

1 **Title**

2 On the cross-population generalizability of gene expression prediction models

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## 27 **Abstract**

28 The genetic control of gene expression is a core component of human physiology. For the past  
29 several years, transcriptome-wide association studies have leveraged large datasets of linked  
30 genotype and RNA sequencing information to create a powerful gene-based test of association  
31 that has been used in dozens of studies. While numerous discoveries have been made, the  
32 populations in the training data are overwhelmingly of European descent, and little is known  
33 about the generalizability of these models to other populations. Here, we test for cross-  
34 population generalizability of gene expression prediction models using a dataset of African  
35 American individuals with RNA-Seq data in whole blood. We find that the default models trained  
36 in large datasets such as GTEx and DGN fare poorly in African Americans, with a notable reduction  
37 in prediction accuracy when compared to European Americans. We replicate these limitations in  
38 cross-population generalizability using the five populations in the GEUVADIS dataset. Via realistic  
39 simulations of both populations and gene expression, we show that accurate cross-population  
40 generalizability of transcriptome prediction only arises when eQTL architecture is substantially  
41 shared across populations. In contrast, models with non-identical eQTLs showed patterns similar  
42 to real-world data. Therefore, generating RNA-Seq data in diverse populations is a critical step  
43 towards multi-ethnic utility of gene expression prediction.

44

45 **Keywords**

46 TWAS, gene expression, admixed populations, GTEx, PrediXcan

47 **Author summary**

48 Advances in RNA sequencing technology have reduced the cost of measuring gene expression at  
49 a genome-wide level. However, sequencing enough human RNA samples for adequately-  
50 powered disease association studies remains prohibitively costly. To this end, modern  
51 transcriptome-wide association analysis tools leverage existing paired genotype-expression  
52 datasets by creating models to predict gene expression using genotypes. These predictive models  
53 enable researchers to perform cost-effective association tests with gene expression in  
54 independently genotyped samples. However, most of these models use European reference  
55 data, and the extent to which gene expression prediction models work across populations is not  
56 fully resolved. We observe that these models predict gene expression worse than expected in a  
57 dataset of African-Americans when derived from European-descent individuals. Using  
58 simulations, we show that gene expression predictive model performance depends on both the  
59 amount of shared genotype predictors as well as the genetic relatedness between populations.  
60 Our findings suggest a need to carefully select reference populations for prediction and point to  
61 a pressing need for more genetically diverse genotype-expression datasets.

## 62 **Introduction**

63 In the last decade, large-scale genome-wide genotyping projects have enabled a revolution in our  
64 understanding of complex traits.[1–4] This explosion of genome sequencing data has spurred the  
65 development of new methods that integrate large genotype sets with additional molecular  
66 measurements such as gene expression. A recently popular integrative approach to genetic  
67 association analyses, known as a transcriptome-wide association study (TWAS)[5,6], leverages  
68 reference datasets such as the Genotype-Tissue Expression (GTEx) repository[7] or the  
69 Depression and Genes Network (DGN)[8] to link associated genetic variants with a molecular trait  
70 like gene expression. The general TWAS framework requires previously estimated *cis*-eQTLs for  
71 all genes in a dataset with both genotype and gene expression measurements. The resulting eQTL  
72 effect sizes build a predictive model that can impute gene expression in an independently  
73 genotyped population. A TWAS is similar in spirit to the widely-known genome-wide association  
74 study (GWAS) but suffers less of a multiple testing burden and can potentially detect more  
75 associations as a result.[5,6]

76  
77 Unlike a normal GWAS, where phenotypes are regressed onto genotypes, in TWAS the phenotype  
78 is regressed onto the imputed gene expression values, thus constituting a new gene-based  
79 association test. TWAS can also link phenotypes to variation in gene expression and provide  
80 researchers with additional biological and functional insights over those afforded by GWAS alone.  
81 While these models are imperfect predictors, predicted gene expression allows researchers to  
82 test phenotype associations to expression levels in existing GWAS datasets without measuring  
83 gene expression directly. In particular, these methods enable analysis of predicted gene

84 expression in very large cohorts ( $\sim 10^4 - 10^6$  individuals) rather than typical gene expression  
85 studies that measure expression directly ( $\sim 10^2 - 10^3$  individuals). Several methods have been  
86 recently developed to perform TWAS in existing genotyped datasets. PrediXcan[6] uses eQTLs  
87 precomputed from paired genotype-expression data, such as those in GTEx, in conjunction with  
88 a new genotype set to predict gene expression. These gene expression prediction models are  
89 freely available online (PredictDB), creating resources for external researchers. Related TWAS  
90 approaches, such as FUSION[5], MetaXcan[9], or SMR[10], leverage eQTL information with GWAS  
91 summary statistics instead, thus circumventing the need for raw individual-level genotype data.

92

93 As evidenced by application to numerous disease domains, the TWAS framework is capable of  
94 uncovering new genic associations.[11–17] However, the power of TWAS is inherently limited by  
95 the data used for eQTL discovery. For example, since gene expression varies by tissue type,  
96 researchers must ensure that the prediction weights are estimated using RNA from a tissue  
97 related to their phenotype, whether that be the direct tissue of interest or one with sufficiently  
98 correlated gene expression.[18] Furthermore, the ability of predictive models to impute gene  
99 expression from genotypes is limited by the heritability in the *cis* region around the gene.[6]

100 Consequently, genes with little or no measurable genetically regulated effect on their expression  
101 in the discovery data are poor candidates for TWAS.

102

103 A subtler but more troubling issue arises from the lack of genetic diversity present in the datasets  
104 used for predictive model training: most paired genotype-expression datasets consist almost  
105 entirely of data from European-descent individuals.[8,18] The European overrepresentation in

106 genetic studies is well documented[19–21] and has severe negative consequences for equity as  
107 well as for gene discovery[22], fine mapping[23–25], and applications in personalized  
108 medicine.[26–34] Genetic architecture, linkage disequilibrium, and genotype frequencies can  
109 vary across populations, which presents a potential problem for the application of predictive  
110 models with genotype predictors across multiple populations.

111  
112 The training data for most models in the models derived from PrediXcan weights in PredictDB  
113 ([predictdb.org](http://predictdb.org)) are highly biased toward European ancestry: GTEx version v6p subjects are over  
114 85% European, while the GTEx v7 and DGN subjects are entirely of European descent. The lack  
115 of suitable genotype-expression datasets in non-European individuals leads to scenarios in which  
116 PredictDB models trained in Europeans are used to predict into non-European or admixed  
117 populations. As shown previously in the context of polygenic risk scores[35], multi-SNP prediction  
118 models trained in one population can suffer from unpredictable bias and poor prediction  
119 accuracy that impair their cross-population generalizability. Recent analyses of genotype-  
120 expression data from the Multi-Ethnic Study of Atherosclerosis (MESA)[36–38], which includes  
121 non-European individuals, explore cross-population transcriptome prediction and conclude that  
122 predictive accuracy is highest when training and testing populations match in ancestry. These  
123 results are consistent with our experience analyzing admixed populations, but offer little insight  
124 into the mechanisms underlying the cross-population generalizability of transcriptome prediction  
125 models, particularly when eQTL architecture is known.

126

127 Here we investigate the cross-population generalizability of gene expression models using paired  
128 genotype and gene expression data and using simulations derived from real genotypic data and  
129 realistic models of gene expression. We analyze prediction quality from currently available  
130 PrediXcan prediction weights using a pilot subset of paired genotype and whole blood  
131 transcriptome data from the Study of African Americans, Asthma, Genes, and Environment  
132 (SAGE).[39–42] SAGE is a pediatric cohort study of childhood-onset asthma and pulmonary  
133 phenotypes in African American subjects of 8 to 21 years of age. To tease apart cross-population  
134 prediction quality, we turn to GEUVADIS and the 1000 Genomes Project datasets.[4,43,44] The  
135 GEUVADIS dataset has been used extensively to validate PrediXcan models.[6,38] However,  
136 recent analyses suggest that GTEx and DGN PrediXcan models behave differently on the  
137 constituent populations in GEUVADIS.[45] To our knowledge, nobody has investigated cross-  
138 population generalizability of new prediction models generated within GEUVADIS. GEUVADIS  
139 provides us an opportunity to investigate predictive models with an experimentally  
140 homogeneous dataset: the GEUVADIS RNA-Seq data were produced in the same environment  
141 under the same protocol, from lymphoblastoid cell lines (LCLs) that, despite some variation in  
142 when cells were collected[46], are derived from similar sampling efforts and treatments, thereby  
143 providing a high degree of technical harmonization. We train, test, and validate predictive models  
144 wholly within GEUVADIS with a nested cross-validation scheme. Finally, to understand the  
145 consequences of eQTL architecture on TWAS, we use existing 1000 Genomes data to simulate  
146 two ancestral populations and an admixed population and then apply the same “train-test-  
147 validate” scheme with various simulated eQTL models to study cross-population prediction  
148 efficacy when a gold standard is known.

## 149 **Results**

### 150 **Concordance of measured gene expression and PrediXcan predictions is lower than expected**

151 We compared transcriptome prediction accuracy in SAGE whole blood RNA using three PredictDB  
152 prediction weight sets for whole blood RNA: GTEx v6p, GTEx v7, and DGN. We also evaluated  
153 expression prediction with all four MESA monocyte weight sets: MESA\_ALL (populations  
154 combined), MESA\_AFA (African Americans), MESA\_AFHI (combined African Americans and  
155 Hispanic Americans), and MESA\_CAU (Caucasians). For each gene where both measured RNA-  
156 Seq gene expression and predictions are available in SAGE, we compute both the coefficient of  
157 determination ( $R^2$ ) and Spearman correlation to analyze the direction of prediction. As we are  
158 primarily interested in describing the relationship between predicted outcome and real outcome,  
159 we prefer Spearman's  $\rho$  to describe correlations, while for determining prediction accuracy, we  
160 use the standard regression  $R^2$ , corresponding to the squared Pearson correlation, to facilitate  
161 comparisons to prior work. We then benchmark these against the out-of-sample  $R^2$  and  
162 correlations from GTEx v7 and MESA as found in PredictDB. Prediction results in SAGE were  
163 available for 11,545 genes with a predictive model from at least one weight set. Not all sets  
164 derived models at the same genes: since the estimation of these prediction models requires both  
165 high quality expression data and inferred eQTLs, each weight set may have a different number of  
166 gene models. Therefore, intersecting seven different weight sets reduces the overall number of  
167 models available for comparison. After applying the recommended filters, the prediction results  
168 across all seven weight sets overlapped at 273 genes, of which 39 genes had predictions with  
169 positive correlation to measurements. This small number of genes in common is largely driven  
170 by MESA\_AFA, the repository with the smallest number of predictive models. However



171 MESA\_AFA contains the models that should best reflect the genetic ancestry of African  
172 Americans in SAGE (Supplementary Table 1). We note that MESA\_AFA also has the smallest  
173 training sample size among our weight sets ( $N = 233$ )[38], so the small number of predicted  
174 genes from MESA\_AFA probably results from the small training sample size and not from any  
175 feature of the underlying MESA\_AFA training data.

176

177 Here, we highlight the union of genes across model sets for investigation. The concordance  
178 between predicted and measured gene expression over the union of 11,545 from all seven  
179 weight sets, with corresponding training metrics from PredictDB as benchmarks, shows worse  
180 performance than expected for  $R^2$  (

181 Figure 1) and correlations (Figure 2). The highest mean  $R^2$  of 0.0298 was observed in MESA\_AFA.

182 We note the intersection of all prediction models is limited, but reflects a similar pattern: results  
183 for the 273 common genes (Supplementary Figure 1) and the 39 genes with positive correlations  
184 (Supplementary Figure 2) showed little difference in the  $R^2$  shown in

185 Figure 1. Because SAGE is an independent validation set for the training populations, we would  
186 expect to observe some deterioration in prediction  $R^2$  due to out-of-sample estimation. However,  
187 Figure 1 shows a marked difference in model performance.

188

189 More noteworthy is the substantial proportion of predictions in SAGE with negative correlations  
190 to the real data. All seven weight sets produced gene expression predictions with negative  
191 correlations, but average performance across genes varied. The least negative mean correlation  
192 (0.00707) was observed with MESA\_AFHI (MESA African Americans and Hispanics), while the

193 most negative mean correlation (-0.00415) was observed with MESA\_AFA (MESA African  
194 Americans, Supplementary Table 1). The observation that correlations to SAGE measurements  
195 are sometimes negative on average suggests that some large  $R^2$  values seen in  
196 Figure 1 may result from gene models with incorrect direction of prediction, thereby limiting  
197 interpretability of results. While there are some fluctuations in prediction accuracy, no prediction  
198 weight set produces practically meaningfully better correlations to data than the others (-  
199 0.00415 to 0.00707). In contrast, the published models for these genes show positive correlations  
200 to their training data, ranging from 0.308 in GTEx\_v7 to 0.379 in MESA\_AFA, indicating no obvious  
201 incapacity for accurate prediction, even with out-of-sample data. However, available predictions  
202 into SAGE from otherwise valid prediction models are uniformly limited in power to capture true  
203 genotype-expression relationships.

204

205 To analyze genes with high prediction  $R^2$  in the original experiment, we focus on genes in GTEx  
206 v7 with cross-validated  $R^2 > 0.2$  in the reference population. Figure 3 compares PredictDB testing  
207  $R^2$  against the empirical  $R^2$  from regressing predictions onto observations in SAGE. In this case,  
208 even the better-imputed gene models derived from PredictDB have limited ability to capture  
209 gene expression accurately in SAGE (mean  $R^2$  0.031, IQR [0.0027, 0.037]).

### 210 **Cross-population prediction quality declines with increasing genetic distance**

211 Real-world comparisons of RNA-Seq datasets can be subject to numerous sources of  
212 heterogeneity besides differential ancestry. Possible confounders include technical differences  
213 in sequencing protocols, differences in the age of participants[47] or cell lines[46], and the  
214 postmortem interval to tissue collection (for GTEx).[48–50] To investigate cross-population

215 generalizability in an experimentally homogeneous context, we turn to GEUVADIS.[43] The  
216 GEUVADIS data include two continental population groups from the 1000 Genomes Project: the  
217 Europeans (EUR373), composed of 373 unrelated individuals from four subpopulations (Utahns  
218 (CEU), Finns (FIN), British (GBR), Toscani (TSI)), and the Africans (AFR) composed of 89 unrelated  
219 Yoruba (YRI) individuals. In light of the known bottleneck in Finnish population history[51], we  
220 analyze EUR373 both as one population and as two independent subgroups: the 95 Finnish  
221 individuals (FIN) and the 278 non-Finnish Europeans (EUR278). We used expression data,  
222 generated and harmonized together by the GEUVADIS Consortium, with matched whole-genome  
223 genotype data in the resulting four populations (EUR373, EUR278, FIN, and AFR) to train  
224 predictive models for gene expression in a nested cross-validation scheme[6] and perform cross-  
225 population tests of prediction accuracy.

226  
227 Table 1 shows  $R^2$  from three training sets (EUR373, EUR278 and AFR) into the four testing  
228 populations (EUR373, EUR278, FIN, and AFR) for genes with positive correlation between  
229 prediction and measurement. While the number of genes with applicable models including  
230 genetic data varies in each train-test scenario (see Supplementary Table 3), we note that not all  
231 predictive models are trained on equal sample sizes, so the resulting  $R^2$  only provide a general  
232 idea of how well one population imputes into another. Analyses within a population use out-of-  
233 sample prediction  $R^2$  to avoid overfitting across train-test scenarios. Predicting from a population  
234 into itself yields  $R^2$  ranging from 0.079 – 0.098 (Table 1) consistent with the smaller sample sizes  
235 in GEUVADIS versus GTEx and DGN. In contrast, predicting across populations yields more  
236 variable predictions, with  $R^2$  ranging from 0.029 – 0.087. At the lower range of  $R^2$  (0.029 – 0.039)

237 are predictions from AFR into European testing groups (EUR373, EUR278, and FIN). Alternatively,  
238 when predicting from European training groups into AFR, the  $R^2$  are noticeably higher (0.051 –  
239 0.054). Prediction from EUR278 into FIN ( $R^2 = 0.087$ ) is better than prediction from EUR278 into  
240 AFR ( $R^2 = 0.051$ ), suggesting that prediction  $R^2$  may deteriorate with increased genetic distance.  
241 A comparison of the 564 genes in common across all train-test scenarios (Table 2) yields a subset  
242 of genes with potentially more consistent gene expression levels. In this case involving better-  
243 predicted genes, we see that prediction quality between the European groups improves  
244 noticeably ( $p$ -value  $\sim 0$ , Dunn test) with  $R^2$  ranging between 0.183 to 0.216, while  $R^2$  between  
245 Europeans and Africans ranges from 0.095 to 0.147, a significant improvement ( $p$ -value  $< 7.07 \times$   
246  $10^{-22}$ , Dunn test) that nonetheless highlights a continental gap in prediction performance. In  
247 general, populations seem to predict better into themselves, and less well into other populations.  
248  
249 Combining all European subpopulations obscures population structure and can complicate  
250 analysis of cross-population prediction performance. To that end, we divide the GEUVADIS data  
251 into its five constituent populations and randomly subsample each of them to the smallest  
252 population size ( $n = 89$ ). We then estimate models from each subpopulation and predict into all  
253 five subpopulations. Table 3 shows average prediction  $R^2$  from each population into itself and  
254 others. The populations consistently predict well into themselves, with prediction  $R^2$  ranging  
255 from 0.104 – 0.136. We observe that prediction quality using models trained in CEU shows a  
256 miniscule decline relative to other EUR subpopulations. This observation is potentially due to the  
257 older age of CEU LCLs[45,52,53], but did not appreciably change our results. In contrast, a more  
258 notable difference exists between the EUR subpopulations and YRI. The cross-population  $R^2$

259 between CEU, TSI, GBR, and FIN ranges from 0.103 to 0.137, while cross-population  $R^2$  from these  
260 populations into YRI ranges from 0.062 to 0.084. Prediction between YRI and the EUR populations  
261 taken together is consistently lower than within the EUR populations (Supplementary Figure 3)  
262 and statistically significant ( $p$ -value  $< 1.36 \times 10^{-4}$ , Dunn test; see Supplementary Table 6). The  
263 cross-population differences remain for the 142 genes with positive correlation in all train-test  
264 scenarios (Table 4), where  $R^2$  for prediction into YRI ranges from 0.166 to 0.244, while  $R^2$  within  
265 EUR populations ranges from 0.239 to 0.331. These results clearly suggest problems for  
266 prediction models that predict gene expression across populations, in similar regimes to those  
267 tested with linear predictive models and datasets of size consistent with current references. In  
268 addition, since AFR is genetically more distant from the EUR subpopulations than they are to each  
269 other, we interpret these results to imply that structure in populations can potentially exacerbate  
270 cross-population prediction quality (Supplementary Figure 4).

### 271 **Admixture influences cross-population gene expression prediction quality under known eQTL** 272 **architecture**

273 The unresolved question is the extent to which these results hold with oracle knowledge of eQTL  
274 architecture, something impossible to investigate in real data when the causal links between  
275 eQTLs and gene expression can only be estimated. To investigate genomic architectures giving  
276 rise to gene expression, and in particular to investigate behavior in admixed populations, we  
277 simulate haplotypes from HapMap3[54] CEU and YRI using HAPGEN2[55] and then sample  
278 haplotypes in proportions consistent with realistic admixture proportions (80% YRI, 20% CEU)[56]  
279 to construct a simulated African-American (AA) admixed population. We simulate eQTL  
280 architectures under an additive model of size  $k$  causal alleles ( $k = 1, 10, 20, \text{ and } 40$ ) and an

281 expression phenotype with *cis*-heritability  $h^2 = 0.15$  (recapitulating average  $h^2$  in GTEx) using the  
282 genomic background of genic regions on chromosome 22, thus testing various model sizes and  
283 LD patterns. To tease apart the effect of shared eQTL architecture, we allow the two ancestral  
284 populations CEU and YRI to share eQTLs with fixed effects in various proportions (0%, 10%, 20%,  
285 ..., 100%) to test a range of eQTL architectures. The admixed population AA always inherited all  
286 eQTLs from the two ancestral populations, which yielded different numbers of eQTLs per gene  
287 depending on how many eQTLs were shared by CEU and YRI. For example, for eQTL model size  $k$   
288 = 10, when CEU and YRI shared all 10 eQTLs, then all three populations had the exact same 10  
289 eQTLs. When CEU and YRI shared half of their eQTLs with each other, then each one had 5  
290 population-specific eQTLs, and AA inherited 15 total eQTLs (5 unique to CEU, 5 unique to YRI, and  
291 5 shared). If CEU and YRI shared no eQTLs, then all eQTLs were population-specific, and AA  
292 inherited 20 eQTLs (10 from CEU and 10 from YRI; see Supplementary Figure 5 for an illustration).  
293 With these simulations providing known architectures for comparison, we then apply the train-  
294 test-validate scheme as before.

295  
296 Figure 4 shows the cross-population Spearman correlations between predicted and simulated  
297 phenotypes in our simulated AA, CEU, and YRI, partitioned by proportion of shared eQTLs, for  $k$   
298 = 10 causal eQTLs. Scenarios with  $k = 20$  and  $k = 40$  causal eQTLs show similar trends  
299 (Supplementary Figure 6 and Supplementary Figure 7). Prediction within a population produced  
300 similar correlations in all cases, ranging from 0.310 to 0.338 (Supplementary Table 4). The case  
301 of models with 100% shared eQTL architecture – where eQTL positions and effects are exactly  
302 the same between the ancestral populations – yields predictions with no loss in cross-population

303 generalizability, with correlations ranging from 0.299 to 0.336 even when predicting across  
304 populations (Supplementary Table 5). This case suggests that eQTLs that are causal in all  
305 populations can impute gene expression reliably regardless of the population in which they were  
306 ascertained, provided that the eQTLs can be correctly mapped and genotyped in all populations,  
307 that the eQTL effects are identical across populations, and that a linear model of eQTLs is  
308 assumed. For cases where eQTL architecture is not fully shared across populations, we see that  
309 prediction from each population into the other improves as the proportion of shared eQTLs  
310 increases (Figure 4). The cross-population correlation between predicted gene expression versus  
311 measurement is highest from YRI to AA (0.238 to 0.338), intermediate from CEU to AA (0.218 to  
312 0.310), and lowest between CEU and YRI (0.0020 to 0.326). Prediction quality from AA to CEU  
313 and YRI interpolates that of YRI to AA and CEU to AA, with correlations ranging from 0.223 to  
314 0.338. Prediction quality from AA to CEU or YRI shows a slight upward trend as more eQTLs are  
315 shared, an artifact of eQTL inheritance in our simulations; as described previously, AA eQTL  
316 models are largest (20 eQTLs) when CEU and YRI share no eQTLs and smallest (10 eQTLs) when  
317 CEU and YRI share all eQTLs. Consequently, when predicting between two populations, the choice  
318 of which population is used to train predictive models can produce differences in prediction  
319 quality. Prediction quality between AA to CEU and AA to YRI is not significantly different (p-value  
320  $\sim 1$ , Dunn test). All other train/test scenarios are significantly different from each other  
321 (Supplementary Table 7). The results for  $k = 10, 20,$  and  $40$  eQTLs show a consistent trend of  
322 prediction quality driven primarily by different in eQTL architecture, with additional minor  
323 influence from ancestral similarity between populations ( $k = 10$ , Figure 4, similar plots in  
324 Supplementary Figure 6 and Supplementary Figure 7). Although less realistic for most

325 genes[5,6,18], we also analyzed models with a single causal eQTL. Trends for single-eQTL models  
326 are more difficult to analyze due the limitations of binary inference as to whether the causal SNP  
327 is identified or not. Nevertheless, when the causal eQTL is identified and shared across  
328 populations, prediction quality is high in call cases. If the causal eQTL differs across populations,  
329 then cross-population prediction between AA and YRI or CEU is noticeably better than prediction  
330 between CEU and YRI (Supplementary Figure 8), in line with results for other values of  $k$  that  
331 suggest that eQTL sharing is the primary driver of gene expression prediction quality.

### 332 **Power to detect associations declines with decreasing shared ancestry**

333 Simulation of gene expression demonstrates that gene expression prediction quality is  
334 modulated by both shared eQTL architecture and shared genetic ancestry. These results suggest  
335 possible effects of cross-population generalizability on the power to detect associations between  
336 a phenotype and gene expression measures in a TWAS. For each of our three populations (AA,  
337 CEU, and YRI), we used the simulated gene expression measures to simulate a continuous  
338 phenotype whose variation depends on expression of a single causal gene. For simplicity, the  
339 phenotypes shared the same causal gene, the same effect size, and the same environmental  
340 noise model. We tested various effect sizes from  $1 \times 10^{-5}$  to 1 and drew the environmental noise  
341 from a zero-mean normal distribution with variance 0.01. The effect sizes produced a continuous  
342 spectrum of genetic heritability values  $h^2$  spanning the full range of heritability for gene  
343 expression. We then regressed the phenotype onto predicted gene expression measures,  
344 resulting in nine association tests, one for each train-test scenario. For simplicity, we focused on  
345 the prediction scenario with  $k = 10$  causal eQTLs per gene. To see how shared eQTL architecture



346 affects power, we used predicted expression measures with 0%, 50%, and 100% shared eQTLs  
347 per gene.

348

349 Figure 5 shows power curves for the association tests for the nine prediction scenarios for all

350 three tested eQTL architectures. Unsurprisingly, power improves as populations share more

351 causal eQTLs. For example, with 100% shared eQTLs and phenotypic heritability 0.205, cross-

352 population power ranges between 0.69 – 0.86. In contrast, average power under a 0% shared

353 eQTL model ranges more broadly, from 0.02 (CEU to YRI, YRI to CEU) to 0.38 (AA to YRI, AA to

354 CEU) to 0.82 (CEU to AA) and 0.88 (YRI to AA), indicating some ability to predict gene expression

355 at genetically controlled genes, even without shared eQTLs. Power also improves with shorter

356 genetic distance between populations. Figure 6, which is a cross-section of Figure 5, shows power

357 for each train-test scenario across various shared eQTL architectures for  $\beta = 0.05$ , corresponding

358 to a phenotype heritability of  $h^2 = 0.205$ , indicating moderate genetic control. TWAS in this case

359 using gene expression imputed from matched populations has higher power across all eQTL

360 architectures, from 0.33-0.85, compared to cross-population TWAS, where power varies

361 substantially. For an architecture with no shared eQTLs, power between CEU and YRI is 0, while

362 power is higher for CEU to AA (0.25) and YRI to AA (0.30). TWAS power for expression imputed

363 from AA to CEU (0.05) or YRI (0.06) is much lower due to the aforementioned structure of eQTL

364 inheritance. As the proportion of shared eQTLs jumps from 0% to 50% and 100%, power increases

365 across all cross-population scenarios, reaching up to 0.31 (YRI to AA, 100% shared eQTLs). When

366 eQTLs are fully shared, power from YRI to AA (0.31) is higher than from CEU to AA (0.25),

367 indicating an effect of genetic distance on prediction quality. Indeed, when controlling for eQTL

368 architecture, increasing genetic similarity between reference and target populations yields more  
369 significant median association test  $t$ -statistics (Supplementary Figure 9).

### 370 **Admixture proportion interpolates power in two-way admixture**

371 The results in Figure 6 show how genetic distance affects power in TWAS association tests for  
372 one particular admixture proportion, but offer limited insight about how power changes across  
373 the admixture spectrum. To understand how admixture proportion affects TWAS power in a  
374 general admixed population with two ancestral populations, we simulated multiple admixed  
375 populations from CEU and YRI with admixture proportions varying at 10% increments. When the  
376 admixed population has 0% YRI admixture, it is fully drawn from haplotypes from CEU, whereas  
377 a population with 100% YRI admixture is drawn exclusively from haplotypes from YRI. It is  
378 important to note that in neither case does the admixed population exactly match the reference  
379 CEU or YRI since the genotypes for the admixed population are formed from an independent  
380 shuffling of the CEU or YRI haplotypes. For each admixed population, we estimated prediction  
381 models of gene expression as done in our previous analyses. For computational efficiency, we  
382 investigated the scenario of 50% shared eQTLs across reference populations and the number of  
383 eQTLs per gene to 10. Populations still shared the same causal gene, effect size, and  
384 environmental noise model.

385

386 Figure 7 shows power across admixture proportions for all cross-population scenarios. The  
387 phenotypes were simulated at effect sizes  $\beta = 0.005, 0.01, \text{ and } 0.025$ , and environmental  
388 variance  $\sigma^2 = 0.01$ , corresponding to heritability  $h^2 = 0.06, 0.20, \text{ and } 0.58$ , respectively. To avoid

389 confusion with previous references to AA, which had a fixed admixture proportion, here we  
390 denote the admixed population for all proportions as AD. As expected, statistical power  
391 increases with the genetic heritability of the phenotype for all prediction scenarios. However,  
392 the different admixture proportions yield directional changes in power when gene expression is  
393 predicted to or from AD. For example, when  $h^2 = 0.20$  and gene expression is predicted from AD  
394 to CEU, power at 0% YRI admixture is 0.56 (95% CI: 0.462 – 0.658) and declines linearly with  
395 increasing YRI admixture; at 100% YRI, statistical power for AD to CEU is 0.46 (95% CI: 0.362 –  
396 0.558). For AD to YRI, power at 0% YRI admixture starts at 0.42 (95% CI: 0.323 – 0.512) and  
397 increases linearly to 0.53 (95% CI: 0.431 – 0.628) at 100% YRI. We observe similar changes in  
398 power for CEU to AD (decreasing power as YRI proportion increases) and YRI to AD (increasing  
399 power as YRI proportion increases). The four directional trends also hold for  $h^2 = 0.06$  and  $h^2 =$   
400 0.58, though power for cross-population scenarios involving AD is much lower in the former  
401 case and almost universally high in the latter case. In essence, the varying admixture  
402 proportions in this two-way admixed population yield a continuous linear trend of statistical  
403 power between the two ancestral populations: when AD is genetically closer to CEU, power for  
404 gene expression predicted these populations is highest, and declines as AD becomes genetically  
405 closer to YRI. Similarly, when predicting from AD to YRI or vice versa, power is lowest when the  
406 two populations are genetically distinct, intermediate as the two populations become more  
407 genetically similar, and maximized when they are most alike.

## 408 **Discussion**

409 Our goal with this study was to understand the extent to which gene expression prediction  
410 models estimated in one population can accurately predict the genetic component of gene

411 expression in a different population. Cross-population generalizability of gene expression  
412 prediction models is an important but understudied issue for TWAS analyses. Among TWAS  
413 resources, we focused on PrediXcan as a test case with openly distributed prediction models  
414 available for multiple populations.[6,38] Using 39 subjects from the SAGE study[39–42] we  
415 compared predicted expression values from PrediXcan models to measured gene expression on  
416 the same subjects and found that predictions matched poorly to measurements. Our  
417 investigation with the GEUVADIS dataset[43] offered us a more homogenous environment in  
418 which to train and test gene expression prediction models. Prediction quality in GEUVADIS using  
419 both continental and constituent subpopulations provided stronger evidence of cross-population  
420 generalizability issues with transcriptome prediction, but could not control for eQTL predictors  
421 that vary between populations. To that end, our simulation of an admixed population from 1000  
422 Genomes CEU and YRI haplotypes[4,44] allowed us to finely control eQTL positions and effects  
423 as well as the causal genes in a TWAS. The simulation results show that both gene expression  
424 prediction accuracy and statistical power decrease as population eQTL models begin to diverge  
425 and genetic distance increases between populations for varying admixture proportions.

426  
427 Our results highlight two points: firstly, since prediction within populations is better than  
428 prediction between populations, our results reaffirm prior investigations[38] that population  
429 matching matters for optimally predicting gene expression. This is consistent with our results of  
430 impaired transcriptome prediction performance in SAGE with currently available resources.  
431 Secondly, despite decreased prediction accuracy when predicting between different populations,  
432 the populations that are more closely genetically related demonstrate somewhat better cross-

433 population prediction and power to detect associations in TWAS. Our simulations of prediction  
434 between ancestral populations and an admixed one under varying admixture proportions neatly  
435 summarize this relationship: the admixture proportion from each ancestral population  
436 interpolates the power available from each ancestral population, and power is maximized when  
437 the admixed population is most closely related to one or the other ancestral population.  
438 However, while the differences in power under varying admixture are statistically meaningful,  
439 they are smaller than differences attributable to different eQTL architectures or to different  
440 levels of genetic heritability of a phenotype.

441  
442 Prediction results from GTEx, DGN, and MESA into SAGE suggest that current predictive models,  
443 even for genes with greater heritability, perform worse than expected despite matching tissue  
444 types. Our investigation into cross-population prediction accuracy with GEUVADIS data replicates  
445 this lack of cross-population generalizability as observed with current predictive models from  
446 PredictDB, demonstrating that heterogeneity in RNA-Seq protocols does not fully explain our  
447 observations. Since transcriptome prediction models use multivariate genotype predictors  
448 trained on a specific outcome, the impaired cross-population application can be viewed as an  
449 analogous observation to that seen previously in polygenic scores.[35]

450  
451 Our simulations control for many technical issues that are otherwise difficult to overcome with  
452 real data, such as oracular knowledge of positions and effect sizes of causal eQTLs. Nevertheless,  
453 in our simulations we see issues with cross-population prediction that we first observed when  
454 applying existing PrediXcan models to SAGE genotype data. Certainly, SAGE differs in important

455 ways from GTEx, DGN, and MESA: SAGE is a pediatric asthma case-control cohort study in African-  
456 American children, so we cannot rule out technical heterogeneity introduced by differences in  
457 age, study design, and ethnicity. Furthermore, our SAGE sample includes RNA-Seq data for  $n = 39$   
458 subjects, a dataset leveraged previously to validate genetic associations, but is nevertheless  
459 somewhat small by contemporary standards.[39] However, technical heterogeneity between  
460 SAGE and existing PrediXcan models cannot solely explain the poor prediction performance. Our  
461 simulation results strongly suggest that problematic cross-population prediction performance  
462 between PrediXcan models and SAGE is deeper than differences in expression data.

463  
464 Our investigations into the architecture of gene expression indicate that the power to detect  
465 associations is primarily determined by the degree of shared eQTLs across populations. In our  
466 simulations, this can be approximated as a (quasi-)linear interpolation of the prediction in the  
467 ancestral or reference populations into the admixed populations. However, the same is not true  
468 of overall levels of power in the admixed population: under 100% shared eQTL scenarios, cross-  
469 population generalizability is high, so the choice of training population matters less. In practical  
470 terms, this result bodes well for prediction of genes with eQTLs that do not vary by population.  
471 It is curious that in high-heritability genes, even models that share no eQTLs still retain power to  
472 detect scenarios: for genetically distant populations (CEU and YRI), power ranges from 0.10-0.14.  
473 Without shared eQTLs, this implies that local linkage disequilibrium between population-specific  
474 eQTLs, combined with high heritability, enables some degree of cross-population prediction.  
475 When cross-population statistical power is driven by LD and  $h^2$  instead of expression signals, then

476 subsequent interpretation of association hits, such as direction and strength of effect, becomes  
477 difficult to link to actual biological relationships between phenotype and gene expression.

478

479 It is important to note that our observations do not reflect shortcomings of either the initial  
480 PrediXcan or TWAS frameworks. Nor do our findings affect the positive discoveries made using  
481 these frameworks over the past several years. These methods fully rely on the data used as input  
482 for training, and the most commonly used datasets for model training are overwhelmingly of  
483 European descent. Here we note that the current models fail to capture the complexity of the  
484 cross-population genomic architecture of gene expression for populations of non-European  
485 descent. Failing to account for this could lead researchers to draw incorrect conclusions from  
486 their genetic data, particularly as these models would lead to false negatives.

487

488 To this end, our simulations strongly suggest that predicting gene expression in a target  
489 population is improved by using predictive models constructed in a genetically similar training  
490 population. Maximizing prediction quality crucially depends on both genetic architecture and  
491 eQTL architecture. If populations share the exact same eQTL architecture, then they are  
492 essentially interchangeable for the purposes of gene expression prediction so long as eQTLs are  
493 genotyped and accurately estimated, which remains a technological and statistical challenge. As  
494 the proportion of shared eQTL architecture decreases between two populations, both cross-  
495 population prediction quality and TWAS power decrease as well. In both SAGE and GEUVADIS,  
496 we observe cross-population patterns consistent with an imperfect overlap of eQTLs across  
497 populations. Ensuring representative eQTL architecture for all populations in genotype-

498 expression repositories will require a solid understanding of true cross-population and  
499 population-specific eQTLs. However, expanding the amount of global genetic architecture  
500 represented in genotype-expression repositories, which can be accomplished by sampling more  
501 populations, provides the most desirable course for improving gene expression prediction  
502 models. Additionally, this presents an opportunity for future research in methods that could  
503 improve cross-population generalizability, particularly when one population is over-represented  
504 in reference data. Tools from transfer learning could facilitate porting TWAS eQTL models from  
505 reference populations to target populations using little or no RNA-Seq data.

506

507 In light of the surging interest in gene expression prediction and TWAS, we see a pressing need  
508 for freely distributed predictive models of gene expression estimated from coupled  
509 transcriptome-genome data sampled in a variety of populations and tissues. The recently  
510 published predictive models with multi-ethnic MESA data constitute a crucial first step in this  
511 direction for researchers working with admixed populations.[38] However, the clinical and  
512 biomedical research communities must push for more diverse genotype-expression resources to  
513 ensure that the fruits of genomic studies benefit all populations.



514 **Online Resources**

515 PredictDB: <http://predictdb.org/>

516 GTEx: <http://gtexportal.org/>

517 DGN: <http://dags.stanford.edu/dgn/>

518 GEUVADIS: <https://www.ebi.ac.uk/Tools/geuvadis-das/>

519 Source code: <https://github.com/asthmacollaboratory/sage-geuvadis-predixcan>

520 Results and simulation data: <https://ucsf.box.com/v/sage-geuvadis-predixcan>

521

## 522 **Methods**

### 523 **Genotype and RNA-Seq data**

524 RNA-Seq (RNA sequencing) data generation and cleaning protocols for 39 SAGE subjects analyzed  
525 here were initially described in (Mak, White, Eckalbar, et al. 2018).[39] Genotypes were  
526 generated on the Affymetrix Axiom array as described previously.[57] Genotypes were then  
527 imputed on the Michigan Imputation Server[58] with EAGLE v2.3[59] and the 1000 Genomes  
528 panel phase 3 v5[44] and then subjected to the following filters: <5% missing sample, <5% missing  
529 genotypes, >1% MAF, >1e-4 HWE, and >0.3 imputation R<sup>2</sup>. The choice of the 1000 Genomes panel  
530 follows GTEx protocol, though GTEx used the smaller 1000 Genomes phase 1 panel.[4] Gene  
531 expression counts were processed through the GTEx v6p eQTL quality control pipeline and as  
532 described previously.[18] This filtering process kept 20,985 genes with Ensembl identifiers for  
533 analysis, of which 20,268 were autosomal genes. We then quantile normalized the remaining  
534 gene expression values across samples as our gene expression measurements.

535

536 GEUVADIS genotype VCF files and normalized gene expression data (filename  
537 GD462.GeneQuantRPKM.50FN.sampname.resk10.txt.gz) were downloaded directly from  
538 the EMBL-EBI GEUVADIS Data Browser. Genotypes were filtered similarly to SAGE subjects. No  
539 manipulation was performed on expression data. This process yielded 23,722 genes for analysis.

### 540 **Running PrediXcan models**

541 We ran PrediXcan on SAGE subjects using PredictDB prediction weights from three paired  
542 genotype-expression datasets from PredictDB: GTEx, DGN, and MESA.[6,9,38,60] For GTEx, we  
543 used both GTEx v6p and GTEx v7 weights. For MESA, we used all weight sets from the freeze

544 dated 2018-05-30: African Americans (MESA\_AFA), African Americans and Hispanics  
545 (MESA\_AFHI), Caucasians (MESA\_CAU), and all MESA samples (MESA\_ALL). Overall, the analysis  
546 included 10,161 genes, of which only 273 had *both* normalized RNA-Seq measures and  
547 predictions from *all* weight sets. Of these, 126 had positive correlation between prediction and  
548 measurement. We assessed prediction quality by comparing PrediXcan predictions to normalized  
549 gene expression from SAGE using linear regression and correlation tests.

### 550 **Estimation of prediction models**

551 We trained prediction models in GEUVADIS on genotypes in a 500Kb window around each of  
552 23,723 genes with measured and normalized gene expression. GEUVADIS subjects were  
553 partitioned into various groups: the Europeans (EUR373), the non-Finnish Europeans (EUR278),  
554 the Yoruba (AFR), and the constituent 1000 Genomes populations (CEU, GBR, TSI, FIN, and YRI).  
555 For each training set, we performed nested cross-validation. The external cross-validation for all  
556 populations used leave-one-out cross-validation (LOOCV). The internal cross-validation used 10-  
557 fold cross-validation for EUR373 and EUR278 and LOOCV for the five constituent GEUVADIS  
558 populations in order to fully utilize the smaller sample size ( $n = 89$ ) compared to EUR278 ( $n = 278$ )  
559 and EUR373 ( $n = 373$ ). Internal cross-validation used elastic net regression with mixing parameter  
560  $\alpha = 0.5$  as implemented in the `glmnet` package in R. The nonzero weights for each SNP from each  
561 LOOCV were compiled and averaged for each gene, yielding a single set of prediction weights for  
562 each gene. Predictions were computed by parsing genotype dosages from the target population  
563 corresponding to the nonzero SNP predictors, and then multiplying dosages against the  
564 prediction weights. The resulting predictions were compared to normalized gene expression  
565 measurements downloaded from the GEUVADIS data portal. The comparison of predictive

566 models cannot easily differentiate predictions of 0 (no gene expression) and NA (missing  
567 expression). We addressed this with two additional filters. Firstly, we removed genes that did not  
568 have any eQTLs in their predictive models. Secondly, genes where fewer than half of the  
569 individuals had nonmissing predictions were removed from further analysis. Coefficients of  
570 determination ( $R^2$ ) were computed with the `lm` function in R. Spearman correlations were  
571 computed with the `cor.test` function in R.

### 572 **Simulation of gene expression**

573 We downloaded a sample of 20,085 HapMap 3 SNPs[54] from each of CEU and YRI on  
574 chromosome 22 as provided by HAPGEN2.[55] The data include 234 phased haplotypes for CEU  
575 and 230 phased haplotypes for YRI. We forward-simulated from these haplotypes to obtain two  
576 populations of  $n = 1000$  individuals each. We then sampled haplotypes in proportions of 80% YRI  
577 and 20% CEU to obtain a mixture of CEU and YRI where the ancestry patterns roughly mimic  
578 those of African Americans. For computational simplicity, and in keeping with the high ancestry  
579 LD present in African Americans[61,62], for each gene we assumed local ancestry was constant  
580 for each haplotype. For each of the three simulated populations, we applied the same train-test-  
581 validate scheme used for cross-population analysis in GEUVADIS. Genetic data for model  
582 simulation were downloaded from Ensembl 89 and included the largest 100 genes from  
583 chromosome 22. We defined each gene as the start and end positions corresponding to the  
584 canonical transcript, plus 1 megabase in each direction. Two genes, PPP6R2 and MOV10L1,  
585 spanned no polymorphic markers in our simulated data, resulting in 98 gene models used for  
586 analysis. To simulate predictive eQTL models, we tested multiple parameter configurations for  
587 each gene: we varied the number of causal eQTL ( $k = 1, 10, 20, \text{ and } 40$ ) and the proportion of

588 shared eQTL positions ( $p = 0.0, 0.1, 0.2, \dots, 0.9, 1$ ) between ancestral populations. The admixed  
589 population always inherited all eQTLs from the ancestral populations. Each model included a  
590 simulated gene expression phenotype with *cis*-heritability set to 0.15. For each parameter  
591 configuration, we ran 100 different random instantiations of the model simulations.

## 592 **Simulation of TWAS**

593 Using the simulated gene expression measures with  $k = 10$  eQTLs per gene, we simulated a  
594 continuous phenotype with a known genetic architecture that depended on 1 causal gene. We  
595 tested prediction scenarios with 0, 5, and 10 eQTLs shared across populations. For each eQTL  
596 architecture, the three populations AA, CEU, and YRI shared the same causal gene  $G$ , the same  
597 causal effect size  $\beta$ , and the same environmental noise  $\varepsilon$ .  $G$  was chosen randomly. Effect sizes  
598 were fixed, and we tested various effect magnitudes  $\beta = 1 \times 10^{-5}, 5 \times 10^{-5}, 1 \times 10^{-4}, \dots, 1 \times 10^{-1}, 5 \times$   
599  $10^{-1}, 1$ . The environmental noise  $\varepsilon$  was drawn from an  $N(0, 0.1^2)$  distribution. Consequently,  
600 phenotypes therefore only varied with the expression measures from  $G$ . For a given population  
601  $c$ , the phenotype  $y_c$  was then simulated as

$$602 \quad y_c = G\beta + \varepsilon.$$

603 For each combination of shared eQTL architecture,  $G$ , and  $\beta$ , this procedure yielded one  $y_c$  per  
604 individual in a population. We then performed a TWAS with  $y_c$  onto the *predicted* gene expression  
605 values, yielding three TWAS per  $y_c$ , one for each reference prediction population. We then  
606 queried the resulting association  $p$ -value at  $G$  and tabulated whether it was declared significant  
607 (yes) or not (no) against a Bonferroni-corrected threshold of  $0.05 / 98$ , accounting for all 98 genes  
608 in the TWAS. We ran this procedure for 100 random instantiations of  $(G, \varepsilon)$  and computed  
609 association test power with a logistic interpolation of the yes/no results.

610 **Analysis tools**

611 Analyses used GNU parallel[63]. The R packages used for analysis include argparser,  
612 assertthat, data.table, doParallel, dunn.test, knitr, optparse, peer, the  
613 Bioconductor packages annotate, biomaRt, and preprocessCore, and the tidyverse  
614 bundle.[64–75] All plots were generated with ggplot2.[76]

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650 **Conflict of Interest Statement**

651 C.R.G. owns stock in 23andMe, Inc. The remaining authors declare no potential conflicts of  
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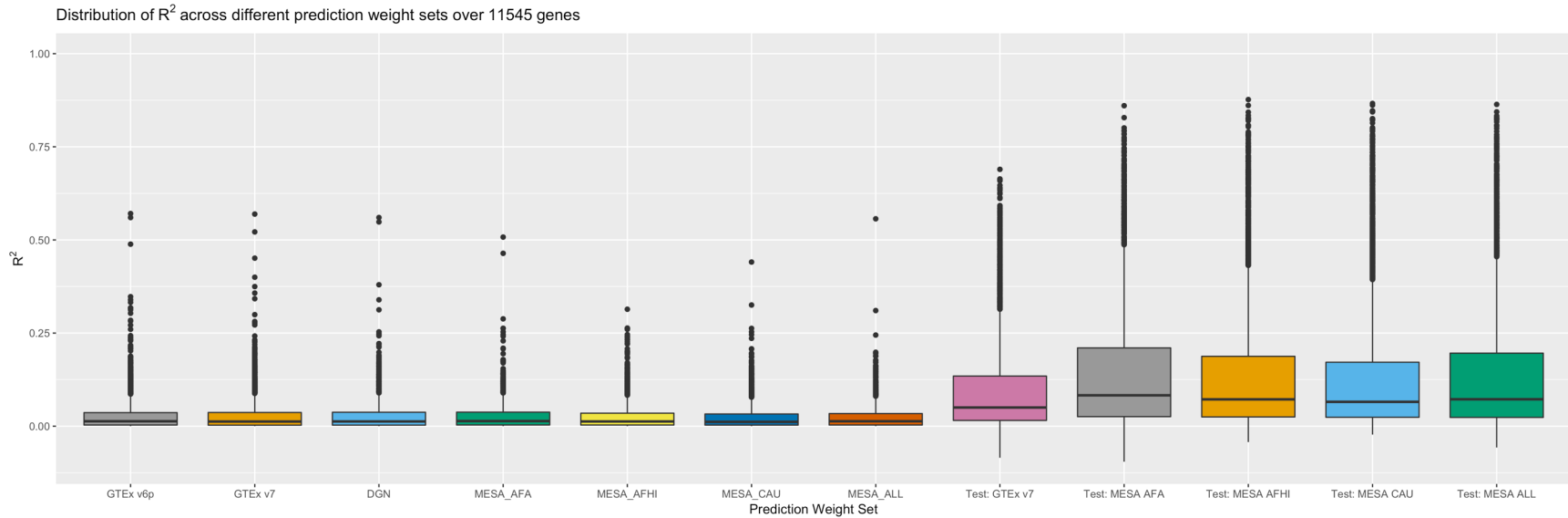
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868 **Figures and Tables**

869

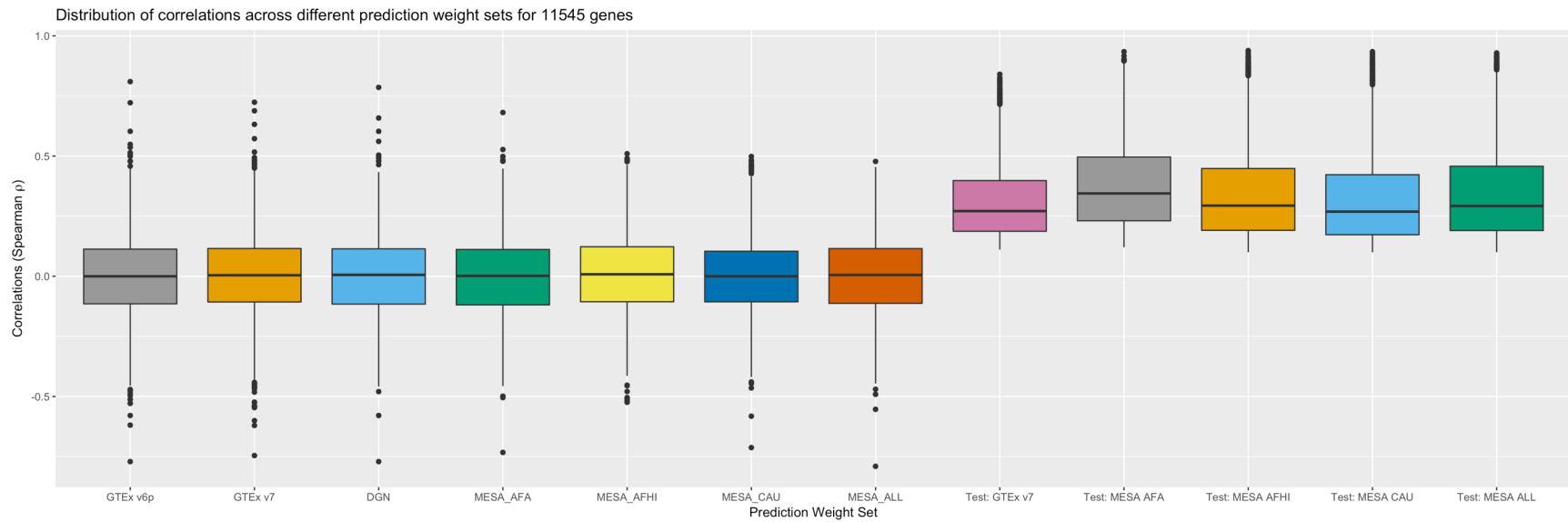


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872 *Figure 1: A comparison of  $R^2$  between prediction and measurement in SAGE, with PredictDB test metrics as benchmarks, for 11,545*  
873 *genes total. The prediction weights used here are, from left to right: GTEx v6p, GTEx v7, DGN, MESA African Americans, MESA African*  
874 *Americans and Hispanics, MESA Caucasians, and all MESA subjects. Test  $R^2$  from model training in GTEx 7 and MESA (“test\_R2\_avg”*  
875 *in PredictDB) appear on the right and provide a performance baseline. The number of genes per weight set varies; see Supplementary*  
876 *Table 1.*

877



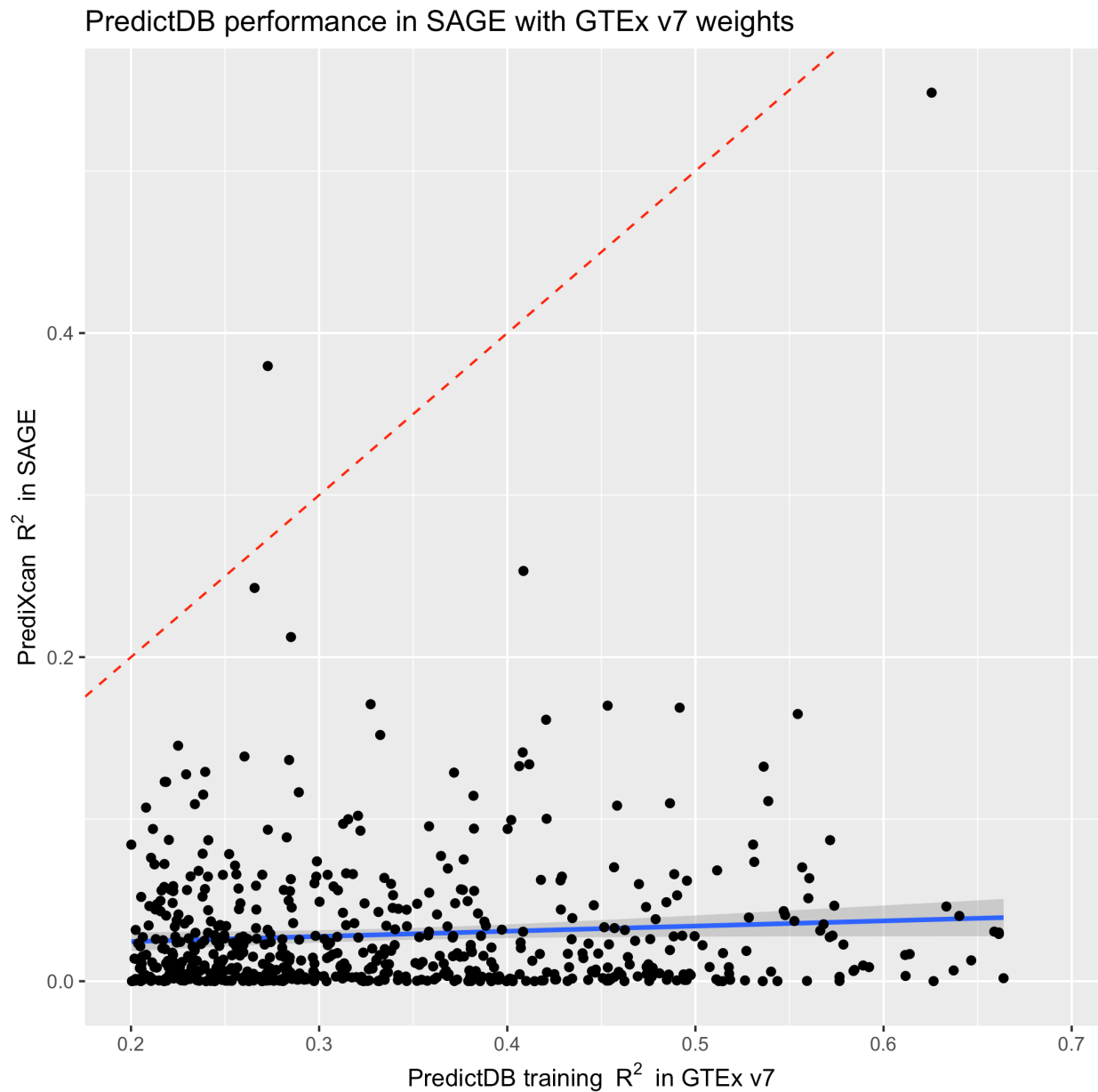
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879 *Figure 2: Spearman correlations of measured gene expression versus predicted expression from PrediXcan. The order of the weight*  
 880 *sets matches*

881 *Figure 1. Test correlations for GTEx v7 and MESA correspond to “rho\_avg” from PredictDB.*

882

883



884

885 *Figure 3: A comparison of  $R^2$  from SAGE and GTEx v7 training diagnostics. The SAGE  $R^2$  are*  
886 *computed from regressing PrediXcan predictions onto gene expression measurements. The GTEx*  
887 *v7  $R^2$  are taken from PredictDB ("test\_R2\_avg"). The red dotted line marks where  $R^2$  between*  
888 *the two groups match, while the blue line denotes the best linear fit.*



889

$R^2$		Train Pop		
		EUR373	EUR278	AFR
Test Pop	EUR373	0.098	n/a	0.029
	EUR278	n/a	0.096	0.030
	FIN	n/a	0.087	0.039
	AFR	0.054	0.051	0.079

890 *Table 1: Prediction  $R^2$  between populations in GEUVADIS for genes with positive correlation*  
 891 *between predictions and measurements. Scenarios where the training sample is contained in*  
 892 *the testing sample cannot be accurately tested and are marked with “n/a”. EUR373 includes all*  
 893 *Europeans, EUR278 includes only non-Finnish Europeans, FIN includes only the Finnish, and AFR*  
 894 *includes only the Yoruba.*

895

$R^2$		Train Pop		
		EUR373	EUR278	AFR
Test Pop	EUR373	0.201	n/a	0.096
	EUR278	n/a	0.183	0.095
	FIN	n/a	0.216	0.111
	AFR	0.147	0.141	0.130

896 *Table 2: Prediction  $R^2$  between populations in GEUVADIS for 564 gene models that show positive*  
 897 *correlation between prediction and measurement in all 9 train-test scenarios that were*  
 898 *analyzed. Scenarios that were not tested are marked with “n/a”. As before, EUR373 includes all*  
 899 *Europeans, EUR278 includes only non-Finnish Europeans, FIN includes only the Finnish, and AFR*  
 900 *includes only the Yoruba.*



R2 Mean (Std Err)		Training population				
		CEU	TSI	GBR	FIN	YRI
Testing Pop	CEU	0.115 (0.139)	0.106 (0.139)	0.107 (0.134)	0.103 (0.133)	0.069 (0.116)
	TSI	0.124 (0.158)	0.121 (0.151)	0.124 (0.149)	0.118 (0.145)	0.083 (0.13)
	GBR	0.132 (0.16)	0.137 (0.155)	0.136 (0.156)	0.133 (0.155)	0.087 (0.132)
	FIN	0.128 (0.158)	0.130 (0.155)	0.130 (0.153)	0.130 (0.152)	0.084 (0.134)
	YRI	0.065 (0.108)	0.069 (0.112)	0.063 (0.1)	0.062 (0.102)	0.104 (0.138)

901 *Table 3: Cross-population prediction performance across all five constituent GEUVADIS*  
902 *populations over genes with positive correlation between predictions and measurements. All*  
903 *populations were subsampled to N = 89 individuals. The number of genes represented varies by*  
904 *training sample (CEU: N = 1029, FIN: N = 1320, GBR: 1436, TSI: 1250, YRI: 914).*

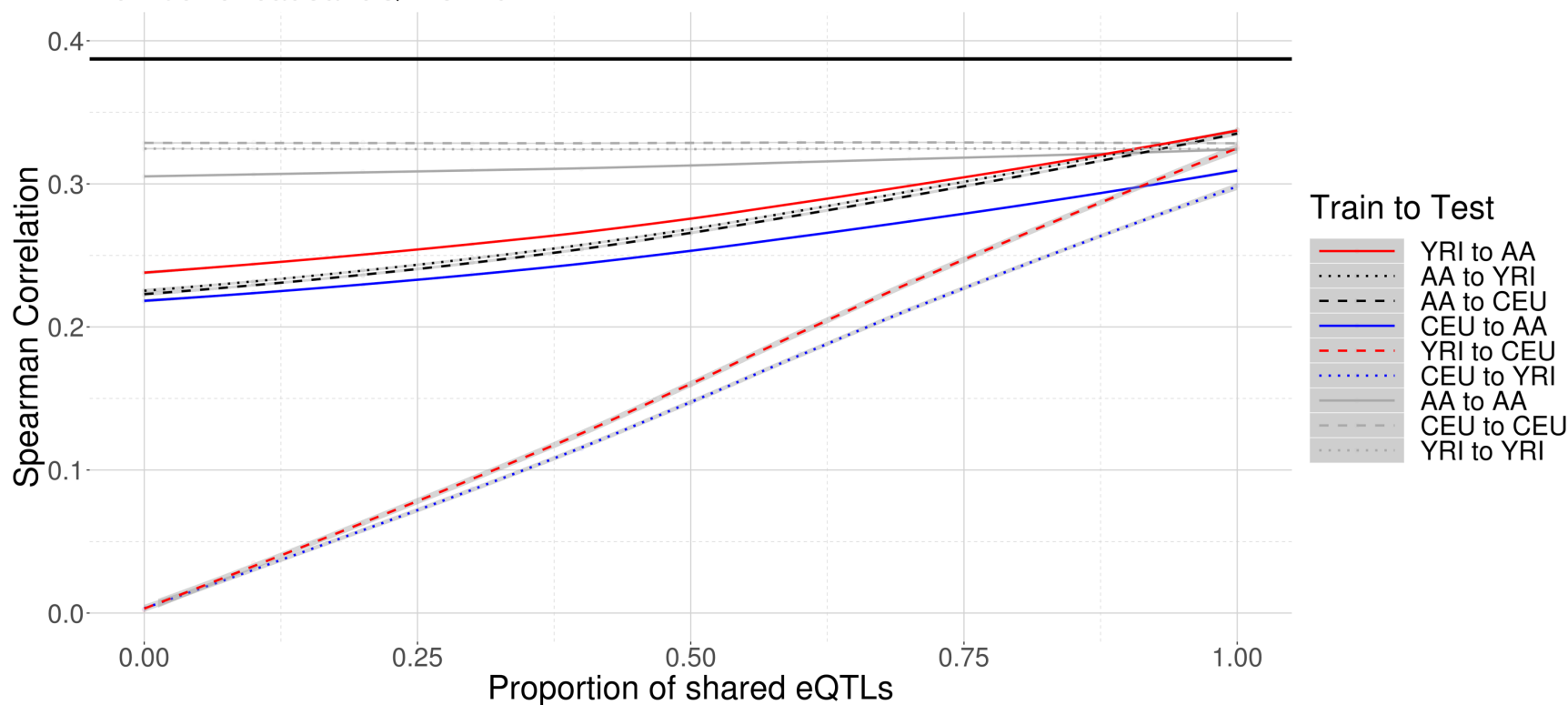
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R2 Mean (Std Err)		Training population				
		CEU	TSI	GBR	FIN	YRI
Testing Pop	CEU	0.239 (0.18)	0.269 (0.177)	0.291 (0.166)	0.297 (0.168)	0.201 (0.164)
	TSI	0.307 (0.188)	0.294 (0.21)	0.331 (0.182)	0.322 (0.185)	0.227 (0.185)
	GBR	0.320 (0.175)	0.326 (0.181)	0.318 (0.191)	0.350 (0.178)	0.235 (0.183)
	FIN	0.318 (0.191)	0.320 (0.198)	0.343 (0.182)	0.323 (0.201)	0.244 (0.192)
	YRI	0.166 (0.164)	0.205 (0.163)	0.195 (0.157)	0.189 (0.156)	0.213 (0.177)

906 *Table 4: Cross-population prediction performance across all five subsampled GEUVADIS*  
907 *populations over the 142 genes with positive correlation between prediction and measurement*  
908 *in all 25 train-test scenarios.*

## Crosspopulation correlations of predicted versus simulated gene expression

Number of causal eQTLs: 10



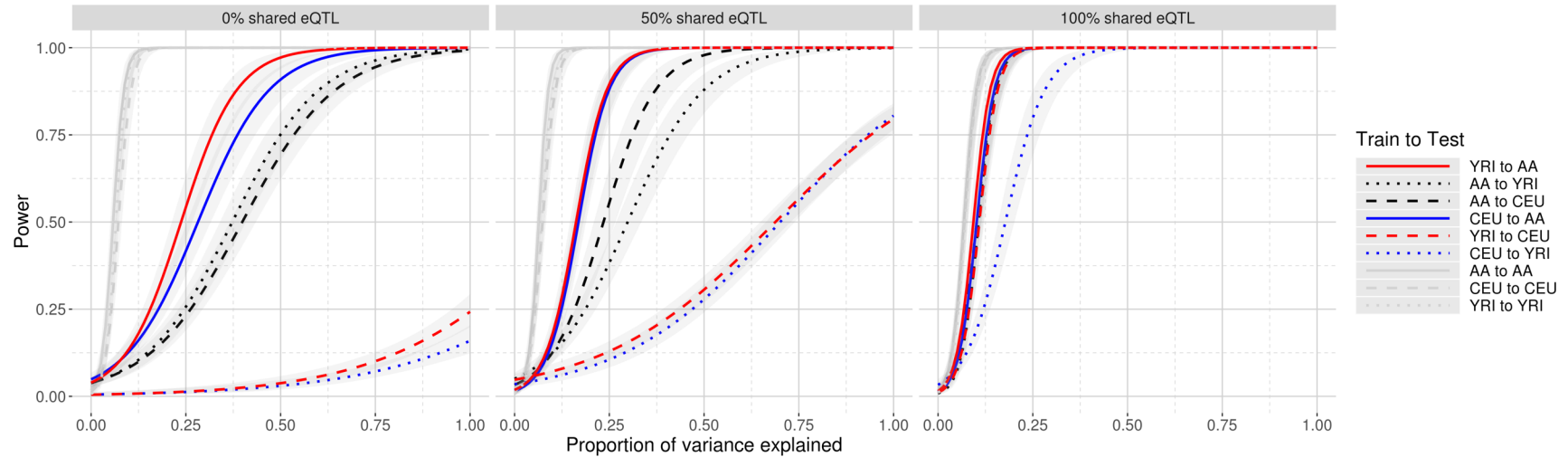
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910 *Figure 4: Correlations between predictions and simulated gene expression measurements from simulated populations across various*  
911 *proportions of shared eQTL architecture with 10 causal cis-eQTLs. Here YRI is simulated from the 1000 Genomes Yoruba, CEU is*  
912 *simulated from the Utahns, and AA is constructed from YRI and CEU. The black line represents the upper bound of correlation 0.387*  
913 *dictated by our choice  $h^2 = 0.15$  for the genetic heritability of expression. Each trend line represents an interpolation of correlation*  
914 *versus shared eQTL proportion. Gray areas denote 95% confidence regions of LOESS-smoothed mean correlations conditional on the*  
915 *proportion of shared eQTLs.*

916

917

Power of TWAS association tests with cross-population predicted expression  
Expression imputed from AA, CEU, and YRI for  $k = 10$  eQTL per gene



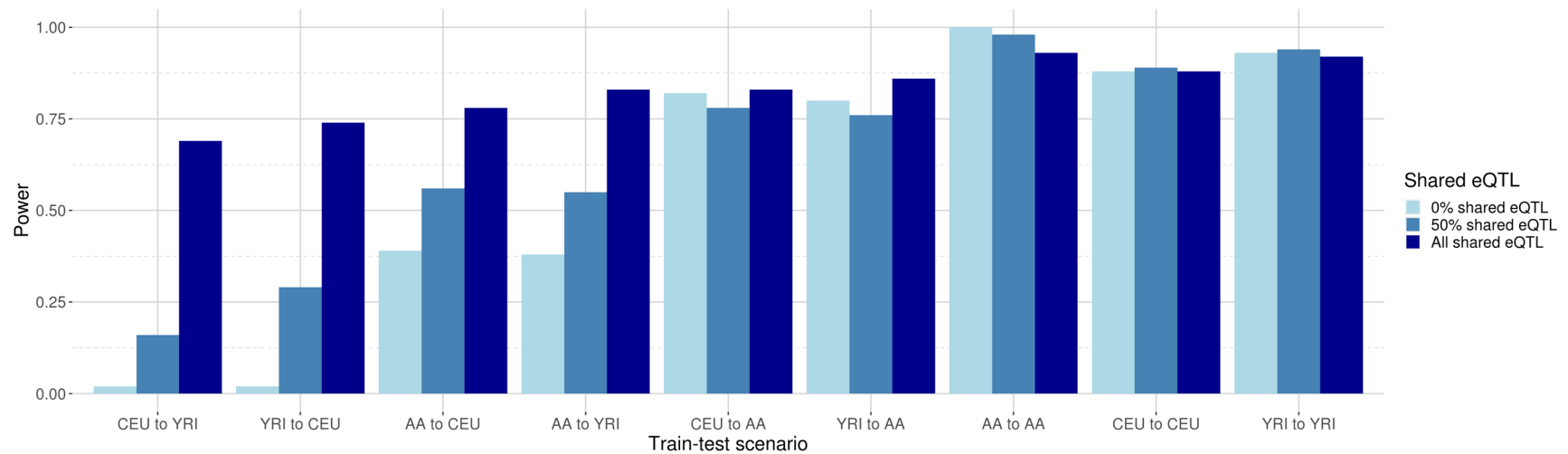
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919 *Figure 5: Curves depicting power to detect association under various TWAS scenarios. The x-axis represents the proportion of*  
920 *phenotypic variance explained by gene expression. As in Figure 4, AA reflects simulated African-Americans constructed from YRI and*  
921 *CEU. The curves represent logistic interpolations of whether or not the causal gene was declared significant in an association test of a*  
922 *phenotype from the testing population with gene expression predicted from a training population into the testing population. Gray*  
923 *areas denote 95% confidence regions of mean power conditional on the effect size. A dotted red line at  $h^2 = 0.95$  marks the power*  
924 *values shown in*

925

### Power of TWAS association tests in AA, CEU, and YRI

Expression imputed from AA, CEU, and YRI for  $k = 10$  eQTL per gene and heritability  $h^2 = 0.205$



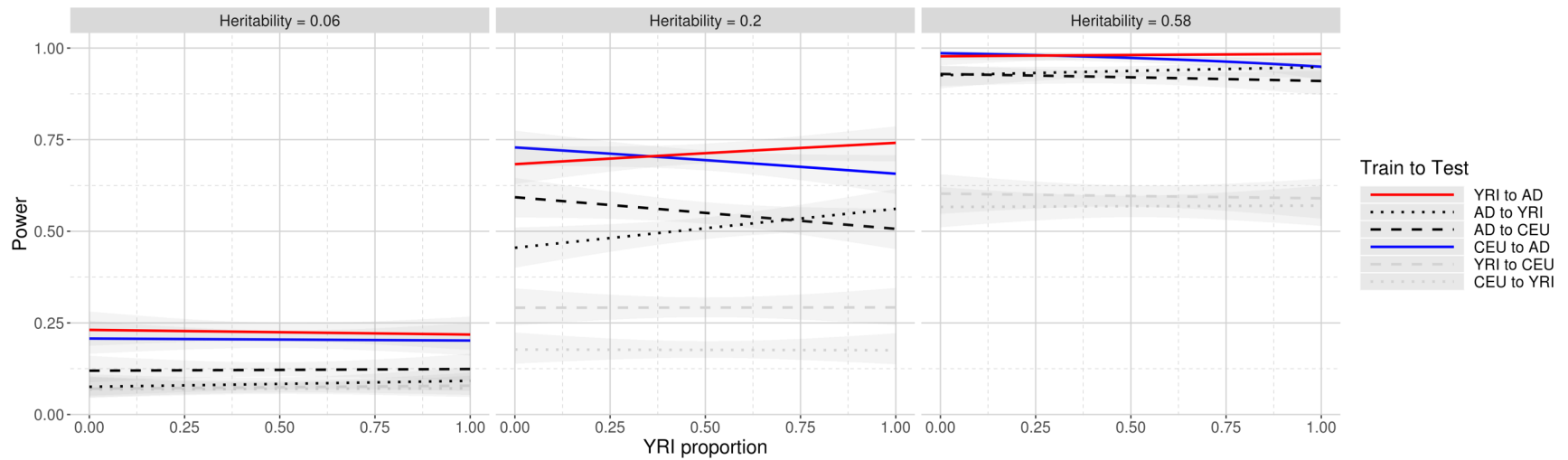
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927 *Figure 6: Power for phenotype-expression association tests with cross-population imputed gene expression for heritability  $h^2 = 0.205$ .*  
928 *The cross-population scenarios are ordered left to right from least shared ancestry (CEU to YRI, 0.0 shared ancestry) to most shared*  
929 *ancestry (YRI to AA, 0.8 shared ancestry). Power increases on two axes: (1) as the proportion of shared eQTL architecture increases,*  
930 *and, to a lesser extent, (2) as genetic distance decreases between reference and target populations. Power is consistently high when*  
931 *training and testing populations match.*

932

933

Power of TWAS association tests for varying proportions of YRI admixture  
k = 10 eQTLs per gene, 50% shared eQTLs between populations



934

935 *Figure 7: Power for various cross-population train-test scenarios with varying YRI admixture for three phenotypic heritability levels  $h^2$*   
936 *= 0.06, 0.20, and 0.58, corresponding to effect sizes 0.005, 0.01, and 0.025, respectively. Power increases as heritability increases, but*  
937 *also as populations become more genetically similar.*

938 **Supplementary Figures and Tables**

<b>Weight set</b>	<b>Gene models</b>	<b>Genes predicted in SAGE</b>	<b>Genes both predicted and measured</b>	<b>Genes with positively correlated predictions and measurements</b>	<b>Mean Correlation (273 common genes)</b>
GTEEx v6p	6588	5773	5348	2730	-0.0044
GTEEx v7	6297	2742	2570	1319	-0.0113
DGN	13171	4033	3678	1819	-0.0124
MESA_AFA	3551	995	982	497	-0.0204
MESA_AFHI	5556	1889	1862	969	-0.0049
MESA_CAU	4674	1654	1633	837	-0.0082
MESA_ALL	6217	2443	2408	1201	-0.0107

*Supplementary Table 1: Summary statistics for analyzing gene expression prediction in SAGE for all seven weight sets in PredictDB. SAGE has measurements for 20,985 genes, of which 20,268 are autosomal. The intersection of genes with both predictions and measurements in SAGE across all seven weight sets is 273, of which 39 produce predictions positively correlated to data in all comparisons.*

939

940

<b>Pop</b>	<b>Measured genes</b>	<b>Predictive Models</b>	<b>With &gt;50% samples predicted</b>	<b>Analyzed prediction v. measurement</b>	<b>Positive correlation</b>
EUR373	23723	20418	11917	11914	5586
EUR278	23723	20182	11043	11043	4817
YRI89	23723	20699	11180	11179	4867

941

*Supplementary Table 2: Summary statistics for each filtering step in the analysis of gene expression models from GEUVADIS for the 3 training populations EUR373, EUR278, and AFR. The analysis of prediction vs. measurement contains 5038 genes in common between all three populations. Of these genes, 1476 genes demonstrate positive correlation between predictions and measurements.*

Training Pop	Testing Pop	R <sup>2</sup>	Correlation	Transcripts
AFR	AFR	0.079	0.2329	2562
AFR	EUR278	0.030	0.1122	2996
AFR	EUR373	0.029	0.1072	3043
AFR	FIN	0.039	0.1377	2908
EUR278	AFR	0.051	0.1632	3079
EUR278	EUR278	0.096	0.2291	2857
EUR278	FIN	0.087	0.2171	3994
EUR373	AFR	0.054	0.1683	3105
EUR373	EUR373	0.098	0.2325	3132

942 *Supplementary Table 3: Summary statistics from training and testing results with continental*  
943 *GEUVADIS populations for gene models with positive correlations. The R<sup>2</sup> correspond to Table 1.*  
944 *The column “Correlation” lists the Spearman correlations for each scenario, while “Transcripts”*  
945 *gives the number of gene models used to compute the R<sup>2</sup> and correlation summaries.*

946



947

Training Pop	Testing Pop	Shared eQTL Proportion	Correlation (Mean)	Correlation (StdErr)
AA	AA	0	0.305	0.039
AA	AA	0.1	0.307	0.039
AA	AA	0.2	0.308	0.038
AA	AA	0.3	0.310	0.038
AA	AA	0.4	0.311	0.038
AA	AA	0.5	0.313	0.038
AA	AA	0.6	0.315	0.036
AA	AA	0.7	0.318	0.036
AA	AA	0.8	0.319	0.036
AA	AA	0.9	0.321	0.036
AA	AA	1	0.324	0.035
CEU	CEU	0	0.329	0.035
CEU	CEU	0.1	0.329	0.035
CEU	CEU	0.2	0.329	0.035
CEU	CEU	0.3	0.328	0.035
CEU	CEU	0.4	0.329	0.035
CEU	CEU	0.5	0.328	0.035
CEU	CEU	0.6	0.329	0.035
CEU	CEU	0.7	0.329	0.035
CEU	CEU	0.8	0.329	0.035
CEU	CEU	0.9	0.328	0.035
CEU	CEU	1	0.329	0.035
YRI	YRI	0	0.324	0.035
YRI	YRI	0.1	0.325	0.035
YRI	YRI	0.2	0.325	0.035
YRI	YRI	0.3	0.324	0.035
YRI	YRI	0.4	0.324	0.035
YRI	YRI	0.5	0.324	0.035
YRI	YRI	0.6	0.325	0.035
YRI	YRI	0.7	0.324	0.035
YRI	YRI	0.8	0.325	0.035
YRI	YRI	0.9	0.324	0.035
YRI	YRI	1	0.324	0.035

*Supplementary Table 4: Spearman correlations between prediction versus simulated measurement from simulated populations to themselves across various shared eQTL proportions for  $k = 10$  causal eQTLs.*

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Correlation Mean (Std Err)		Train-test direction		
		AA	CEU	YRI
Training Pop	AA	0.324 (0.0352)	0.309 (0.0399)	0.337 (0.0306)
	CEU	0.335 (0.0335)	0.328 (0.0348)	0.325 (0.0389)
	YRI	0.337 (0.0302)	0.298 (0.0459)	0.324 (0.0347)

949 *Supplementary Table 5: Prediction performance under fully shared eQTL architecture for k = 10*  
 950 *eQTLs yields reliable cross-population gene expression prediction. Results for other sizes of eQTL*  
 951 *models are similar.*

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R <sup>2</sup>	AFR to AFR	AFR to EUR	EUR to AFR
AFR to EUR	1.222 x 10 <sup>-12</sup>		
EUR to AFR	1.705 x 10 <sup>-24</sup>	6.636 x 10 <sup>-06</sup>	
EUR to EUR	1.357 x 10 <sup>-04</sup>	1.487 x 10 <sup>-112</sup>	1.753 x 10 <sup>-228</sup>

957 *Supplementary Table 6: A Dunn test shows statistically significant differences when predicting*  
 958 *between AFR and EUR populations versus predicting between EUR populations.*

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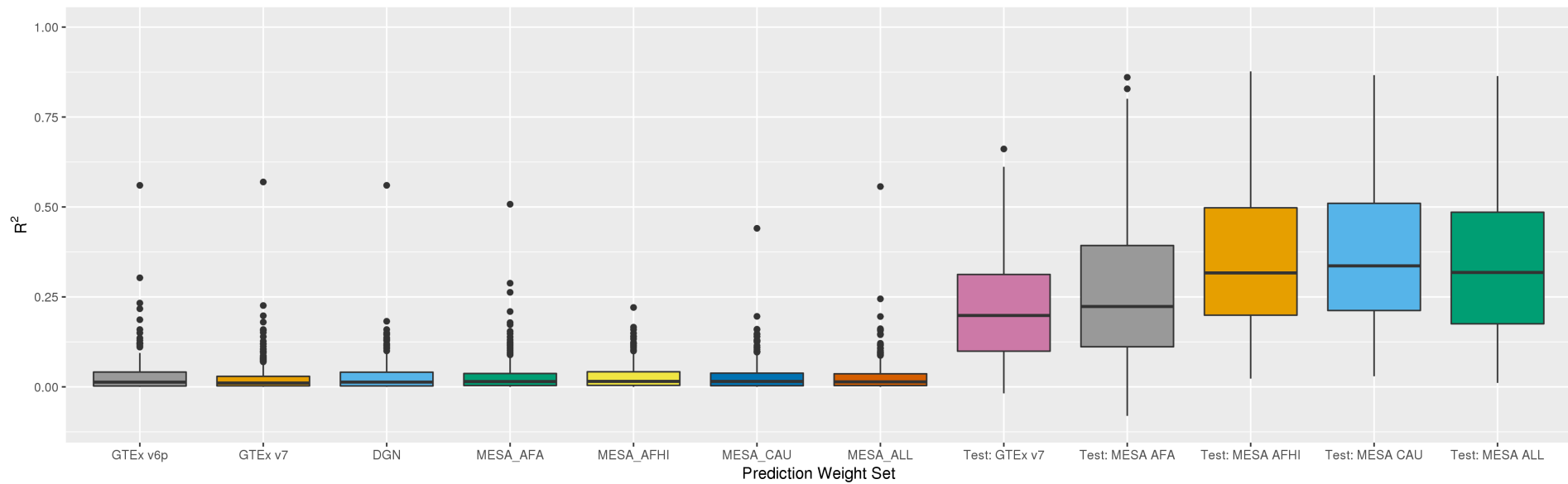
Z-score (p-value)		Train-test direction				
		AA to CEU	AA to YRI	CEU to AA	CEU to YRI	YRI to AA
Train-test direction	AA to YRI	-1.401 (p < 1.00E+00)				
	CEU to AA	6.712 (p < 1.44E-10)	8.113 (p < 3.68E-15)			
	CEU to YRI	28.517 (p < 5.32E-178)	29.919 (p < 8.34E-196)	21.805 (p < 1.55E-104)		
	YRI to AA	-5.391 (p < 5.23E-07)	-3.990 (p < 4.95E-04)	-12.104 (p < 7.51E-33)	-33.909 (p < 3.62E-251)	
	YRI to CEU	24.146 (p < 0.00E+00)	25.547 (p < 0.00E+00)	17.433 (p < 0.00E+00)	-4.371 (p < 0.00E+00)	29.538 (p < 0.00E+00)

960 *Supplementary Table 7: Differences in cross-population prediction performance are statistically significant, with a few notable*  
961 *exceptions. Prediction from AA to CEU or YRI is essentially the same, but all other scenarios are different, indicating that the direction*  
962 *of prediction does matter.*

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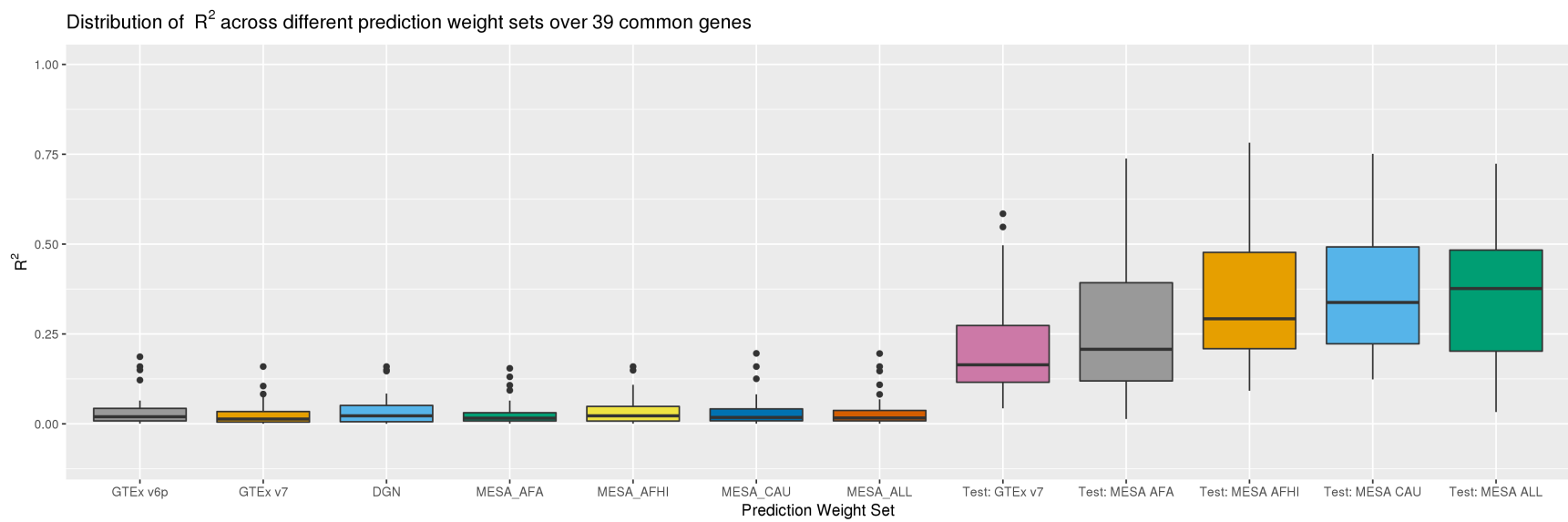
Distribution of  $R^2$  across different prediction weight sets over 273 common genes



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966 *Supplementary Figure 1:  $R^2$  of measured gene expression versus predictions from PrediXcan. The prediction weights used here are,*  
967 *from left to right: GTEx v6p, GTEx v7, DGN, MESA African Americans, MESA African Americans and Hispanics, MESA Caucasians, and*  
968 *all MESA subjects. Test  $R^2$  from model training in GTEx 7 and MESA (“test\_R2\_avg” in PredictDB) appear on the right and provide a*  
969 *performance baseline.*

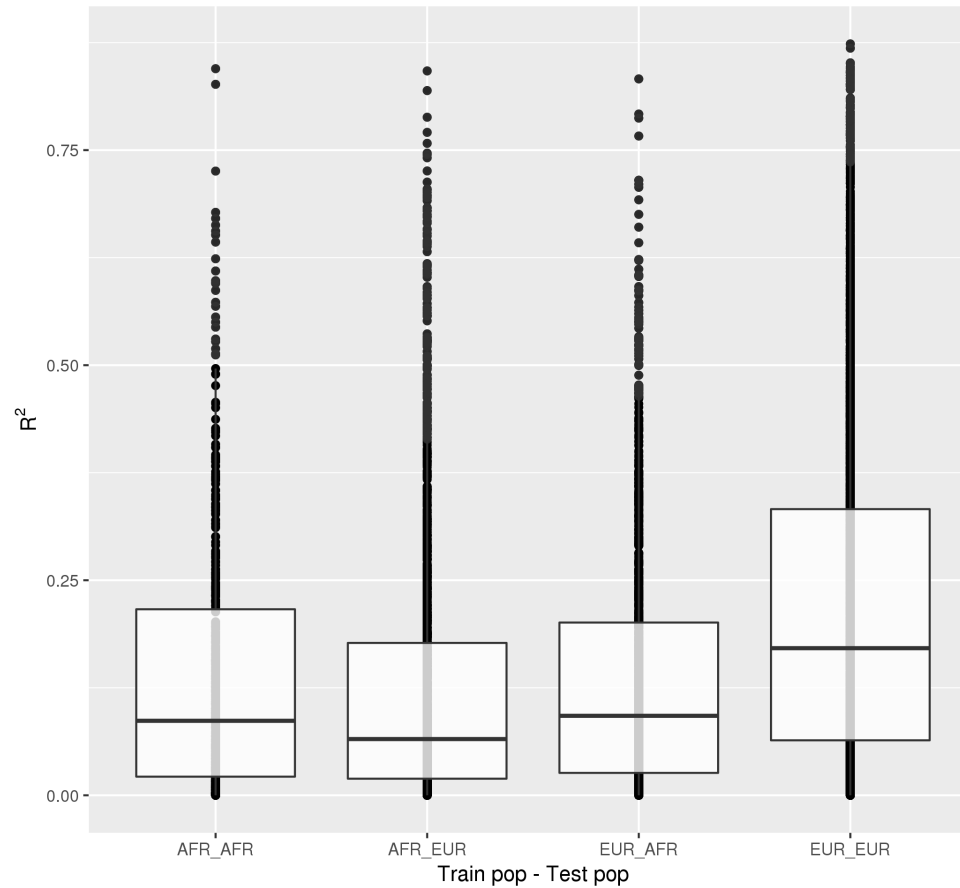
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 972 *Supplementary Figure 2:  $R^2$  between prediction and measurement in SAGE only using the 39 genes with positive correlation between*  
 973 *prediction and measurement in all weight sets and benchmarks.*

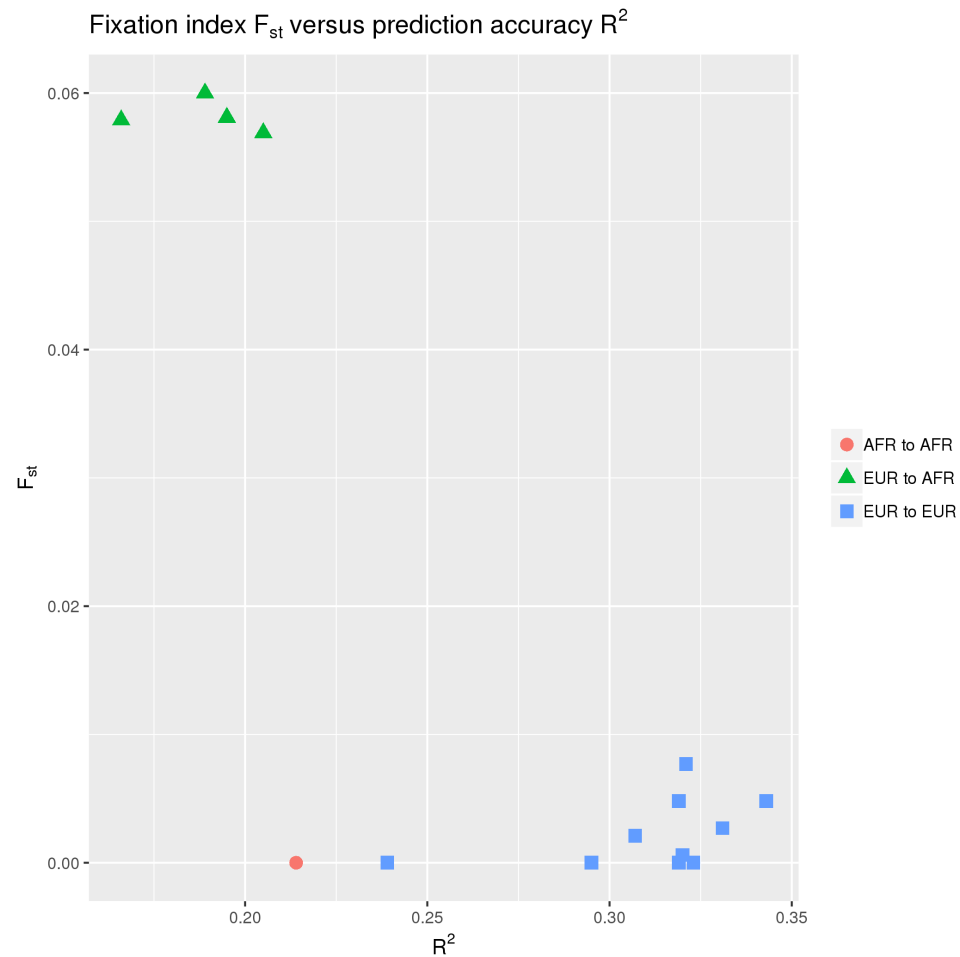
Comparison of  $R^2$  between continental GEUVADIS populations

N = 521 common genes



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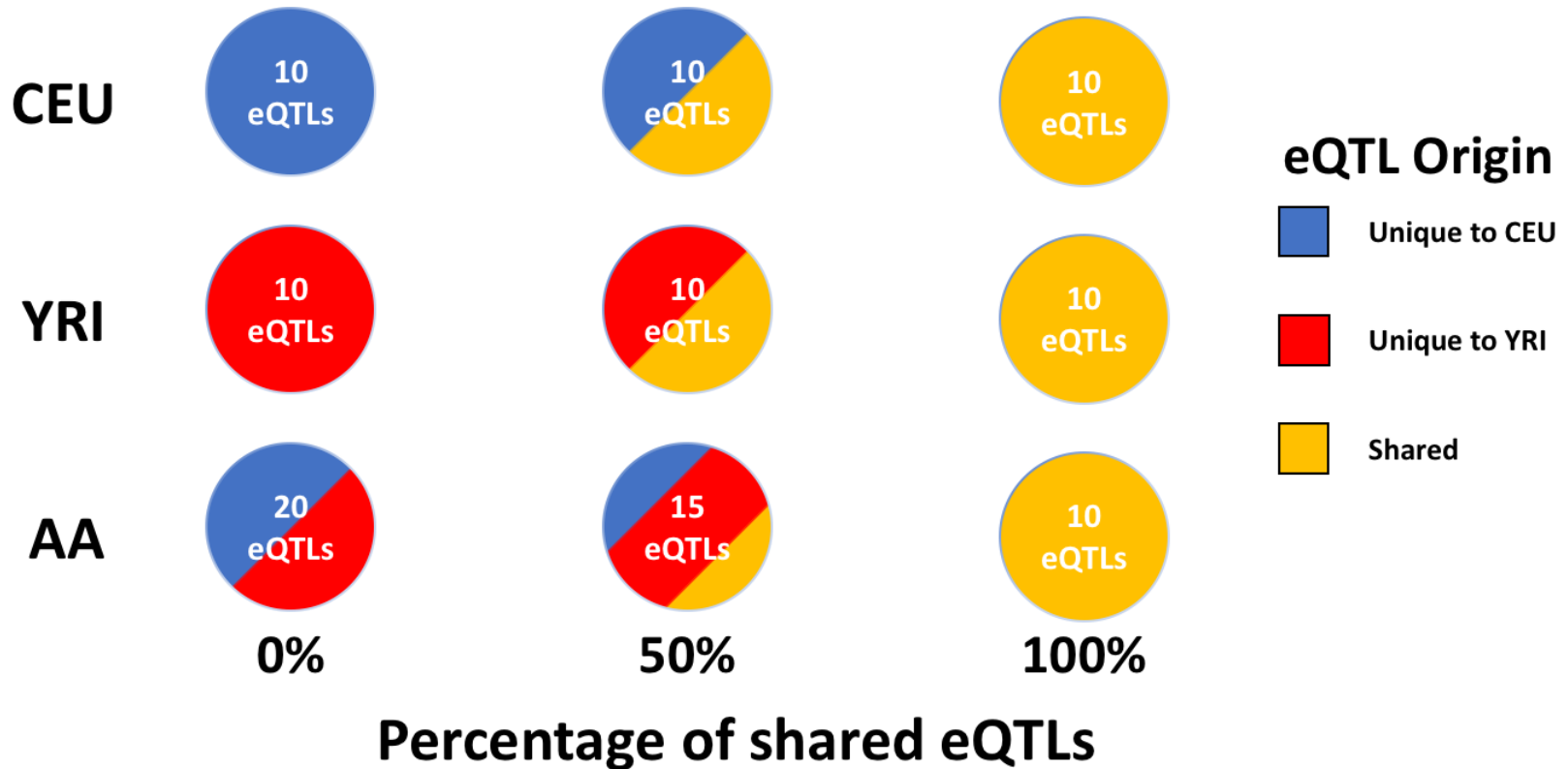
975 *Supplementary Figure 3: Prediction  $R^2$  between AFR (YRI) and EUR (CEU, TSI, GBR, and FIN). Predicting into and from AFR produces*  
976 *consistently lower  $R^2$  than predicting within EUR, suggesting a potential decrease in prediction accuracy when predicting across*  
977 *continental population groups.*



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980 *Supplementary Figure 4: Genetic distance versus prediction accuracy over 142 genes with positive correlation across all train-test*  
 981 *scenarios. Here the GEUVADIS populations are arranged into three groups. AFR to AFR includes prediction from YRI into itself; EUR to*  
 982 *AFR includes prediction into YRI from CEU, GBR, TSI, and FIN; and EUR to EUR includes prediction within and between all European*  
 983 *populations in GEUVADIS. Clustering by genetic distance separates prediction between European populations from prediction*  
 984 *between European populations and AFR.  $F_{ST}$  are taken from the 1000 Genomes Project (Table S11).[77]*

## Simulated eQTL architectures



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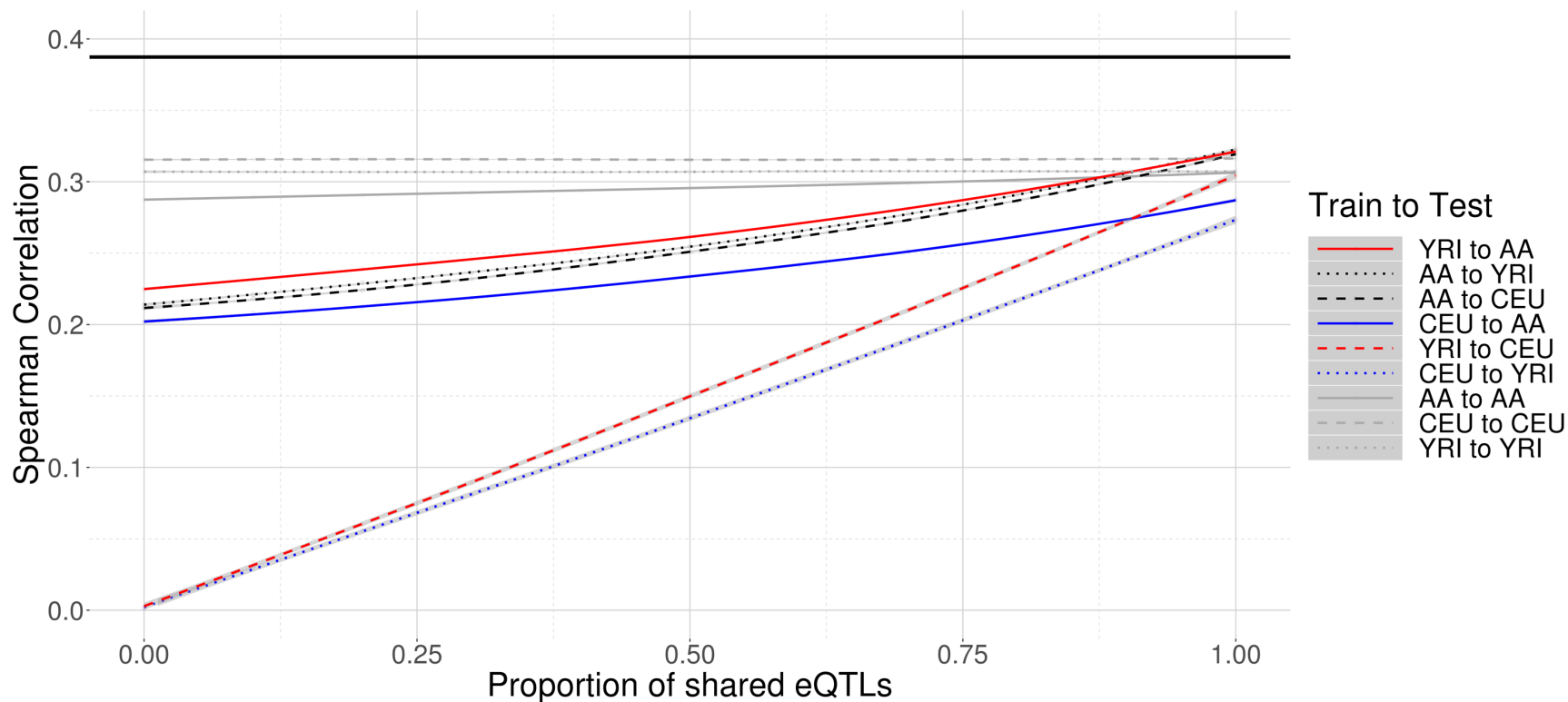
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*Supplementary Figure 5: A schematic of three shared eQTL architectures for the case of  $k = 10$  eQTLs per gene. Blue encodes eQTLs specific to CEU; red encodes eQTLs specific to YRI; and gold encodes eQTLs shared between CEU and YRI. Models for CEU and YRI always had  $k$  eQTLs. AA always inherited all eQTLs from the ancestral populations. Consequently, the number of eQTLs in AA varied depending on how many eQTLs CEU and YRI shared.*



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### Crosspopulation correlations of predicted versus simulated gene expression Number of causal eQTLs: 20

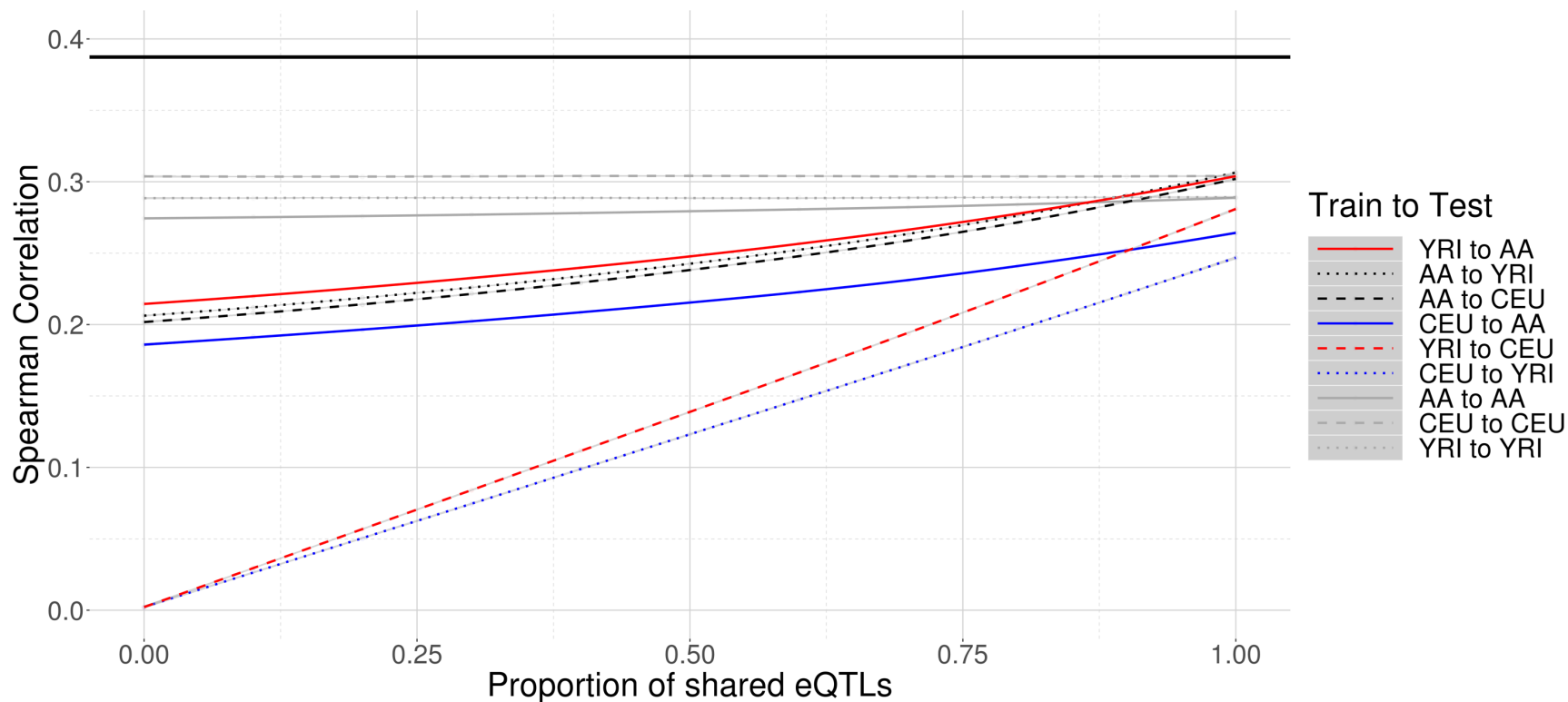


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Supplementary Figure 6: Correlations between predictions and simulated gene expression measurements from simulated populations across various proportions of shared eQTL architecture with 20 causal cis-eQTLs.

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### Crosspopulation correlations of predicted versus simulated gene expression Number of causal eQTLs: 40

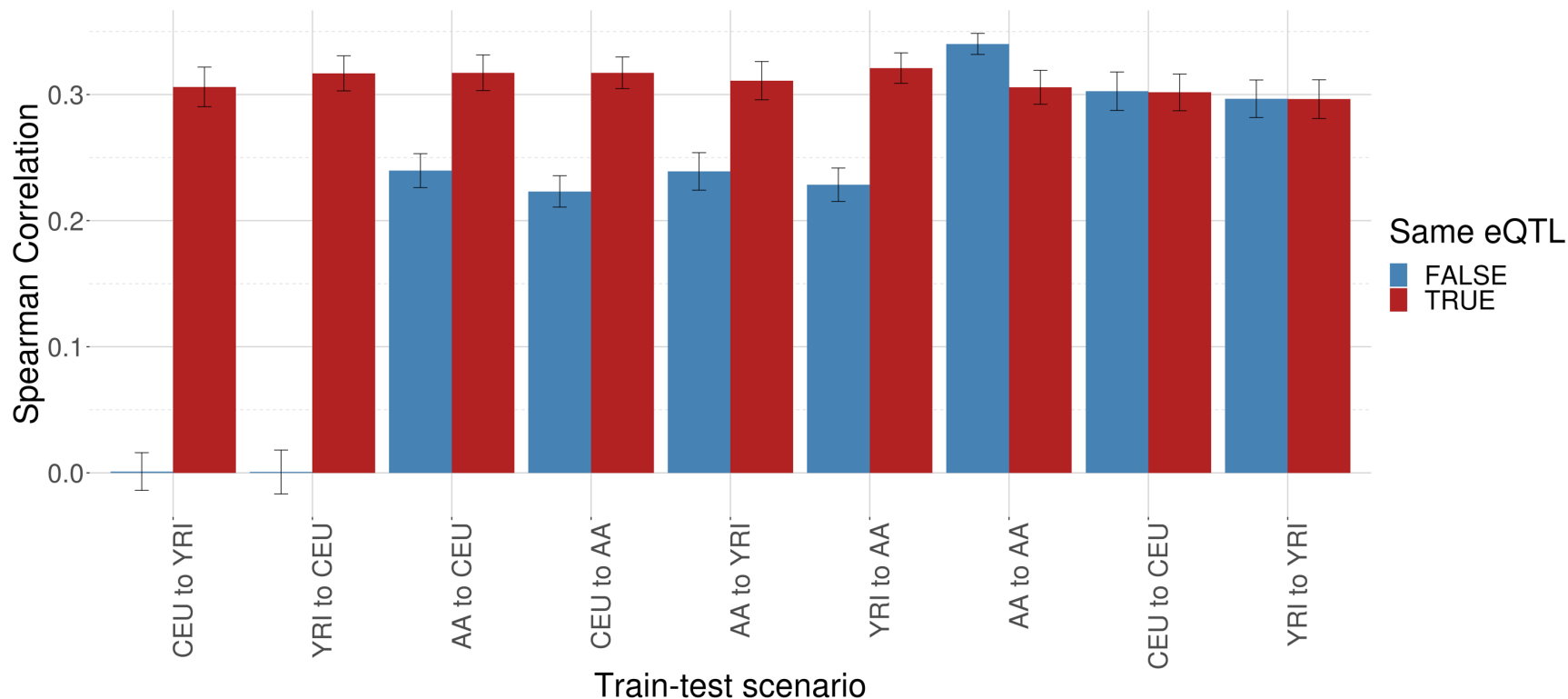


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Supplementary Figure 7: Correlations between predictions and simulated gene expression measurements from simulated populations across various proportions of shared eQTL architecture with 40 causal cis-eQTLs.

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### Crosspopulation correlations of predicted versus simulated gene expression Number of causal eQTL: 1

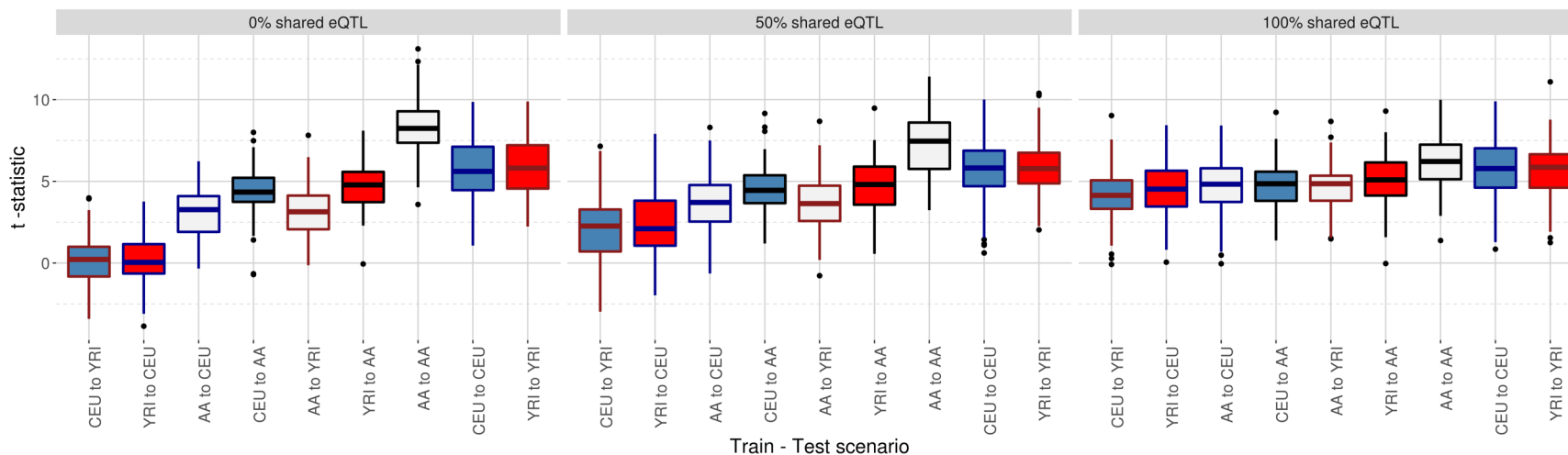


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1004 *Supplementary Figure 8: Mean correlations between predictions and simulated gene expression measurements from simulated*  
1005 *populations for a single causal cis-eQTL. For this simplified eQTL architecture, the ancestral populations (CEU and YRI) either share*  
1006 *the causal eQTL (TRUE) or not (FALSE). In the TRUE case, AA has 1 eQTL shared with CEU and YRI; in the FALSE case, it has 2 unique*  
1007 *eQTLs, one from each of CEU and YRI. Error bars denote 95% confidence intervals.*

Distributions of t-statistics from TWAS association tests in AA, CEU, and YRI

Expression imputed from AA, CEU, and YRI for  $k = 10$  eQTL per gene and heritability  $h^2 = 0.205$



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 1009 *Supplementary Figure 9: Distributions of t-statistics across various shared eQTL proportions for all nine train-test scenarios with 1000*  
 1010 *Genomes populations for a fixed TWAS effect size and fixed number of causal eQTLs. The labels are ordered from left to right from*  
 1011 *least shared ancestry (CEU to YRI, shared ancestry proportion 0) to most shared ancestry (YRI to AA, shared ancestry proportion 0.8),*  
 1012 *with train-test scenarios from a population into itself on the right of each panel. Increasing proportions of shared eQTLs yield*  
 1013 *stronger association statistics from cross-population predictions. Fully shared eQTL architectures yield consistently high power across*  
 1014 *populations. Median t-statistics increase as populations share more haplotypes, while association tests with gene expression*  
 1015 *predicted in the same population show consistently high power.*

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