varepsilon_f\}$ are male and female errors that were assumed to follow normal distributions with zero mean and sex-specific variances. Female-specific and male-specific SNP effects are defined as $\beta_{ij} = b_0 + b_i$ and $\beta_m = b_0 + b_m$, respectively.

**Prior assumptions:** For SNP effects, we adopted priors from the spike-slab family with a point of mass at zero and a Gaussian slab (Habier et al. 2011); specifically, $Pr(b_k) = \pi_k N(0, \sigma^2_{b_k}) + (1 - \pi_k) 1(b_k = 0)$, where $k = 0, f$, or $m$. Here, $\pi_k$ and $\sigma^2_{b_k}$ are hyper-parameters representing the proportion of nonzero effects and the variance of the slab; these hyper-parameters were treated as unknown and given their own hyper-priors.

**Local-regression:** Implementing the above model with whole-genome SNPs ($p \sim 600K$) and very large sample size ($n \sim 300K$) is computationally extremely challenging. However, LD in homogeneous unstructured human populations spans over relatively short regions ($R^2$ between allele dosages typically vanishes within 1–2 Mb; Supplemental Material, Figure S1). Therefore, we applied LBR to long, overlapping chromosome segments (Figure 1). Specifically, we divided the genome into “core” segments containing 1500 contiguous SNPs (roughly 8 Mb, on average), then applied the regression in Equation 1 to SNPs in the core segment plus 250 SNPs (i.e., roughly 1 Mb) in each flanking region, which were added to account for LD between SNPs at the edge of each core segment with SNPs in neighboring segments.

**Inferences:** We used the BGLR (Pérez and De Los Campos 2014) software to draw samples from the posterior distribution of the model parameters, and used these samples to make inference about individual SNP effects including: (i) the posterior probability that the $j^{th}$ SNP has a nonzero effect in males (PPM$_{SNP}$) and females (PPF$_{SNP}$), and (ii) the posterior probability that the female and male effects are different (PPDiff$_{SNP}$).

In regions involving multiple SNPs in strong LD, inferences at the individual-SNP level may be questionable. Therefore, we borrowed upon previous work by Fernando et al. (2017), enabling us to aggregate multiple sex-specific SNP effects within relatively small regions using “window variances.” For each SNP $j$ we defined a window $j^*$ around the SNP based on local LD patterns. We then defined the male-specific and female-specific window variances as $\sigma^2_{s_{ij}} = var(X_j \beta_i)$ and $\sigma^2_{s_{ij}} = var(X_j \beta_i)$, respectively. Here, $X_j$ represent genotypes at SNPs within the $j^*$ window, and $var()$ is the sample variance operator. Prior to model fitting, the phenotype is scaled across sexes; thus, sex-specific window variances may be interpreted as the proportion of total phenotypic variance explained by sex-specific SNP effects. From samples of sex-specific window variances, we computed the posterior probability of (i) nonzero male-specific window variance (PPM$_{s_{ij}}$), (ii) nonzero female-specific window variance (PPF$_{s_{ij}}$), and (iii) sex difference in window variances (denoted as PPDF$_{s_{ij}}$).

**Overview of simulations**

We used simulations to assess the power and FDR of LBR, and to compare them with that of standard single-marker-regression (SMR). Traits were simulated using SNP genotypes from the UK Biobank (119,190 males and 139,738 females, all distantly related Caucasians), thus providing realistic LD patterns. We simulated a highly complex trait with one causal variant per $\sim 2$ Mb, which, on average, explained a proportion of the phenotypic variance equal to $3.3 \times 10^{-4}$. Our simulations used a total of 60,000 genotyped SNPs ($\sim$one-tenth of the genome, consisting of 6000 consecutive SNPs taken from 10 different chromosomes) and 150 causal variants; on the complete human genome “scale” this corresponds to a trait with 1500 causal variants and a heritability of 0.5 (see Supplemental Methods for further details). Of the causal variants, 40% (a total of 60 SNPs) had differing sex-specific effects and the remaining 60% (90 SNPs) had effects that were the same in males and females. Estimates of power and FDR were based on 30 Monte Carlo (MC) replicates.

**Data availability**

The authors state that all data necessary for confirming the conclusions presented in the article are represented fully.

---

Bayesian Sex-Specific Genetic Analysis 233
within the article. Genotype and phenotype data from the UK Biobank are available to all researchers upon application at http://www.ukbiobank.ac.uk/register-apply/. The script used to simulate phenotypes is available at https://github.com/funkhou9/LBR-sex-interactions. For eQTL enrichment analysis, single-tissue cis-eQTL data (significant variant-gene associations based on permutations) from GTEx V7 was downloaded from https://gtexportal.org/home/datasets.

Supplemental Methods, Figure S1 through S5, and Table S1 through S4 are available at Figshare at https://doi.org/10.25386/genetics.11900247.

Results

**LBRs offer improved power with lower FDRs**

**Power and FDR when causal variants are genotyped:** First, we analyzed the simulated phenotypes using all SNPs (including all 150 causal SNPs). Initially interested in inferring G×S interactions, we ranked SNPs based on the PPDiffSNP metric of LBR and on SMR’s P-value for sex difference (P value-diff, see Supplemental Methods) and used the two ranks to estimate power and FDR as a function of the number of SNPs selected (Figure 2). We observed little variation in power and false discoveries across MC replicates (Table S2); this was expected because each MC replicate involved 60,000 loci, 150 of which had causal effects. LBR showed consistently higher power (achieving a power of ~75% when selecting the top 50 SNPs with highest PPDiffSNP) and lower FDR than SMR. The FDR of LBR was very low when selecting the top 50 SNPs with highest PPDiffSNP and exhibited a very sharp phase-transition with fast increase in FDR thereafter.

We also compared the two methods based on arbitrary, albeit commonly used, mapping thresholds for SMR and LBR. At PPDiffSNP ≥ 0.95 [a posterior probability threshold used in GWAS to minimize the local false discovery rate (Efron 2008)], LBR selected an average (across simulation replicates) of 38.33 SNPs with an estimated power of 0.634 and estimated FDR of 0.007. Conversely, at P value-diff ≤ 5 × 10^{-8} [a P-value threshold routinely used in human GWA studies, based on the number of approximately independent SNPs in the human genome (International HapMap Consortium et al. 2007)] SMR selected an average of 50.7 SNPs with an estimated power of 0.436 and estimated FDR of 0.451. Altogether, these results suggest that for G×S discovery, LBR offers higher power and lower FDR than SMR—the method most widely used in GWA studies—at least when G×S interactions are observed.

When trying to map SNPs that had effect in at least one sex, we used PPSNPj = max{PPMSNPj, PPFSNPj} and P-values from an F-test (see Supplemental Methods) as metrics for LBR and SMR methods, respectively. Again, LBR showed higher power with lower FDR than a standard SMR P-value (Figure S2). At traditional mapping thresholds, LBR and SMR had similar power but LBR achieved that power with much lower FDR; at PPSNP ≥ 0.95, the average number of SNPs selected was 120.83 with an estimated power of 0.799 and estimated FDR of 0.009, whereas at P-value ≤ 5 × 10^{-8}, the number of SNPs selected was 374.56 with an estimated power of 0.794 and FDR of 0.66.

**Power and FDR when causal variants are masked:** In a second round of analyses, we removed all causal variants from the panel of SNPs used in the analysis to represent a situation where causal variants are not observed, and genotyped SNPs are tagging causal variants at varying degrees. We initially assessed the relative performance of LBR to infer segments harboring G×S interactions. Power and FDR were assessed at several resolutions: 1 Mb, 500 kb, and 250 kb regions around each causal variant. At each resolution, a discovery was considered true if the finding laid within a segment harboring a G×S causal variant. In this scenario, we again observed that LBR had small variability in power and false discoveries between MC replicates (Table S3). Power
and FDR were computed at different thresholds (using PPDiff\textsubscript{SNP} and PPDiff\textsubscript{w} for LBR and P value-diff for SMR; Figure 3). When using a 1 Mb target area—such that correct G\times S discoveries must be within 500 kb on either side of a true G\times S event—PPDiff\textsubscript{w} thresholds (LBR's window-based metric) provided highest power within an FDR range of 0–0.3; thereafter, SMR provided slightly higher power. As expected, when removing causal variants, power was estimated to be much lower than when causal variants were observed; at PPDiff\textsubscript{w} \approx 0.95, the estimated power and FDR were 0.454 and 0.004, respectively, while at P value-diff (on the −log10 scale) \leq 5 \times 10^{-8}, estimated power and FDR were 0.22 and 0.006. As seen in Figure 3, when considering a finer resolution (500 kb and 250 kb) the performance of both LBR-based approaches was more robust than that of SMR. Altogether this indicates that for the discovery and mapping of unobserved G\times S interactions, LBR's window-based metric provides higher power with equivalent FDR and finer resolution than single-marker regression methods.

To infer segments containing causal variants that affect at least one sex, we again used LBR to decide whether either sex-specific effect was nonzero at the level of individual SNPs or windows. Using a 1-MB target area, LBR's window-based metrics provided the highest power within an FDR range of 0–0.025. When decreasing the target area, LBR provided the highest power over larger FDR ranges (Figure S3).

**For real human traits, many novel G\times S interactions showed relatively small sex-specific effects**

We analyzed four complex human traits (height, BMI, BMD, and WHR) measured among \sim 259,000 distantly related Caucasians from the UK Biobank (\sim 119,000 males and \sim 140,000 females). For each trait, we fit the LBR model (Equation 1) across the entire autosome consisting of 607,497 genotyped SNPs using 417 overlapping segments (Figure 1) and obtained evidence of G\times S interactions at the level of SNP j and window j\textsuperscript{*}.

To compare both the magnitude and sign of sex-specific SNP effects, we plotted each $\hat{\beta}_j$ against $\hat{\beta}_m$ (Figure 4A). The trait was scaled across sexes prior to model fitting; thus, male- and female- specific effects were not constrained to the same scale. In this way, one might expect male-specific SNP effects to uniformly differ from female-specific SNP effects by a multiplicative factor if the variance of the phenotype is different between sexes (sample statistics within each sex are provided within Table S1). Surprisingly, we did not observe evidence of sex-specific SNP effects uniformly differing due to differences in phenotypic scale; for height, BMD, and BMI, as seen in Figure 4A, most large effect SNPs lie near the blue diagonal line. For WHR, we observed largely consistent results from prior studies (Heid et al. 2010; Randall et al. 2013; Winkler et al. 2015): namely the prevalence of numerous SNPs with relatively large effects in females but little to no effect in males. No traits exhibited evidence of any SNPs
with (i) high confidence male- and female- specific effects (no SNPs with PPM$_{SNP}$ ≥ 0.9 and PPF$_{SNP}$ ≥ 0.9) and (ii) differing signs between sexes.

We then aggregated sex-specific SNP effects within small LD-based regions to estimate sex-specific window variances $\sigma^2_{g_m}$ and $\sigma^2_{g_f}$ and compared the magnitude of each (Figure 4B). Interestingly, for traits such as height, many large effect regions bear slightly larger window variances for males than for females. This was not observed at the single SNP level, suggesting that many regions bearing numerous small effect SNPs produce aggregate effects that are potentially larger (although not reaching a PPDiff$_{g_f}$ ≥ 0.9 threshold) in males than in females. One example is the GDF5 locus, previously known to strongly associate with adult height (Sanna et al. 2008), where a peak PPDiff$_{g_f}$ signal centered on rs143384 had slightly different estimated sex-specific window variances ($\sigma^2_{g_m} = 3.0 \times 10^{-3}$ and $\sigma^2_{g_f} = 2.6 \times 10^{-3}$) but weak evidence of a G×S interaction (PPDiff$_{g_f}$ = 0.544). For BMD, several large effect regions show suggestive evidence of G×S interactions, including the AKAP11 locus and the CCDC170 locus (PPDiff$_{g_f}$ ≥ 0.856 and 0.745, respectively), both previously associated with BMD (Mullin et al. 2016, 2017; Correa-Rodríguez et al. 2018; Zhu et al. 2018).

To make G×S inferences at the level of window variances irrespective of the magnitude of sex-specific effects, we adopted a PPDiff$_{g_f}$ threshold of 0.9, which, in simulations (Figure 3), provided optimal power at an estimated FDR of 0.029 when using a 1-MB target area. For height, a total of eight distinct regions possessed a PPDiff$_{g_f}$ ≥ 0.9, with none reaching a more stringent PPDiff$_{g_f}$ ≥ 0.95 threshold, and

Figure 4 Comparing sex-specific genetic effects. (A) Plot of estimated female SNP effects against estimated male SNP effects for all 607,497 genotyped autosomal SNPs. Points are colored by their posterior probability of sex difference at the level of individual SNPs. (B) Plot of estimated female window variances against estimated male window variances for all 607,497 LD-based windows, with each window $j^*$ centered on a different focal SNP $j$. Points are colored by their posterior probability of sex difference at the level of window variances. (C) Miami-like plot depicting location and magnitude of G×S interactions identified through sex-specific window variances. For each trait, showing estimated male window variance above the x-axis and estimated female window variance below the x-axis. Vertical lines denote changing chromosomes. A sample of windows is labeled with nearest gene annotation, obtained from Axiom UKB WCSG annotations, release 34. Gray labels indicate nearest genes with relatively large window variances evidently shared across sexes, while red labels indicate nearest genes with detected G×S interactions.
none overlapping with two previously suggested BMI G×S SNPs (Locke et al. 2015). As seen in Figure 4C, inferred G×S interactions for height and BMI possess relatively small sex-specific window variances; for example, for height, the window centered on SNP rs1535515 (near LRR26C) had a PDIFF < 0.96, whereas $\sigma^2_{2m} = 2.1 \times 10^{-5}$ and $\sigma^2_{2F} = 1.1 \times 10^{-4}$. For BMI, seven regions reached a 0.9 PDIFF threshold, while none had a higher-confidence G×S interaction (PDIFF < 0.95) was detected within ABO, the gene controlling blood type.

For WHR, roughly 45 distinct genomic regions possessed a PDIFF < 0.9, while 34 of these possessed a PDIFF < 0.95. We found many previously detected G×S interactions known to associate with WHR or a related trait, WHR adjusted for BMI (WHRadjBMI) (Heid et al. 2010; Randall et al. 2013; Shungin et al. 2015; Winkler et al. 2015). These included interactions at LYPLA1, MAP3K1, COBBL1, RSPO3, and VEGFA, among others. We also detected numerous novel G×S interactions (Table 1) near physiologically intriguing genes such as the estrogen receptor gene ESR1 and the ATP binding cassette transporter A1 gene ABCA1 known to play a role in HDL metabolism (PDIFF < 0.95). As seen in Table 1, both novel signals possessed a high-confidence female-specific effect with weak evidence for a male-specific effect (PPF < 0.95; PPM < 0.6); however, the magnitude of the female-specific effect was relatively small.

### Table 1 G×S interactions inferred through sex-specific window variances.

| Focal SNP | trait | $\sigma^2_{2m}$ | $\sigma^2_{2F}$ | PPM | PPF | PDIFF | Nearest gene | Location |
|-----------|-------|----------------|----------------|-----|-----|--------|--------------|----------|
| rs8176719 | BMD   | 0.06           | 0.00182        | 1   | 0.794 | 1      | ABO         | Exon/frameshift | Yes |
| rs1535515 | height| 0.00117        | 0.819          | 0.999 | 0.956 | LRR26C    | Intron       | Yes |
| rs1544926 | height| 0.00035        | 0.983          | 0.418 | 0.955 | COL2A3A1  | UTR-3        | Yes |
| rs6905288 | WHR   | 0.00567        | 0.921          | 1    |      | VEGFA     | Downstream   |        |
| rs7296101 | WHR   | 0.00132        | 0.916          | 1    |      | RSPO3     | Downstream   |        |
| rs1128249 | WHR   | 0.00107        | 0.916          | 1    |      | COBBL1    | Intron       | Yes |
| rs1202272 | WHR   | 0.00117        | 0.916          | 1    |      | LYPLA1    | Downstream   |        |
| rs1776897 | WHR   | 0.00311        | 0.909          | 1    |      | HMGA1     | Upstream     |        |
| rs1105740 | WHR   | 0.00438        | 0.846          | 1    |      | CDDC92    | Exon/missense|        |
| rs1777718 | WHR   | 0.00031        | 0.779          | 1    |      | CMIP       | Intron       |        |
| rs4607103 | WHR   | 0.00195        | 0.916          | 1    |      | ADAMT95-AS2 | Intron       | Yes |
| rs6937293 | WHR   | 0.00457        | 0.839          | 1    |      | LOC728012 | Downstream   |        |
| rs1686137 | WHR   | 0.00066        | 0.389          | 1    | 0.995 | PLXN1     | Intron       | Yes |
| rs7068463 | WHR   | 0.00068        | 0.461          | 1    |      | SNX10     | Intron       | Yes |
| rs9376422 | WHR   | 0.00107        | 0.524          | 1    |      | LOC645434 | Upstream     |        |
| rs6867938 | WHR   | 0.00192        | 0.44           | 1    | 0.998 | MAP3K1    | Upstream     |        |
| rs2171522 | WHR   | 0.00236        | 0.561          | 1    | 0.998 | ITTPR2    | Downstream   |        |
| rs3810068 | WHR   | 0.00026        | 0.174          | 1    |      | EMLN2     | Upstream     |        |
| rs5600000 | WHR   | 0.00129        | 0.809          | 1    |      | NKKX2-6   | Upstream     |        |
| rs1332955 | WHR   | 0.00647        | 0.97           | 1    | 0.973 | LOC284688 | Downstream   |        |
| rs1313354 | WHR   | 0.00195        | 0.969          | 1    | 0.991 | FAM13A    | Intron       | Yes |
| rs1126364 | WHR   | 0.00107        | 0.723          | 1    | 0.991 | MYEOV     | Intron       | Yes |
| rs2800999 | WHR   | 0.00201        | 0.691          | 1    | 0.979 | TSHZ2     | Intron       |        |
| rs2244506 | WHR   | 0.00101        | 0.453          | 0.985 | 0.985 | MIR5694   | Downstream   |        |
| rs7259285 | WHR   | 0.00182        | 0.767          | 1    | 0.989 | HAUS8     | Downstream   |        |
| rs4450871 | WHR   | 0.0002        | 0.527          | 1    |      | CYTL1     | Downstream   |        |
| rs4080890 | WHR   | 0.00153        | 0.594          | 0.999 | 0.975 | KCN2J     | Downstream   |        |
| rs4684859 | WHR   | 0.00039        | 0.33           | 0.998 | 0.994 | PPARG     | Downstream   |        |
| rs7704120 | WHR   | 0.0049         | 0.476          | 0.998 | 0.991 | STC2      | Downstream   |        |
| rs1099141 | WHR   | 0.00123        | 0.339          | 0.986 | 0.966 | ABCA1     | Intron       | Yes |
| rs1245471 | WHR   | 0.00087        | 0.36           | 0.996 | 0.965 | BCL2      | Intron       |        |
| rs62070804 | WHR | 0.00004        | 0.052          | 0.969 | 0.961 | ABHD15    | Exon/missense|        |
| rs10760322 | WHR | 0.00027        | 0.282          | 0.986 | 0.968 | LHK2      | Downstream   |        |
| rs1361024 | WHR   | 0.00022        | 0.203          | 0.982 | 0.962 | ESR1      | Intron       |        |
| rs1358503 | WHR   | 0.00021        | 0.309          | 0.999 | 0.966 | SEMA3C    | Upstream     | Yes |
| rs13156948 | WHR | 0.00016        | 0.079          | 0.97  | 0.957 | IRX1      | Downstream   |        |
| rs12423763 | WHR | 0.0174        | 0.00074        | 1    | 0.552 | STXBP6    | Upstream     |        |

Listed are loci with at least 0.95 posterior probability that sex-specific window variances differ. The table is sorted first by trait, then by magnitude of the female-specific window variance. Results are filtered such that each window listed consisted of a distinct set of SNPs. A full list of all G×S signals at a PDIFF > 0.90 threshold is provided in Table S4.

- **a** Focal SNP is defined as the center SNP $j$ in window $j^*$.
- **b** The proportion of variance explained by male-specific SNP effects, expressed as a percentage.
- **c** The proportion of variance explained by female-specific SNP effects, expressed as a percentage.
- **d** Nearest gene and location identifier through Axiom UKB WCGS annotations, release 34. The gene/locus is bold if it has been previously detected as a G×S interaction for WHR or WHR adjusted for BMI (Heid et al. 2010; Randall et al. 2013; Shungin et al. 2015; Winkler et al. 2015).
- **e** If "yes," the focal SNP is significantly associated with gene expression in at least one tissue, according to GTEx V7.
to low power. Lastly, for WHR, most of the high-confidence small sex-specific effects are enriched in eQTL with associated eGenes (including ABO and CYP3A5) expressed in the adrenal gland, among other tissues. For height, we observed small enrichment P-values across many tissues since G×S focal SNPs are enriched in eQTL with associated eGenes (including LOC101927975 and CNDP2) expressed across many tissues. Lastly, for WHR, we observed G×S detections to be heavily enriched in eQTL with associated eGenes expressed in fibroblast, adipose, and skin tissues.

Discussion

We have investigated the degree to which sex-specific genetic architectures differ at local regions, using large biobank data (N ~119,000 males and ~140,000 females) and Bayesian multiple regression techniques that estimate sex-specific marker effects accounting for local LD patterns. The flexibility of the Bayesian approach enables multi-resolution inference of sex-specific effects, from individual SNP effects to window-variances that aggregate SNP effects within chromosome segments. These inferences can all be drawn using the results of the same model fit (Equation 1), but different post-processing of samples of SNP effects from the posterior distribution.

The Bayesian multiple regression technique performed in this study, along with estimation of window variances, was largely inspired by Fernando et al. (2017). In that study, windows were defined using disjoint, fixed intervals. In contrast, for each SNP, we define a window based on local LD patterns, resulting in heavily overlapping, dynamically sized windows. The methods presented here also bear resemblance to those of Vilhjálmsdóttir et al. (2015), which utilized point-normal priors to estimate human SNP effects after accounting for local LD patterns. In that study, posterior means of SNP effects were estimated for the purposes of prediction, whereas, in this study, we derive the full posterior distribution numerically, allowing for inference of non-null SNP effects and window variances.

Through simulations, we showed that LBR provides superior power and precision to detect causal variants and those specifically bearing G×S interactions. We rationalize improvements in power upon traditional SMR methods by noting that the magnitude of a typical causal variant or G×S interaction is exceedingly small, and can elude hypothesis testing, due partly to the burden of multiple test correction. We also note that the resolution (peak size) in SMR signals is relatively large when using large sample sizes (due to not fully accounting for local LD patterns). To overcome this problem, we provided evidence that LBR methods—either by estimating conditional (accounting for local LD) marker effects or by aggregating conditional marker effects within relatively small regions—can achieve improved resolution when working with large sample sizes such as biobank-level data.

When using LBR to analyze real human traits, we have provided credence to our posterior probability-based discoveries by determining that LBR-detected G×S interactions are

\[ \hat{\theta}^2 \approx 1.4 \times 10^{-4} \]. As evident from Table 1, most novel GWAS interactions detectable with LBR are those with relatively small sex-specific effects.

Additionally, we utilized a traditional SMR approach (see Supplemental Methods) for the discovery of G×S interactions among traits to compare \( P \text{ value}-\text{diff} \) signals to PPDiff \( \hat{\theta}^2 \) signals (Figure S4). At \( P \text{ value}-\text{diff} \approx 5 \times 10^{-8} \), there were no genome-wide significant G×S-interacting SNPs for height, one significant SNP for BMI near a window with PPDiff \( \hat{\theta}^2 \approx 0.9 \), and one significant peak within ABO for BMD (the same signal detected using PPDiff \( \hat{\theta}^2 \)). Regions with a PPDiff \( \hat{\theta}^2 \approx 0.9 \) generally coincided with at least nominally significant \( P \text{ value}-\text{diff} \) signals; for height and BMD, regions with PPDiff \( \hat{\theta}^2 \approx 0.9 \) also possessed a peak SNP with \( P \text{ value}-\text{diff} \approx 0.01 \). For BMI, PPDiff \( \hat{\theta}^2 \approx 0.9 \) signals possessed a peak SNP of \( P \text{ value}-\text{diff} \approx 0.1 \). This, together with the fact that novel G×S interactions found using LBR possess relatively small sex-specific effects, suggests that LBR may be detecting G×S interactions that are otherwise missed due to low power. Lastly, for WHR, most of the high-confidence PPDiff \( \hat{\theta}^2 \approx 0.9 \) signals coincided with clear and obvious \( P \text{ value}-\text{diff} \) peaks.

**Inferred G×S interactions were enriched in tissue-specific eQTL**

As seen previously, many G×S interactions inferred using LBR have exceedingly small sex-specific effects. To further investigate whether G×S detections using the PPDiff \( \hat{\theta}^2 \) metric may be functionally relevant, we inferred whether such signals are enriched in eQTL identified from GTEx. Specifically, using a hyper-geometric test we asked whether PPDiff \( \hat{\theta}^2 \)-selected focal SNPs (SNP \( j \) within window \( j^* \)) were enriched in eQTL, then compared to eQTL enrichment from \( P \text{ value}-\text{diff}-\text{selected} \) SNPs as a function of the number of SNPs selected (Figure S5). PPDiff \( \hat{\theta}^2 \)-selected focal SNPs showed consistently higher eQTL enrichment than \( P \text{ value}-\text{diff}-\text{selected} \) SNPs for all traits except WHR. For instance, at PPDiff \( \hat{\theta}^2 \approx 0.9 \), the total number of windows (focal SNPs) selected was 36, 264, 34, and 13, for height, WHR, BMD, and BMI, respectively. With these selections, eQTL enrichment \( P \)-values were \( 2.39 \times 10^{-4} \), \( 1.52 \times 10^{-12} \), \( 2.01 \times 10^{-12} \), and \( 8.33 \times 10^{-4} \), for height, WHR, BMD, and BMI, respectively. When selecting the same number of SNPs using \( P \text{ value}-\text{diff} \)-enrichment \( P \)-values were \( 2.25 \times 10^{-2} \), \( 1.56 \times 10^{-28} \), \( 5.54 \times 10^{-8} \), 1.93 \( \times 10^{-1} \), for height, WHR, BMD, and BMI, respectively.

To provide more information about how genetic regions bearing G×S interactions may impact gene expression in specific tissues, we determined whether focal SNPs at PPDiff \( \hat{\theta}^2 \approx 0.9 \) are enriched in tissue-specific eQTL (Figure 5). For height, BMD, and WHR, such SNPs showed significant eQTL enrichment in at least one tissue, using a conservative Bonferroni corrected enrichment \( P \)-value of \( 2.6 \times 10^{-4} \) (correcting for 192 tests in total; 48 tissues and four traits). Interestingly, BMD G×S signals are very strongly enriched in eQTL with associated eGenes (including ABO and CYP3A5)
Evidence that LBR-identified G×S interactions are enriched in tissue-specific eQTL. Plotted on the x-axis is the P-value obtained from a hypergeometric test providing evidence that focal SNPs selected using PPDiff_2^s ≥ 0.9 are enriched in tissue-specific eQTL. The dashed line represents a Bonferroni corrected significance threshold of 2.6 × 10^{-4}.

Figure 5
generally more enriched in eQTL than SMR-detected interactions. For BMD, we provided new evidence that sex-specific effects differ within ABO, and that G×S interactions are highly enriched in adrenal gland-specific eQTLs. This encourages the hypothesis that some G×S are eQTL that may modulate gene expression in the adrenal gland, with gene function dependent on the level of sex hormones. This was also an intriguing finding given that ABO blood groups have been known to associate with osteoporosis and osteoporosis severity (Choi and Pai 2004; Lu and Li 2011). For WHR, we detected previously known, large-magnitude G×S interactions that were discovered using WHR or WHRadjBMI (Heid et al. 2010; Randall et al. 2013; Shungin et al. 2015; Winkler et al. 2015), but additionally discovered novel, small magnitude G×S interactions near such genes as ESR1 and ABCA1. In a previous work analyzing WHRadjBMI, ABCA1 showed a significant female-specific genetic effect only; however, the test for G×S interaction failed to reach significance (Shungin et al. 2015).

For traits like height and BMI, large effect loci are estimated to have very similar effects between males and females, and loci with evidence of G×S interactions were those possessing relatively small sex-specific effects. As seen in Figure 4B, many relatively large window variances for height are estimated to be slightly higher for males than for females, albeit not reaching a PPDiff$g_0^2 \geq 0.9$ threshold. This is consistent with the fact that the global genomic variance for height was estimated to be higher in males than in females in a previous study using the interim release of the UK Biobank (Rawlik et al. 2016). Similarly, the same prior study estimated the global genomic variance of BMI to be higher in females than in males, and we observe, if anything, evidence of sex-specific window variances leading to the same conclusion. These observations may potentially indicate that relatively large causal variants have slightly different sex-specific effects for traits like height and BMI; however, if that is the case, we are still underpowered to confidently detect such interactions.

It is important to acknowledge that, while the methods presented here appear useful to decipher sex-specific genetic architectures from large human samples, additional work will be required to determine how these techniques may infer heterogeneous genetic effects in other contexts (other types of gene-by-covariate interactions), or when using different sample sizes or samples from different populations. With large sample sizes, the increased power and flexibility of LBR comes at the cost of a significantly larger computational burden than that involved in the traditional SMR approach; however, working with large datasets can be made manageable by adjusting the size of each fitted segment (Figure 1) and parallel processing the fitting of each segment. Alternatively, LBR may be used as a follow up to traditional SMR tests, using preselected regions of interest. Another limitation inherent to aggregating SNP effects using window variances is that the sign of the effect is lost. In this way, when inferring G×S interactions through window variance differences, we cannot comment on whether sex-specific effects had the same sign or differing signs.

To conclude, we have demonstrated the powerful and flexible use of local Bayesian regressions for GWA to infer sex-specific genetic effects and G×S interactions using the UK Biobank. This was done largely by showing various means to utilize estimates of conditional (accounting for local LD), sex-specific SNP marker effects for GWA even when causal variants are not on the SNP panel for analysis. We anticipate that many more traits will be analyzed with this method to increasingly learn more about what is contributing to differences between males and females in human populations.

Acknowledgments

We thank two anonymous reviewers and the associate editor for the comments they provided. We would also like to thank Michigan State University’s High Performance Computing Cluster for providing all computing resources. Funding sources were provided by the National Institutes of Health (grants R01GM099992 and R01GM101219) and by the United States Department of Agriculture National Institute of Food and Agriculture (USDA NIFA) predoctoral fellowship award no. 2017-67011-26074.

Literature Cited

Ayers, K. L., and H. J. Cordell, 2010 SNP Selection in genome-wide and candidate gene studies via penalized logistic regression. Genet. Epidemiol. 34: 879–891. https://doi.org/10.1002/gepi.20543

Choi, J. W., and S. H. Pai, 2004 Associations between ABO blood groups and osteoporosis in postmenopausal women. Ann. Clin. Lab. Sci. 34: 150–153.

Correa-Rodriguez, M., J. S. Rio-Valle, and B. Rueda-Medina, 2018 AKAP11 gene polymorphism is associated with bone mass measured by quantitative ultrasound in young adults. Int. J. Med. Sci. 15: 999–1004. https://doi.org/10.7150/ijms.25369

de los Campos, G., D. Gianola, D. B. Allison 2010 Predicting genetic predisposition in humans: the promise of whole-genome markers. Nat. Rev. Genet. 11: 880–886. https://doi.org/10.1038/nrg2898

de los Campos, G., A. I. Vazquez, R. Fernando, Y. C. Klimentidis, and D. Sorensen, 2013 Prediction of complex human traits using the genomic best linear unbiased predictor. PLoS Genet. 9: e1003608. https://doi.org/10.1371/journal.pgen.1003608

de los Campos, G., D. Sorensen, and D. Gianola 2015a Genomic heritability: what is it? PLoS Genet. 11: e1005048. https://doi.org/10.1371/journal.pgen.1005048

de los Campos, G., Y. Veturi, A. I. Vazquez, C. Lehermeier, and P. Pérez-Rodríguez 2015b Incorporating genetic heterogeneity in whole-genome regressions using interactions. J. Agric. Biol. Environ. Stat. 20: 467–490. https://doi.org/10.1007/s13253-015-0222-5

Efron, B., 2008 Microarrays, empirical Bayes and the two-groups model. Stat. Sci. 23: 1–22. https://doi.org/10.1214/07-STS236

Fernando, R., A. Toosi, A. Wole, D. Garrick, and J. Dekkers, 2017 Application of whole-genome prediction methods for...
gu

Lynch, M. W. J., 1998 Bayesian variable selection regression for genome-wide association studies and other large-scale problems. Ann. Appl. Stat. 5: 1780–1815. https://doi.org/10.1214/11-AOAS455

Habier, D., R. L. Fernando, K. Kizilkaya, and D. J. Garrick, 2011 Extension of the Bayesian alphabet for genomic selection. BMC Bioinformatics 12: 186. https://doi.org/10.1186/1471-2105-12-186

Heid, I. M., A. U. Jackson, J. C. Randall, T. W. Winkler, L. Qi et al., 2010 Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat. Genet. 42: 949–960 [corrigenda: Nat. Genet. 43: 1164 (2011)]. https://doi.org/10.1038/ng.685

Hoffmann, T. J., G. B. Ehret, P. Nandakumar, D. Ranatunga, C. Schaefer et al., 2017 Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. Nat. Genet. 49: 54–64. https://doi.org/10.1038/ng.3715

International HapMap Consortium, Frazer, K. A., D. G. Ballinger, D. Cox, D. A. Hinds, L. L. Stuve et al., 2007 A second generation human haplotype map of over 3.1 million SNPs. Nature 449: 851–861. https://doi.org/10.1038/nature06258

Karaskis, D., and S. L. Ferrari, 2008 Contribution of gender-specific genetic factors to osteoporosis risk. Ann. Hum. Genet. 72: 696–714. https://doi.org/10.1111/j.1469-1809.2008.00447.x

Lello, L., S. G. Avery, L. Tellier, A. I. Vazquez, G. de los Campos et al., 2018 Accurate genomic prediction of human height. Genetics 210: 477–497 [corrigenda: Genetics 214: 231 (2020)]. https://doi.org/10.1534/genetics.118.301267

Li, C.-T., K. Estrada, L. M. Yerges-Armstrong, N. Amin, E. Evangelou et al., 2012 Assessment of gene-by-sex interaction effect on bone mineral density. J. Bone Miner. Res. 27: 2051–2064. https://doi.org/10.1002/jbmr.1679

Locke, A. E., B. Kahali, S. I. Berndt, A. E. Justice, T. H. Pers et al., 2015 Genetic studies of body mass index yield new insights for obesity biology. Nature 518: 197–206. https://doi.org/10.1038/nature14177

Lu, B. B., and K. H. Li, 2011 Association between ABO blood groups and osteoporosis severity in Chinese adults aged 50 years and over. J. Int. Med. Res. 39: 929–933. https://doi.org/10.1177/147323001139900327

Lynch, M. W. J., 1998 Genetics and Analysis of Quantitative Traits, Sinauer Associates, Sunderland, Massachusetts

Meeuwissen, T. H. E., B. J. Hayes, and M. E. Goddard, 2001 Prediction of total genetic value using genome-wide dense marker maps. Genetics 157: 1819–1829 https://doi.org/10.1146/annurev.genet.34.1.1819

Mullin, B. H., J. P. Walsh, H. F. Zheng, S. J. Brown, G. L. Surdulescu et al., 2016 Genome-wide association study using family-based cohorts identifies the WLS and CCDC170/ESR1 loci as associated with bone mineral density. BMC Genomics 17: 136. https://doi.org/10.1186/s12864-016-2481-0

Mullin, B. H., J. H. Zhao, S. J. Brown, J. R. B. Perry, J. Luan et al., 2017 Genome-wide association study meta-analysis for quantitative ultrasound parameters of bone identifies five novel loci for broadband ultrasound attenuation. Hum. Mol. Genet. 26: 2791–2802. https://doi.org/10.1093/hmg/ddx174

Pérez, P., and G. De Los Campos, 2014 Genome-wide regression and prediction with the BGLR statistical package. Genetics 198: 483–495. https://doi.org/10.1534/genetics.114.164442

Randall, J. C., T. W. Winkler, Z. Kutalik, S. I. Berndt, A. U. Jackson et al., 2013 Sex-stratified Genome-wide Association Studies Including 270,000 Individuals Show Sexual Dimorphism in Genetic Loci for Anthropometric Traits. PLoS Genet. 9: e1003500. https://doi.org/10.1371/journal.pgen.1003500

Rawlik, K., O. Canela-Xandri, and A. Tenesa, 2016 Evidence for sex-specific genetic architectures across a spectrum of human complex traits. Genome Biol. 17: 166. https://doi.org/10.1186/s13059-016-1025-x

Sanna, S., A. U. Jackson, R. Nagaraja, C. J. Willer, W. M. Chen et al., 2008 Common variants in the GDF5–UQCC region are associated with variation in human height. Nat. Genet. 40: 198–203. https://doi.org/10.1038/ng.74

Shungin, D., T. W. Winkler, D. C. Croteau-Chonka, T. Ferreira, A. E. Locke et al., 2015 New genetic loci link adipose and insulin biology to body fat distribution. Nature 518: 187–196. https://doi.org/10.1038/nature14132

Veturi, Y., G. de los Campos, N. Yi, W. Huang, A. I. Vazquez et al., 2019 Modeling heterogeneity in the genetic architecture of ethnically diverse groups using random effect interaction models. Genetics 211: 1395–1407. https://doi.org/10.1534/genetics.119.301909

Vilhjálmsson, B. J., J. Yang, H. K. Finucane, A. Gusev, S. Lindström et al., 2015 Modeling linkage disequilibrium increases accuracy of polygenic risk scores. Am. J. Hum. Genet. 97: 576–592. https://doi.org/10.1016/j.ajhg.2015.09.001

Weiss, L. A., L. Pan, M. Abney, and C. Ober, 2006 The sex-specific genetic architecture of quantitative traits in humans. Nat. Genet. 38: 218–222. https://doi.org/10.1038/ng1726

Winkler, T. W., A. E. Justice, M. Graff, L. Barata, M. F. Feitoza et al., 2015 The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. PLoS Genet. 11: e1005378. https://doi.org/10.1371/journal.pgen.1005378

Yang, J., B. Benyamin, B. P. McEvoy, S. Gordon, A. K. Henders et al., 2010 Common SNPs explain a large proportion of the heritability for human height. Nat. Genet. 42: 565–569. https://doi.org/10.1038/ng.608

Yang, J., A. Bakshi, Z. Zhu, G. Hemani, A. A. E. Vinkhuyzen et al., 2015 Genome-wide genetic homogeneity between sexes and populations for human height and body mass index. Hum. Mol. Genet. 24: 7445–7449. https://doi.org/10.1093/hmg/ddv443

Yi, N., V. George, and D. B. Allison, 2003 Stochastic search variable selection for identifying multiple quantitative trait loci. Genetics 164: 1129–1138.

Zeng, J., M. Pszczola, A. Wolc, T. Strabel, R. L. Fernandez et al., 2012 Genomic breeding value prediction and QTMLasso data using Bayesian and GBLUP methods. BMC Proc. 6: 57. https://doi.org/10.1186/1753-5461-6-S2-S7

Zhu, D.-L., X.-F. Chen, W.-X. Hu, S.-S. Dong, B.-J. Lu et al., 2018 Multiple functional variants at 13q14 risk locus for osteoporosis regulate RANKL expression through long-range superenhancer. J. Bone Miner. Res. 33: 1335–1346. https://doi.org/10.1002/jbmr.3419

Zillikens, M. C., M. Yazdanpanah, L. M. Pardo, F. Rivadeneira, Y. S. Aulchenko et al., 2008 Sex-specific genetic effects influence variation in body composition. Diabetologia 51: 2233–2241. https://doi.org/10.1007/s00125-008-1163-0

Communicating editor: M. Calus

Bayesian Sex-Specific Genetic Analysis