S1 | APPENDIX: ADDITIONAL FIGURES AND TABLES

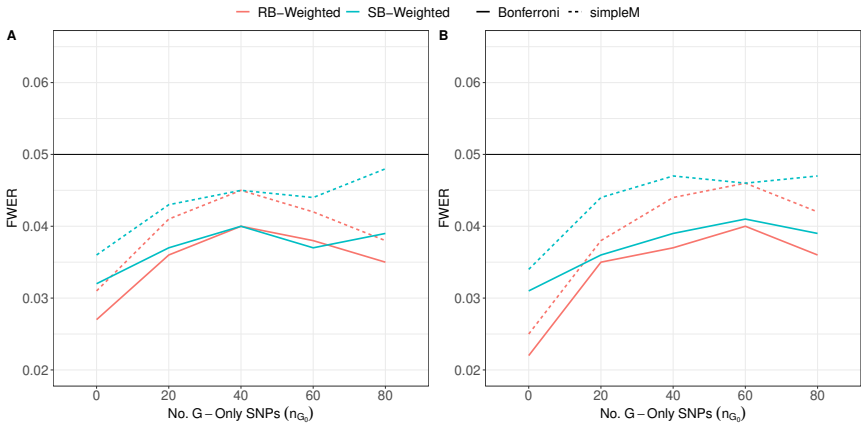

FIGURE S1 Estimated FWER when n_G G-only effects are present ($n_G \in \{10, 20, 40, 80\}$) each explaining $R^2_G \times 100\%$ of the variation in the quantitative trait. RB-Weighted: Rank-based two-step weighted testing with initial bin size 5 in Step 1; SB-Weighted: Significance-based weighted hypothesis testing with $\tau = (0, 5/25000, 15/25000, \ldots, 1)$ as the p-value cutoffs in Step 1. Bonferroni: Standard Bonferroni correction within bin; simpleM: The simpleM procedure proposed by Gao et al. (2008) with $C = 0.995$. Results are averaged over 5000 simulations. Panel A: $R^2_{G_{25}} = R^2_{G_{25}\times E} = R^2_G = 0.01$, $R^2_E = 0.005$, $N = 2,000$; Panel B: $R^2_{G_{25}} = R^2_{G_{25}\times E} = R^2_G = 0.005$, $R^2_E = 0.0025$, $N = 4,000$.

TABLE S1 Estimated FWER when n_G G-only effects are present ($n_G \in \{10, 20, 40, 80\}$) and the total amount of variation explained is fixed at 40% ($R^2_G = 0.4/n_G$). RB-Weighted: Rank-based weighted hypothesis testing proposed by Ionita-Laza et al. (2007) with $B_0 = 5$; SB-Weighted: Our proposed significance-based weighted hypothesis testing with $\tau = (0, 5/25000, 15/25000, \ldots, 1)$ as the p-value cutoffs. Bonferroni: Standard Bonferroni correction within bin; simple$M$: The simpleM procedure proposed by Gao et al. (2008) with $C = 0.995$. Results are averaged over 5000 simulations.

$n_G =$	10	20	40	80
$R^2_G =$	0.04	0.02	0.01	0.005
RB-Weighted				
Bonferroni	0.044	0.040	0.035	0.036
simple$M$	0.045	0.045	0.039	0.039
SB-Weighted				
Bonferroni	0.037	0.037	0.036	0.036
simple$M$	0.045	0.045	0.043	0.044

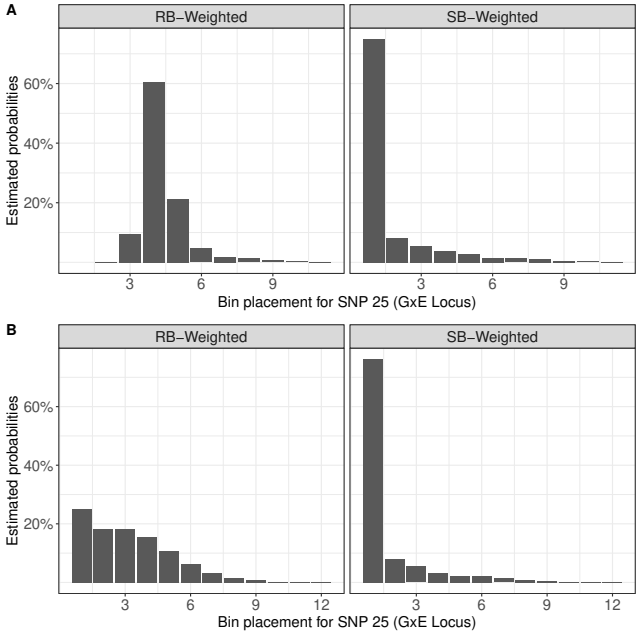

FIGURE S2 Bar chart of bin placement for the 25th SNP (i.e. $G \times E$ locus) in Step 1 over 5,000 simulations. RB-Weighted: Rank-based weighted hypothesis testing using with initial bin size B_0 in Step 1; SB-Weighted: Significance-based weighted hypothesis testing using $\tau = (0, B_0/25000, 3B_0/25000, \ldots, 1)$ as the p-value cutoffs in Step 1. Simulation parameters: $R^2_{G_{25}} = R^2_{G_{25}\times E}, R^2_E = 0.005, N = 2,000, M = 25,000$. Panel A) $n_G = 10$ G-only SNPs each with $R^2_G = 0.04$; Panel B: $n_G = 80$ G-only SNPs each with $R^2_G = 0.005$.

S2 | APPENDIX: SIMULATION SETUP

Let $\mathbf{G}$ be an $N \times M$ genotype matrix for N individuals and M SNPs. We partition the M SNPs into blocks of 50 SNPs such that $\mathbf{G} = [\mathbf{G}_1, \mathbf{G}_2, \ldots]$ where $\mathbf{G}_j$ is the jth block of $N \times 50$ SNPs. Each $\mathbf{G}_j$ is simulated based on sampled minor allele frequencies (MAFs) and LD-matrices from the 1000 Genomes Project. For clarity, we denote G_j as the jth SNP and $\mathbf{G}_j$ as the jth block. Quantitative traits are simulated according to the following linear model:

$$Y = \beta_{G_{25}} G_{25} + \beta_E E + \beta_{G_{25}\times E}(G_{25} \times E) + \sum_{j \in \mathcal{G}} \beta_{G_j} G_j + \epsilon,$$

where $\epsilon \sim \mathcal{N}(\mathbf{0}, \sigma^2_\epsilon I)$ for some $\sigma^2_\epsilon > 0$, E is the exposure variable (assumed to be binary) with $\Pr(E = 1) = 0.3$ and $\mathcal{G}$ corresponds to the set of SNPs that are only marginally associated with the outcome but have no $G \times E$ effect (G-only loci). By construction, the 25th SNP within block 1 ($\mathbf{G}_1$) has a true $G \times E$ effect on the outcome (i.e. the $G \times E$ locus). σ^2_ϵ was chosen to explain the remaining variance in the outcome after accounting for the variance explained by the causal $G \times E$ locus, the exposure, and the G-only loci across the different scenarios outlined in the main text.

The $M = 25,0000$ genotypes are simulated in blocks ($\mathbf{G} = [\mathbf{G}_1, \mathbf{G}_2, \ldots, \mathbf{G}_{500}]$) such that each block consists of 50 SNPs drawn from a mean zero multivariate normal distribution with variance-covariance matrix based on the LD pattern derived from a sampled region of the 1000 Genomes Project. The normal variates are then trichotomized into genotypes based on the 1000 Genomes Project derived MAFs assuming Hardy-Weinberg equilibrium. Thus, genotypes are correlated within a block but independent across blocks. Define $\mathbf{V} = [\mathbf{V}_1, \ldots, \mathbf{V}_{500}]$ and $\mathbf{f} = (\mathbf{f}_1, \ldots, \mathbf{f}_{500})$, where $\mathbf{V}_j$ is a 50×50 LD matrix and f_j is the corresponding vector of minor allele frequencies (MAF) of the 50 SNPs for $j = 1, \ldots, 500$. Both $\mathbf{V}_j$ and f_j are derived from a randomly sampled region from the 1000 Genomes Project. To avoid storing 500 unique values of $\mathbf{V}_j$ and f_j, we only store 50 unique values (randomly sampled regions), and recycled them such that the $(\mathbf{V}_1, \mathbf{f}_1) = (\mathbf{V}_{51}, \mathbf{f}_{51}) = (\mathbf{V}_{101}, \mathbf{f}_{101}), \ldots,$ $(\mathbf{V}_2, \mathbf{f}_2) = (\mathbf{V}_{52}, \mathbf{f}_{52}) = (\mathbf{V}_{102}, \mathbf{f}_{102}), \ldots, (\mathbf{V}_3, \mathbf{f}_3) = (\mathbf{V}_{53}, \mathbf{f}_{53}) = (\mathbf{V}_{103}, \mathbf{f}_{103}), \ldots$.

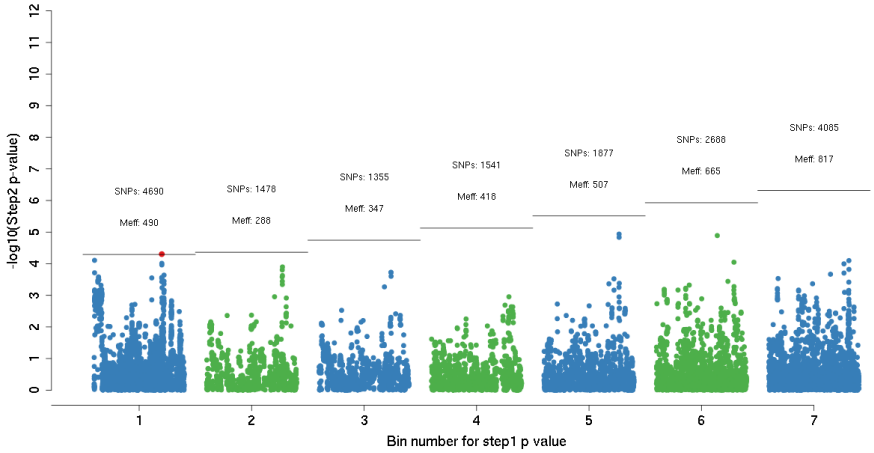

FIGURE S3 Results from the supplemental G-by-sex interaction scan using the SB-weighted testing approach applied to the FIGI consortium data ($N = 89,304$, $M = 7,809,725$) with relaxed bin thresholding. x-axis: Bins are based on the marginal outcome-gene association statistic (e.g. SNPs that have a Step 1 statistic $< 15/M$ are included in bin 1). y-axis: p-value of the $G \times E$ association provided by the GWIS (on the $-\log_{10}$ scale). Number of SNPs in each bin as well as the effective number of independent SNPs (Meff) using the simple$M$ approach are included. Horizontal line indicates the threshold the Step 2 p-value must cross to be statistically significant, maintaining the overall FWER=0.05. Only SNPs in the first 7 bins are shown in this figure.

To simulate allelic dosages, first let $\mathbf{X} = [\mathbf{X}_1, \mathbf{X}_2, \ldots, \mathbf{X}_{500}] \sim \mathcal{N}(\mathbf{0}, \mathbf{V})$ be a $N \times M$ matrix of mean zero normal variates with block correlation structure $\mathbf{V}$. Letting $G_{i,k}$ and $X_{i,k}$ be the ith row of the kth column of $\mathbf{G}$ and $\mathbf{X}$ ($i = 1, \ldots, N; k = 1, \ldots, M$), respectively, and f_k being the kth element of $\mathbf{f}$,

$$G_{i,k} = \begin{cases} 0 & \text{if } X_{i,k} < \Phi(f_k^2) \\ 1 & \text{if } \Phi(f_k^2) \leq X_{i,k} < \Phi(f_{1,j}^2 + 2f_k(1 - f_k)) \\ 2 & \text{if } \Phi(f_k^2 + 2f_k(1 - f_k)) \leq X_{i,k} \end{cases}$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution.

□