1 **Quantifying Heterogeneity in the Genetic Architecture of Complex Traits Between Ethni-**

2 **cally Diverse Groups using Random Effect Interaction Models**

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26   **ABSTRACT.** In humans, most genome-wide association studies have been conducted using data

27   from Caucasians and many of the reported findings have not replicated in other populations. This

28   lack of replication may be due to statistical issues (small sample size, confounding) or perhaps

29   more fundamentally to differences in the genetic architecture of traits between ethnically diverse

30   subpopulations. What aspects of the genetic architecture of traits vary between subpopulations

31   and how can this be quantified? We consider studying effect heterogeneity using random-effect

32   Bayesian interaction models. The proposed methodology can be applied using shrinkage and var-

33   iable selection methods and produces useful information about effect heterogeneity in the form

34   of whole-genome summaries (e.g., SNP-heritability and the average correlation of effects) as

35   well as SNP-specific attributes. Using simulations, we show that the proposed methodology

36   yields (nearly) unbiased estimates of genomic heritability and of the average correlation of ef-

37   fects between groups when the sample size is not too small relative to the number of SNPs used.

38   Subsequently, we used the proposed methodology for the analyses of four complex human traits

39   (standing height, high-density lipoprotein, low-density lipoprotein, and serum urate levels) in

40   European-Americans (EAs) and African-Americans (AAs). The estimated correlations of effects

41   between the two subpopulations was well below unity for all the traits, ranging from 0.73 to

42   0.50. The extent of effect heterogeneity varied between traits and SNP-sets. Height showed less

43 differences in SNP effects between AAs and EAs whereas HDL, a trait highly influenced by life-

44 style, exhibited greater extent of effect heterogeneity. For all the traits we observed substantial

45 variability in effect heterogeneity across SNPs, suggesting it varies between regions of the ge-

46 nome.

47

48 **P**opulation structure is a pervasive feature in plant, animal, and human populations (Gaggiotti *et*

49 *al.* 2009; Pfenninger *et al.* 2011; Puckett *et al.* 2014). In population genetics, differentiation be-

50 tween subpopulations is often measured by comparing allele frequencies, e.g., using the 'F-

51 statistic' (Malécot 1947; Wright 1949) and (Cockerham 1969). In genome-wide association stud-

52 ies (GWAS), population differentiation is predominantly viewed as a confounder (Astle and

53 Balding 2009) that can lead to spurious associations (Lander and Schork 1994; Deng 2001;

54 Marchini *et al.* 2004; Liu *et al.* 2011). To address this problem a variety of methods have been

55 proposed (Price *et al.* 2010). However, rather than a confounder, population stratification can act

56 as an effect-modifier, leading to heterogeneity in the genetic architecture of traits.

57 The evolutionary dynamics involved in the processes that lead to population structure can

58 result in subpopulations with heterogeneity in allele frequencies and linkage disequilibrium (LD)

59 patterns (Gabriel 2002). Moreover, in some instances, ethnic background correlates with envi-

60 ronmental exposures (e.g., diet, income, lifestyle) and this can lead to genetic-by-environment

61 interactions. All these differences between ethnic groups can induce heterogeneity in the genetic

62 architecture of traits (de los Campos and Sorensen 2014). Quantifying the extent of effect heter-

63 ogeneity between ethnically diverse groups is relevant across disciplines and can shed light on

64 whether results obtained in one group are expected to replicate in others. This is particularly im-

65 portant when we consider that the vast majority of GWAS have been conducted using data from

66   Caucasians and that results reported from these studies do not always replicate in other popula-

67   tions, which may indicate differences in genetic architectures between ethnic groups (Greene *et*

68   *al.* 2009a; Kraft *et al.* 2009; Ng *et al.* 2014).

69   Several studies have demonstrated (or alluded to) effect heterogeneity between ethnic groups

70   (Ntzani *et al.* 2012; de Candia *et al.* 2013; Li and Keating 2014; Brown *et al.* 2016). Most of the-

71   se studies measured effect heterogeneity by estimating the average correlation of marker effects

72   between two or more ethnically diverse groups.

73   One may attempt to estimate effect correlations by quantifying the average correlation of es-

74   timated effects from GWAS conducted in different ethnic groups. However, estimation errors

75   make the simple correlation of estimates of effects a seriously biased (towards zero) estimate of

76   the correlation of (true) effects (see Appendix C for a simple demonstration of this). To over-

77   come this problem, several studies have used multivariate Gaussian random regression models.

78   Such methods have been considered in both animal and plant breeding (Wei and Werf 1994;

79   García-Cortés and Toro 2006; Karoui *et al.* 2012; Olson *et al.* 2012; Christensen *et al.* 2014;

80   Lehermeier *et al.* 2015) as well as in human genetics (e.g. de Candia et al., 2013; Lee et al.,

81   2012). Another approach estimates the correlation of effects using an extension of the LD-score

82   regression (Brown *et al.* 2016).

83   The methods above described provide whole-genome summaries such as SNP-heritability

84   and average correlation of effects. However, they don't shed light on how effect heterogeneity

85   may vary across regions of the genome or between SNP sets. Moreover, the random regression

86   methods commonly used to estimate the average correlation of effects make the Gaussian as-

87   sumption; therefore, they cannot be used with priors that induce differential shrinkage of esti-

88   mates (e.g., double-exponential (Park and Casella 2008) or a combination of shrinkage and vari-

4

89 able selection (e.g. spike slab, Ishwaran and Rao 2005)) . To overcome this limitation, we con-

90 sider modeling effect heterogeneity using a Bayesian random-effect interaction model that de-

91 composes SNP effects into main and interaction components. Unlike previously used methods,

92 the proposed approach can be applied with both shrinkage and variable selection priors and of-

93 fers both whole-genome and SNP-specific measures of effect heterogeneity. In addition to esti-

94 mating average correlation of effects, the proposed method can also estimate the proportion of

95 non-zero effects in the considered SNP set; we will consider both measures when quantifying

96 effect heterogeneity.

97   Using simulations, we demonstrate that the proposed method yields nearly unbiased esti-

98 mates when sample size (n) is not too small relative to the number of markers (p) used. Subse-

99 quently, using data from the multi-ethnic Atherosclerosis Risk in Communities (ARIC) study, we

100 applied the proposed method to conduct joint analyses of individuals of European and African

101 ancestry [hereinafter referred to as European-Americans (EAs) and African-Americans (AAs),

102 respectively] for traits with varying genetic architectures. These subpopulations have important

103 differences in allele frequencies, LD decay (Shifman 2003) and cultural and socio-economic fac-

104 tors that are linked to environmental exposures.

105   Our results show that for the four traits there is a large extent of effect heterogeneity with av-

106 erage correlations of effects well below one. However, the extent of effect heterogeneity between

107 EAs and AAs also varies between traits (the correlation of effects was highest for height and

108 lower for lipid traits). Moreover, we show that for HDL, LDL and serum urate there is great deal

109 of variability in effect heterogeneity between SNPs with many SNPs showing almost no effect

110 heterogeneity and others exhibiting substantial effect differences between AAs and EAs.

111

112   **Materials and Methods**

113   Meuwissen et al. (2001) proposed to analyze and predict complex traits by regressing phenotypes

114   on whole-genome panels of SNPs. Their model was developed with reference to a homogeneous

115   population. Here, following (de los Campos *et al.* 2015), we consider extending the whole ge-

116   nome regression model by including random-effect interactions between markers and groups.

117   Considering two groups, the regression of phenotypes ($\boldsymbol{y}_k = \{y_{k1}, \dots, y_{kn_k}\}$, where $k = 1,2$ in-

118   dexes groups and n_k denotes the number of individuals in the kth group) on p markers (e.g.,

119   SNPs) can be represented as follows:

120    $$\begin{bmatrix} \boldsymbol{y}_1 \\ \boldsymbol{y}_2 \end{bmatrix} = \begin{bmatrix} 1\mu_1 \\ 1\mu_2 \end{bmatrix} + \begin{bmatrix} \boldsymbol{X}_1 \\ \boldsymbol{X}_2 \end{bmatrix} \boldsymbol{b}_0 + \begin{bmatrix} \boldsymbol{X}_1 \\ 0 \end{bmatrix} \boldsymbol{b}_1 + \begin{bmatrix} 0 \\ \boldsymbol{X}_2 \end{bmatrix} \boldsymbol{b}_2 + \begin{bmatrix} \boldsymbol{\varepsilon}_1 \\ \boldsymbol{\varepsilon}_2 \end{bmatrix} \qquad (1)$$

121   where μ_1 and μ_2 are group-specific intercepts, $\boldsymbol{b}_0 = \{b_{0j}\}_{j=1}^{p}$ is a vector of 'main effects',

122    $\boldsymbol{b}_1 = \{b_{1j}\}_{j=1}^{p}$ and $\boldsymbol{b}_2 = \{b_{2j}\}_{j=1}^{p}$ are group-specific interactions and $\boldsymbol{\varepsilon}_1 = \{\varepsilon_{1i}\}_{i=1}^{n_1}$ and $\boldsymbol{\varepsilon}_2 =$

123    $\{\varepsilon_{2i}\}_{i=1}^{n_2}$ are error terms. In our models, we assume IID Gaussian errors with group-specific vari-

124   ances that is $\varepsilon_{1i} \overset{iid}{\sim} N(0, \sigma_1^2)$ and $\varepsilon_{2i} \overset{iid}{\sim} N(0, \sigma_2^2)$.

125   **Marker effects** in groups 1 and 2 are defined by the sum of the main and group-specific

126   terms, that is, $\beta_{1j} = b_{0j} + b_{1j}$ and $\beta_{2j} = b_{0j} + b_{2j}$, respectively. Since the number of markers is

127   usually large relative to sample size we treat both main and interaction effects as random. De-

128   pending on the distribution assigned to SNP effects the model can induce variable selection,

129   shrinkage, or a combination of both (Ishwaran and Rao 2005; Gianola *et al.* 2009; de los Campos

130   *et al.* 2013). To illustrate, we considered two priors for main and interaction effects: a Gaussian

131   distribution and a prior with a point of mass at zero and a Gaussian slab, also known as BayesC

132   (Habier *et al.* 2011).

6

133   In the **Gaussian setting** we assign independent Normal priors with null mean and with dif-

134   ferent variances for the main and interaction effects, that is

135    $$b_{0j} \overset{iid}{\sim} N\left(0, \sigma_{b_0}^2\right), \ b_{1j} \overset{iid}{\sim} N\left(0, \sigma_{b_1}^2\right) \text{ and } b_{2j} \overset{iid}{\sim} N\left(0, \sigma_{b_2}^2\right).$$

136   Above, $\sigma_{b_0}^2$, $\sigma_{b_1}^2$ and $\sigma_{b_2}^2$ represent the prior variances of the main and interaction effects, respec-

137   tively.

138   For the **Spike-Slab prior** we adopt the assumptions of model BayesC (Habier *et al.* 2011),

139   with set-specific variances and proportions of non-zero effects, that is

140    $$b_{0j} \overset{iid}{\sim} p\left(\pi_0, \tilde{\sigma}_{b_0}^2\right), \ b_{1j} \overset{iid}{\sim} p\left(\pi_1, \tilde{\sigma}_{b_1}^2\right) \text{ and } b_{2j} \overset{iid}{\sim} p\left(\pi_2, \tilde{\sigma}_{b_2}^2\right),$$

141   where $p\left(b_{.j} | \pi_., \tilde{\sigma}_b^2\right)$ is a mixture distribution of the form $p\left(b_{.j} | \pi_., \tilde{\sigma}_b^2\right) = (1 - \pi_.)1\left(b_{.j} = 0\right) +$

142    $\pi_. N\left(0, \tilde{\sigma}_b^2\right)$, for "."=0,1,2. Here, $\pi_.$ represents the proportion of non-null effects.

143   **Hyper-parameters**. In the Gaussian model the hyper-parameters are the error variance and

144   the three variances of effects, that is $\Omega = \left\{\sigma_1^2, \sigma_2^2, \sigma_{b_0}^2, \sigma_{b_1}^2, \sigma_{b_2}^2\right\}$. In BayesC the hyper-parameters

145   also include the proportion of non-null effects; therefore: $\Omega = \left\{\sigma_1^2, \sigma_2^2, \tilde{\sigma}_{b_0}^2, \tilde{\sigma}_{b_1}^2, \tilde{\sigma}_{b_2}^2, \pi_0, \pi_1, \pi_2\right\}$.

146   These parameters control the extent of shrinkage and variable selection and how the architecture

147   of effects may vary between groups. In our implementation, we treat them as unknown and

148   therefore assign prior distributions to them. For variance parameters, the conjugate prior is the

149   scaled-inverse chi-squared. However, this prior can have some influence on inference. Therefore,

150   instead we use a prior for variance parameters that is a transformation of the beta distribution

151   (Appendix A). For the proportion of non-zero effects $\{\pi_0, \pi_1, \pi_2\}$ we use independent identical

152   beta priors. This allows us to accommodate different effect distributions for different traits and

153   sets of SNPs. Further details about this are provided in the Data Analysis section below.

154   The models described above can be used to estimate several parameters that are descriptive

155   of the trait architecture. Whole-genome summaries of the trait architecture and of effect hetero-

156   geneity include *the proportion of variance explained by SNPs* (or genomic heritability, e.g., de

157   los Campos et al., 2014) in each of the ethnic groups, the *average correlation of effects* and the

158   *average proportions of non-zero effects* (either main effects, interaction terms or total effects).

159   Samples from the posterior distribution can also be used to estimate SNP-specific parameters

160   such as the posterior correlation of a SNP effect, $\rho_j = Cor(\beta_{1j}, \beta_{2j})$.

161   Genomic variance, genomic heritability and the average correlation of effects were estimated

162   using the methods described by Lehermeier et al. (2017). Briefly, at each iteration of an MCMC

163   algorithm, we used the samples of the main and interaction effects to form marker effects,

164    $\beta_{1j(s)} = b_{0j(s)} + b_{1j(s)}$ and $\beta_{2j(s)} = b_{0j(s)} + b_{2j(s)}$ (here, $s=1,...,N$ is an index for the N samples

165   collected). A sample from the posterior distribution of the correlation of effects was obtained

166   from $\rho_s = Cor(\beta_{1j(s)}, \beta_{2j(s)})$ where $Cor(\ )$ represents Pearson's product moment correlation.

167   Likewise, at each iteration genomic values can be obtained from $\boldsymbol{u}_{1(s)} = \boldsymbol{X}_1\boldsymbol{\beta}_{1(s)}$ and $\boldsymbol{u}_{2(s)} = $

168    $\boldsymbol{X}_2\boldsymbol{\beta}_{2(s)}$. Therefore, a sample for the posterior distribution of the genomic variances for each

169   group was computed as $\sigma^2_{g1(s)} = (n_1 - 1)^{-1}\sum_i (u_{1i(s)} - \bar{u}_{1(s)})^2$ and $\sigma^2_{g2(s)} = (n_2 -$

170    $1)^{-1}\sum_i (u_{2i(s)} - \bar{u}_{2(s)})^2$, where $\bar{u}_{.(s)} = n_.\sum_i u_{.i(s)}$. Finally, samples from the posterior distri-

171   bution of genomic heritability were obtained using the following: $h^2_{g1(s)} = \frac{\sigma^2_{g1(s)}}{\sigma^2_{g1(s)}+\sigma^2_{1(s)}}$ and

172    $h^2_{g2(s)} = \frac{\sigma^2_{g2(s)}}{\sigma^2_{g2(s)}+\sigma^2_{2(s)}}$.

173

174 ***Data***

175 Our simulation and real data analyses were based on data from the Atherosclerosis Risk in

176 Communities (ARIC) study. ARIC is a prospective epidemiologic study sponsored by the Na-

177 tional Heart, Lung, and Blood Institute (NHLBI) conducted in four U.S. communities to study

178 the causes of atherosclerosis and other cardiovascular risk factors such as blood lipids, lipopro-

179 tein cholesterols, and apolipoproteins. It has a total sample size of 15,792 AA and EA men and

180 women aged 45-64. A total of 13,113 individuals were genotyped using the Affymetrix array

181 with a total of 934,940 SNPs. Genotype and phenotype data from the ARIC study was acquired

182 through the dbGaP (IRB number 15-745; r050661 and study accession number

183 phs000280.v1.p1).

184

185 ***Genotypes***

186 We retained SNPs that had minor allele frequency higher than 1% in at least one of the two eth-

187 nic groups (SNPs that are monomorphic in only one of the two groups are clearly heterogene-

188 ous), had higher than 95% calling rate, and were mapped to one of the 23 human chromosomes.

189 After QC, we retained 828,822 SNPs. Individuals with a 5% missing rate in their genotypes were

190 removed. Individuals were classified as EA or AA based on self-reported ethnicity. We con-

191 firmed this assignment by deriving principal components from the genomic relationship matrix

192 (Figure S1). Subsequently we computed genomic relationships within each ethnic group and re-

193 moved those that had within-group genomic relationships higher than 0.075; this ensured that we

194 only retained distantly related individuals. After standardization to an average diagonal value of

195 1, the diagonal elements of the marker-derived genomic relationship matrix ranged between 0.85

196   and 1.15. Thus, the final data sets comprised only distantly related individuals including 6,627

197   EAs and 1,601 AAs.

198

199   ***Simulations***

200   We simulated phenotypes using genotype data from the ARIC study from 6,627 EAs and 1,601

201   AAs. Phenotypes were simulated under an additive genetic model with a heritability of 0.5 for

202   both groups. We considered scenarios with the number of markers (n) varying from 100 to

203   10,000 and the true correlations of effects between groups varying from 0.2 to 0.8. In a first sim-

204   ulation setting we assumed that all the markers had effects on both groups. In a second setting,

205   we assumed that 50% of the loci had effects on both groups, 20% had effects on EAs but not on

206   AAs, 20% had effects on AAs but not on EAs and 10% had no effects on either group (non-

207   causal variants). Further details of the simulation are given in Appendix B.

208

209   ***Analyses of Four Complex Human Traits***

210   For our real-data analyses we considered four complex phenotypes: human height (cm), HDL

211   (mmol/L) and LDL (mmol/L) cholesterol and serum urate (mg/dL). Individuals with height <

212   147 cm, LDL > 10 mmol/L and serum urate > 15 mg/dL were removed. We did not identify

213   clear outliers for HDL. Transformation of the traits was not considered necessary (Figure S2).

214   Phenotypes were pre-corrected for ethnicity, age and sex.

215   Models were fitted to subsets of SNPs selected based on single-marker regression (GWAS)

216   p-values derived from data that did not include ARIC. For height, GWAS p-values were derived

217   from the full release of the UK Biobank. For HDL and LDL p-values were from the Global Li-

218   pids Genetics Consortium (GLGC) computed after excluding data from ARIC. Finally, for serum

219   urate, p-values were from the Global Urate Genetics Consortium (GUGC), also derived without

220   using data from ARIC. The simple ranking of markers based on association *p*-values would lead

221   to sets of highly redundant markers, i.e., markers in high LD (see Figure S3). To avoid this, we

222   designed a windows-based selection algorithm where a window was defined as a set of consecu-

223   tive SNPs that exceeded a given $-\log_{10}(p$-value) cutoff (this was done on a per-trait basis). The

224   goal of this method was to avoid oversampling SNPs from genomic regions of high LD. Win-

225   dows were made on a per-trait basis at $-\log_{10}(p$-value) cutoffs of 2, 2.3, 2.6, 3, 5, and 8 (Table

226   S1). SNPs that cleared a given $-\log_{10}(p$-value) cutoff were termed "significant" at that cutoff

227   (See Figure S4).

228   We fitted the interaction model to each of the four traits and each of the SNP-sets above de-

229   scribed. As part of sensitivity analyses, we also fitted the same models to randomly chosen sets

230   of SNPs (of sizes 500, 1,000, 2,500, 5,000, and 10,000 SNPs, respectively). Finally, we also

231   evaluated the estimates obtained within the EA ethnic group label randomly permuted.

232

233   ***Software***

234   Models were fitted using a modified version of the BGLR (Pérez and de los Campos 2014) R

235   package   (available   at: https://github.com/gdlc/BGLR-R   and   at   https://cran.r-

236   project.org/web/packages/BGLR/index.html) that implements a weakly informative prior for var-

237   iance parameters based on a transformation of the beta distribution (de los Campos *et al.* 2009)

238   described above. We ran the Monte Carlo Markov Chain algorithm for 45,000 iterations; the first

239   15,000 iterations were discarded as burn-in and the remaining samples were thinned at a thinning

240   interval of 5.

241   **Hyper-parameters**. BGLR assigns a beta prior to the proportion of non-zero effects, we

242   choose the shape parameters of the beta prior to be equal to 1, which gives a uniform prior in the

243   0-1 interval. For variance parameters we devised a prior which is a modified version of the Beta

244   prior (see Appendix A) and used shape parameters equal to 1.01 to obtain an almost uniform pri-

245   or for variance parameters within the interval [0,K] where K was twice the variance of the phe-

246   notype.

247

248   *Data availability*

249   Supplemental files are available as a zipped folder (not on FigShare). File S1 contains supple-

250   mentary figures, tables and Appendices. The IRB number for ARIC dataset is 15-745; r050661

251   and the study accession number for ARIC dataset: phs000280.v1.p1.

252

253   **Results**

254   *Simulations*

255   In both simulation settings, the *genomic heritability* was estimated with almost no bias using

256   both Gaussian and BayesC priors (see Figures 1 and S5 for the first and second simulation sce-

257   narios, respectively). The standard errors were higher for AAs as compared to EAs, which was

258   expected given that the sample size was smaller for AAs. As one would expect, the standard er-

259   rors also increased with the number-of-loci/sample-size ratio. Using the BayesC prior, the esti-

260   mates of genomic heritability were mildly biased across all values of true effect correlation when

261   the number of QTL was greater than 10,000. There was a mild downward bias when the true cor-

262   relation was very low (0.2 or 0.4) and there was a mild upward bias when the true correlation

263   was high (0.8).

264 **FIGURE 1**

265 Estimates of *effect correlations* were also nearly unbiased (see Figures 2 and S6). However, the

266 standard errors were very large, particularly when the correlations were low. In scenarios involv-

267 ing more than 5,000 QTL we observed a small downward-bias. Likewise, we observed a small

268 upward bias for the Gaussian prior when the number of QTL was 100 (Figure 2 and Figure S6).

269 The average standard error of the estimated correlation was high with the smallest (100) and the

270 largest (10,000) numbers of QTL and lower for scenarios in between.

271 **FIGURE 2**

272 ***Analyses of Four Complex Human Traits***

273 Since our simulations revealed that n/p ratio of at least 1/3 results in nearly unbiased estimates

274 of genomic heritability, we fit our model to subsets of markers instead of using whole-genome

275 data (see methods for a description of how these subsets were obtained). Figure 3 shows the es-

276 timated *genomic heritability* obtained using the BayesC prior, by trait, ethnicity and the set of

277 SNPs used. (The results obtained with the Gaussian prior are displayed in Figure S7). As ex-

278 pected, the estimated genomic heritability increased with the number of SNPs used. Interesting-

279 ly, this parameter was systematically higher in EAs than in AAs for height and HDL, and the or-

280 der was reversed in other traits (LDL and serum urate). However, the credibility intervals be-

281 tween both ethnic groups overlapped for all traits except height. The genomic heritability esti-

282 mates obtained with the Gaussian prior were similar to the ones found with the BayesC prior (see

283 Figure S7) for all traits except serum urate, which yielded larger estimates for AAs than those

284 obtained using the BayesC prior.

285 **FIGURE 3**

286 Figure 4 shows the estimated *correlation of effects* between AAs and EAs obtained with the

13

287   BayesC prior, by the set of SNPs used in the analysis. The estimated average correlation of ef-

288   fects ranged from 0.711 (for height with the SNP-set obtained with $-\log_{10}(p\text{-value})$ cutoff of 8) to

289   0.500 (for HDL with the SNP-set obtained with a $-\log_{10}(p\text{-value})$ cutoff of 2.3). Overall the cor-

290   relation of effects was highest for height and serum urate and lowest for LDL and HDL. In all

291   traits except HDL the correlation of effects tended to decrease as more SNPs were added in the

292   model; however, the confidence regions for the different SNP sets overlapped. The estimated

293   correlation of effects with the Gaussian prior for marker effects was similar to those obtained

294   using the BayesC prior, with subtle differences between the two priors for height, HDL and LDL

295   (Figure S8).

296   **FIGURE 4**

297   Figure 5 shows the estimated proportion of non-zero SNP effects obtained with the BayesC pri-

298   or, by trait, ethnic group and SNP-set. For both groups, the proportions of non-zero effects were

299   high at large $-\log_{10}(p\text{-value})$ cutoffs and decreased as the number of markers included in the

300   model increased. For height, the proportions of non-zero effects were similar between EAs and

301   AAs. However, for LDL (and serum urate to a lesser extent) the decrease in the proportion of

302   non-zero effects was stronger in EAs. Figure S9 displays the proportion of non-zero main and

303   interaction effects. The proportion of non-zero main effects decreased as the number of SNPs

304   increased and the proportion of non-zero interaction terms tended to remain constant (except for

305   the LDL-interactions for EAs). Interestingly, the proportion of non-zero effects dropped very fast

306   with the number of SNPs for HDL, LDL and serum urate, suggesting for these traits that the ef-

307   fect architecture may be highly heterogeneous between AAs and EAs.

308   **FIGURE 5**

14

309   Figures 3-5 (and the corresponding supplementary figure S9), correspond to whole-genome

310   summaries (SNP-heritability, average correlation of effects, proportion of non-zero effects).

311   However, the models also render SNP-specific summaries. Figure 6 shows the posterior mean of

312   the correlation of effects between ethnic groups for individual SNPs by trait for the SNP set ob-

313   tained using a $-\log_{10}(p\text{-value})$ cutoff of 2. We had no SNP with negative posterior correlation of

314   effect. For height, the posterior correlation of individual-SNP effects ranged from 0.4-0.8. How-

315   ever, for HDL, LDL and serum urate, there was more variability among SNPs, with several

316   SNPs having posterior correlation of effects greater than 0.8 and many with posterior correlation

317   of effects smaller than 0.4.

318   **FIGURE 6**

319   **Discussion**

320   Genome-Wide Association (GWA) studies have discovered large numbers of variants associated

321   with important traits and diseases in humans (Welter *et al.* 2014) but have been conducted pre-

322   dominantly in Caucasian populations (Haga 2010; Rosenberg *et al.* 2010). Although more recent

323   works have recognized inclusion of diverse ethnic groups, especially African Americans (e.g.

324   Brant et al., 2017; Park et al., 2017; Taylor et al., 2016) the total number of GWAS studies for

325   African Americans is still fairly low compared to populations of European ancestry (Peprah *et al.*

326   2015) and replication of signals in African American populations is much less common

327   (Marigorta and Navarro 2013). Moreover, the associations reported to be strong in Caucasians

328   have been weaker (or even non-significant) in other ethnic groups (Gudbjartsson *et al.* 2007;

329   Omori *et al.* 2008; Yamada *et al.* 2009; Barnholtz-Sloan *et al.* 2011; Tsai *et al.* 2014; Prasad *et*

330   *al.* 2017) and some studies have reported effects with opposite sign in different populations

331   (Lewis *et al.* 2008; Yamada *et al.* 2009). Other recent studies have also indicated presence of ge-

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332   netic heterogeneity between ethnic groups for different quantitative/binary traits (Brown *et al.*

333   2016; de Vlaming *et al.* 2017; Zhou *et al.* 2018). While some of these differences could be at-

334   tributed to dissimilarities in LD and sample sizes (e.g. some well-powered studies have shown

335   strong overlaps in GWAS-significant variants between Europeans and other ethnic groups

336   (Franceschini *et al.* 2013; Okada *et al.* 2014)), there could also be novel variants specific to the

337   ethnic group (Chen *et al.* 2017), indicating that genetic heterogeneity could depend on other ge-

338   netic factors and be trait-specific. Understanding the reasons that underlie these differences and

339   quantifying the degree of similarity in the architecture of a trait across populations represents an

340   important research goal.

341   A naïve approach for assessing the degree of similarity in the genetic architecture of a trait

342   between two groups would be to simply correlate estimated effects obtained from stratified anal-

343   yses (e.g., GWAS conducted within each group). However, errors in estimates of effects make

344   this estimator highly biased towards zero (see Appendix C). Our empirical results verified this

345   (Table S2): the sample correlation of estimated effects was consistently lower than the one esti-

346   mated using variance components (a nearly unbiased estimator from our simulations). Our re-

347   sults also showed that the difference between the naïve estimator of the correlation and the one

348   based on variance components increases as more small-variance markers are used in the model.

349   In humans, Brown et al. 2016 considered quantifying the average correlation of effects using

350   summary-based association statistics. Their approach extended LD score regression (Bulik-

351   Sullivan *et al.* 2015) to multiple ethnic groups and has the advantage, relative to the method dis-

352   cussed here, that it can be used with summary statistics. However, some authors have questioned

353   the assumptions of the LD score regression method (Speed *et al.* 2018) and accurate estimation

354   requires using several thousands of SNPs. Thus, the method is not well-suited for studying effect

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355   similarity within genomic regions, something that the proposed method can achieve. Also, the

356   LD-score method requires access to good quality external reference panels (especially for non-

357   European populations) to construct population LD matrices, assumes normal distribution of

358   marker effects (infinitesimal model) and is not directly applicable to admixed populations (or

359   populations that have long range LD).

360   In this study, we propose to study ethnic differences in the architecture of traits using a ran-

361   dom effect Bayesian interaction model. The proposed approach can be used to estimate whole-

362   genome summaries such as (a) the proportion of variance explained by SNPs, (b) the average

363   effect correlation, (c) proportion of non-zero effects, as well as finer features of the trait architec-

364   ture (e.g. SNP-specific correlation of effects). Similar approaches have been considered in ani-

365   mal and plant breeding (e.g., Christensen et al., 2014; García-Cortés and Toro, 2006; Lehermeier

366   et al., 2015; Wei and Werf, 1994) and in human genetics (e.g., de Candia et al., 2013; Lee et al.,

367   2012) for the analysis of data from heterogeneous populations. However, previous studies were

368   based on Gaussian assumptions and only offered whole-genome summaries of the trait architec-

369   ture. The approach presented in this study is more flexible in that it can be used with both

370   shrinkage and variable selection priors (Ishwaran and Rao 2005; Park and Casella 2008) and can

371   be used to infer not only whole-genome features but also regional and SNP-specific features of

372   the trait architecture.

373   Among many parameters, the proposed method yields an estimate of effect correlation. This

374   parameter, should not be confounded with the classical concept of genetic correlation (Reeve

375   1953). While the former provides a measure of the extent of effect similarity/heterogeneity be-

376   tween two groups for the same trait, the latter is defined between two traits for the same individ-

377   ual. Moreover, the forces that contribute to the genetic correlation between traits (pleiotropy and

17

378   LD between alleles at causal loci affecting different traits) are different from the forces that may

379   contribute to effect heterogeneity between ethnic groups (e.g., differences in allele frequency and

380   genetic by-environmental interactions). Thus, genetic correlation and correlation of effects be-

381   tween ethnically diverse groups should be treated as conceptually different.

382   We evaluated the proposed methodology under two different priors (Gaussian and BayesC)

383   using simulations and applied it to real human data to study the genetic architecture of four traits

384   (Height, HDL, LDL, Serum urate) in EAs and AAs. Our simulation study revealed that both

385   Gaussian and BayesC priors yield nearly unbiased estimates of genomic heritability and effect

386   correlations. From our real data analyses, we observed similar proportions of variance explained

387   with both BayesC and Gaussian priors for marker effects (Figure 3 and S7). Except height, the

388   average proportions of variance explained across all marker sets were similar between EAs and

389   AAs. For height, the average proportion of variance explained was greater among EAs than

390   among AAs. This is likely due to the fact that the SNPs used for the analysis of height were se-

391   lected using GWAS results entirely based on data from Caucasians (UK Biobank); the same

392   trend was not observed for other traits perhaps because there was some mixture in ethnicity in

393   the other GWAS consortia from which markers were chosen (GLGC, GUGC). When we fit simi-

394   lar models using randomly chosen markers (Figure S10), we observed that the proportion of var-

395   iance explained by randomly selected markers was smaller than that explained by regression on

396   markers selected from GWAS results for both EAs and AAs. This showed that indeed, selection

397   based on GWAS results leads to more informative markers in both populations.

398   Our analyses also revealed important differences in correlation of effects between traits. The

399   **estimated correlation of effects** ranged from 0.482-0.728, indicating the presence of genetic

400   heterogeneity across all four traits, even for strongly associated markers (Figure 4). For height

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401   the correlation of effects was highest when using SNPs that had the smallest GWAS p-value

402   (likely SNPs with relatively large effect and not very extreme allele frequency), suggesting that

403   the correlation of effects may be lower for SNPs with small effects and those with extreme allele

404   frequencies.

405   Height had higher correlation of effects than serum urate and lipid traits, suggesting that

406   height may have a more similar genetic architecture between EAs and AAs than the other traits

407   (especially than the lipid traits). We also obtained far smaller values of effect correlation with

408   randomly chosen markers than with previously published GWAS. (Figure S11). These results

409   reinforce the idea that QTL have greater similarity of effects between EAs and AAs (lower ge-

410   netic heterogeneity), whereas random markers seem to have different effects in different popula-

411   tions (greater genetic heterogeneity).

412   Finally, we found differences in the estimated proportion of non-zero effects between EAs

413   and AAs for HDL, LDL, and serum urate but not for height, reinforcing that the genetic architec-

414   ture of height may be more similar between EAs and AAs in comparison to the other three traits

415   (Figure 5 and S9). The proportion of non-zero effects markedly decreased with the -logP value

416   threshold implying that large-effect QTL have a greater proportion of non-zero effects than

417   small-effect QTL, especially for lipid traits. This trend is largely driven by the proportion of non-

418   zero *main* effects for both ethnic groups (i.e. effects common to both ethnic groups – Figure S9).

419   Finally, we also observed greater variability in posterior correlation of effects among lipid traits

420   and serum urate in comparison to height (Figure 6).

421   Since we "pruned" our SNP subsets to minimize the influence of LD (see methods), other

422   factors such as epistasis and genetic-by-environmental interaction (G×E) could explain the pres-

423   ence of effect heterogeneity for the traits considered in this study. Indeed, if ethnicity correlates

424   with lifestyle, diet, income and other factors that may induce (G×E), then SNP effects can be-

425   come population-specific. The estimated proportion of non-zero effects for height was in general

426   higher than that of LDL, HDL and serum urate: three traits that are more affected by diet and

427   lifestyle. Likewise, epistasis may be responsible for the vast majority of small additive effects

428   (Mackay and Moore 2014) and previous studies have attributed the non-replication of genetic

429   associations in different populations to epistasis (Greene *et al.* 2009b). Thus, epistatic gene ac-

430   tion can also have a role in explaining differences in the allelic substitution effects of SNPs and

431   can consequently induce effect heterogeneity (observed in our study as lower proportion of non-

432   zero effects for small-effect QTL), especially if allele frequencies vary between the two popula-

433   tions (Mackay and Moore 2014; Wei *et al.* 2014) (Figure S12).

434   In **conclusion**, we have proposed a versatile methodology based on random-effects interac-

435   tions that can apply non-Gaussian priors to marker effects for quantifying the extent of effect

436   heterogeneity between ethnically diverse groups using a combination of variable selection and

437   shrinkage. This proposed approach can yield estimates of SNP-heritability, average correlation

438   of effects, proportion of non-zero effects as well as SNP-specific attributes in genomic regions of

439   interest. Of the traits considered in our study, effect heterogeneity was lower for height than for

440   traits influenced by lifestyle. We postulate that differences in allele frequency and in LD pat-

441   terns, together with epistasis and G×E can contribute to effect heterogeneity between AAs and

442   EAs. Further research on interactions between genes and proteins as well as signaling pathways

443   is needed to understand the functional mechanisms underlying effect heterogeneity between eth-

444   nic groups for complex human traits and diseases.

445

446 **Acknowledgments**

454

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606

607   **Figures**

608   **Figure 1**. **Average estimates of genomic heritability obtained in the <u>first simulation scenar-</u>**

609   **<u>io,</u> by prior and number of SNPs used.** The simulated heritability was 0.5, bars represent the

610   average estimates over 200 Monte Carlo replicates and the vertical lines gives +/- standard er-

611   rors. Results for the 2nd simulation scenario are presented in Figure S5.

612

613   **Figure 2**. **Average estimates of the correlation of effects in the first simulation scenario by**

614   **prior and number of SNPs used.** The simulated heritability was 0.5; bars represent the average

615   estimates over 200 Monte Carlo replicates and the vertical lines gives +/- standard errors. Results

616   for the 2nd simulation scenario are presented in Figure S6.

617

618   **Figure 3. Proportion of variance explained by subsets of SNPs obtained with the BayesC-**

619   **interaction model, by trait, ethnicity and SNP set.** Estimated (median) genomic heritability (y-

620   axis) is plotted by trait, ethnicity and $\log_{10}(p\text{-value})$ cutoff used to choose markers from GWAS

621   consortia (excluding ARIC). Numerals above the bars indicate the proportion of variance ex-

622   plained by either ethnic group and the corresponding number of SNPs used for model fitting (in

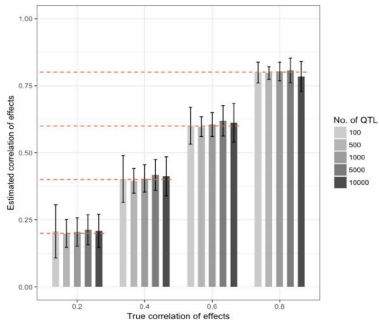623   parentheses at the bottom). Vertical lines give estimates of +/- posterior standard deviation.

624

625   **Figure 4. Estimated correlation of effects between African Americans (AAs) and European**

626   **Americans (EAs) obtained with the BayesC-interaction model, by trait and SNP set.** Esti-

627   mated correlation of effects between AAs and EAs (y-axis) is plotted by trait using markers se-

628   lected from GWAS consortia (excluding ARIC). In each plot, the numerals above the bars indi-

629   cate the median correlation of effects and the number of SNPs used for model fitting (in paren-

630   theses at the bottom). Vertical lines give estimates of +/- posterior standard deviation.

631

632   **Figure 5. Estimated proportion of non-zero effects between African Americans (AAs) and**

633   **European Americans (EAs) obtained with the BayesC-interaction model, by trait and SNP**

634   **set.** Estimated proportion of non-zero effects between AAs and EAs (y-axis) is plotted by trait

635   using markers selected from GWAS consortia (excluding ARIC) at 6 different $-\log_{10}(p\text{-value})$

636   cutoffs. In each plot, the numerals above the bars indicate the proportion of non-zero effects ob-

637   tained using either ethnic group and the corresponding number of SNPs used for model fitting (in

638   parentheses at the bottom). Vertical lines give estimates of +/- posterior standard deviation.

639

640   **Figure 6. Posterior correlation of individual SNP effect between African Americans (AAs)**

641   **and European Americans (EAs), by trait for SNPs that clear a $-\log_{10}(p\text{-value})$ of** 2. Plots are

642   categorized by trait and in each plot, the estimated effect correlation of individual SNP effects

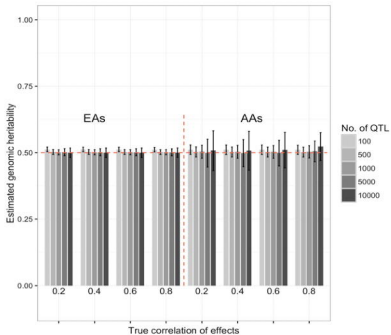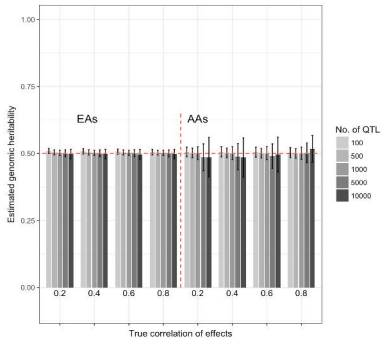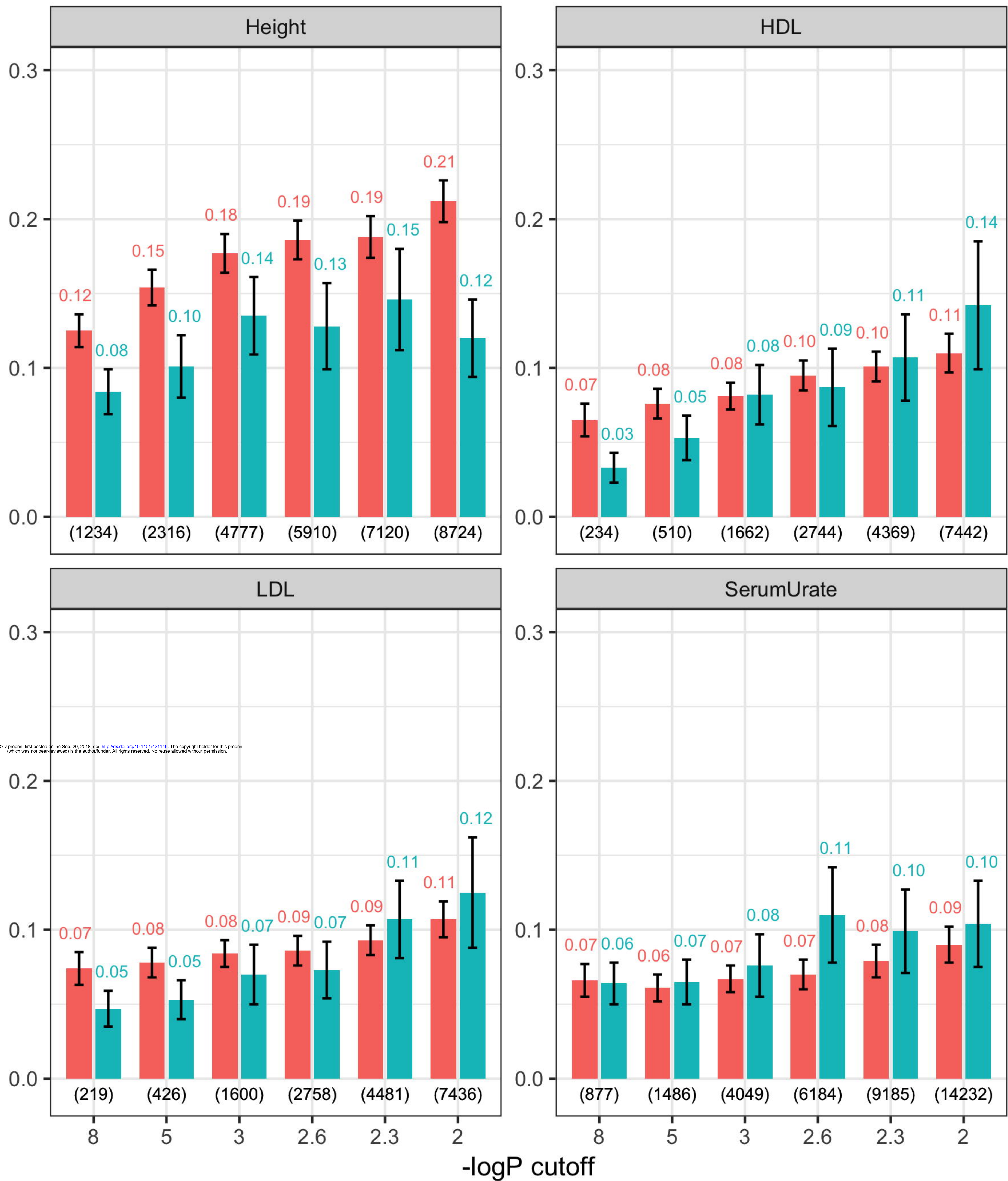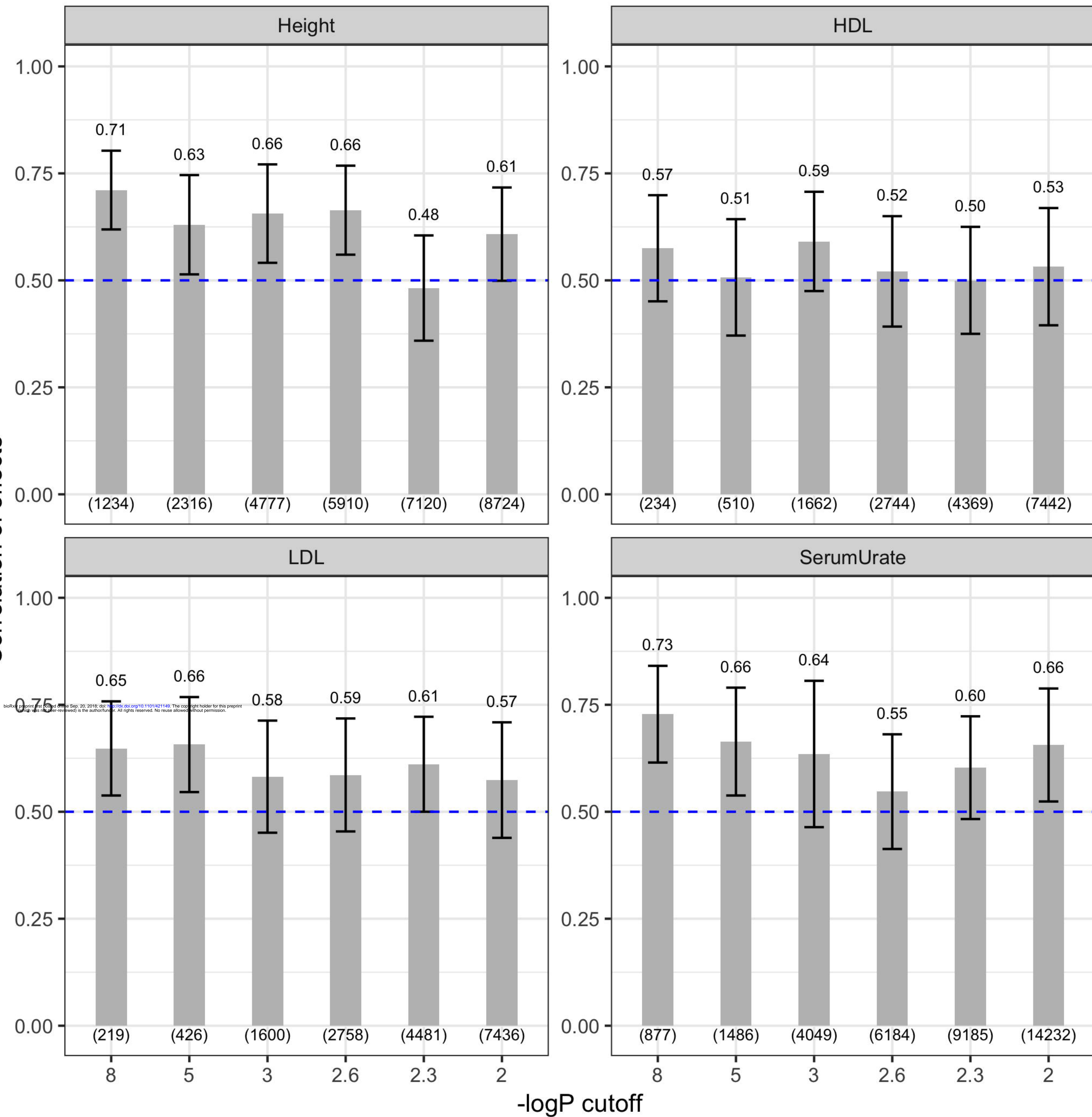643   (y-axis) is plotted against chromosome number (x-axis).

Gaussian prior
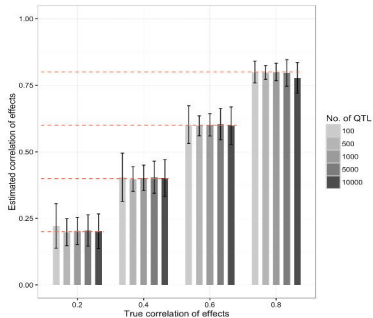
BayesC prior

Gaussian prior

BayesC prior