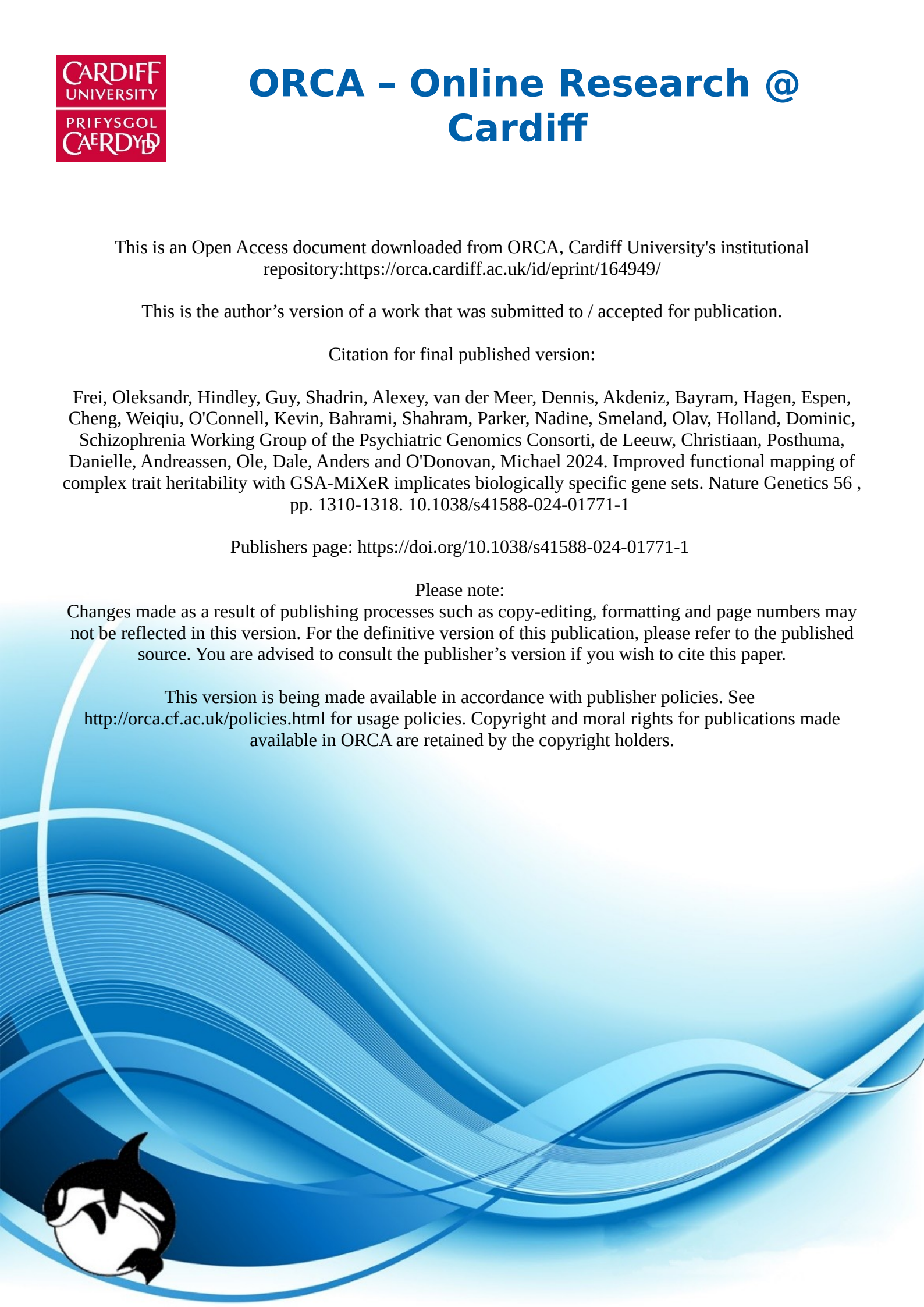

SUPPLEMENTARY NOTE 1.

The GSA-MiXeR model

Assuming a simple additive genetic model, a quantitative phenotype $y \in \mathbb{R}$ is modeled as a linear combination of genotype dosages g_i with weights β_i:

$$y = \sum_{i=1}^{\bar{M}} g_i \beta_i + \epsilon_y \ ,$$

where the index i runs over $\bar{M}$ genetic variants, weights $\beta_i \in R$ are known as *additive effects of allele substitution*, and the $\epsilon_y \sim N(0, 1-h^2)$ term is a normally distributed residual, which reflects contributions from the environment and non-additive genetic effects. The quantitative phenotype y is assumed to be centered and scaled, $E[y] = 0, \mathrm{Var}[y] = 1$, implying that the variance $\mathrm{Var}[\sum_i \beta_i g_i]$ is equal to each trait's SNP heritability, $h^2 \in [0, 1]$. Genotype dosages g_i are assumed to be centered but not scaled, i.e., $g_i \in \{0 - 2f_i, 1 - 2f_i, 2 - 2f_i\}$, where f_i is allele frequency of the i-th variant.

In the GSA-MiXeR model, we postulate a spike-and-slab prior on β_i:

$$\beta_i \sim (1-\pi_1)\delta_0 + \pi_1 N(0, \sigma_i^2) \ ,$$

where the $\pi_1 \in [0, 1]$ parameter defines weights in a two-component mixture distribution. π_1 is interpreted as the prior probability of a genetic variant to have a non-zero effect. $N(\mu, \sigma^2)$ denotes the Gaussian distribution with mean μ and variance σ^2, and δ_0 indicates a distribution with probability mass at 0 (the Dirac delta function). We will also let $N(x|\mu, \sigma^2) = \frac{1}{\sigma\sqrt{2\pi}} \exp(-\frac{(x-\mu)^2}{2\sigma^2})$ denote the probability density of a normal distribution at point x.

The parameter σ_i^2 defines the variance of effect sizes, with each variant having its own σ_i^2 value reflecting our prior information. The basline and full GSA-MiXeR models parametrizes σ_i^2 as follows:

$$\begin{aligned}
\sigma^2_{base,i} &= \Big(\sigma^2_{A,0} + \sum_{p=1}^{N_a} [i \in A_p]\sigma^2_{A,p}\Big)\Big(\sigma^2_{G,0} + [i \in G]\sigma^2_{G}\Big) H_i^S L_i^\ell, \\
\sigma^2_{full,i} &= \Big(\sigma^2_{A,0} + \sum_{p=1}^{N_a} [i \in A_p]\sigma^2_{A,p}\Big)\Big(\sigma^2_{G,0} + \sum_{q=1}^{N_g} [i \in G_q]\sigma^2_{G,q}\Big) H_i^S L_i^\ell.
\end{aligned} \tag{1}$$

Here, the $H_i = 2f_i(1-f_i)$ term denotes heterozygosity of the i-th variant, such that H_i^S term models allele frequency dependent architectures, with the S parameter controlling the effect size distribution with regards to allele frequency. Similarly, the L_i^ℓ term allows modeling linkage disequilibrium (LD) dependent architectures, where L_i denotes the total LD score of i-th variant, and ℓ denotes the parameter controlling the effect size distribution with regards to LD score. Each of the other two multiplicative factors in Eq. (1) control differential enrichment across genomic annotations and

across genes. The index p runs across annotation categories $\{A_1, A_2, \ldots, A_{Na}\}$, while the parameter $\sigma^2_{A,p}$ represents the contribution of the p-th annotation category to the variance of i-th genetic variant, given that the i-th variant belongs to the p-th category, as specified in Eq. (1) via the indicator variable $[i \in A_p]$, using square brackets notation to transform a logical statement from true or false into 1 and 0, respectively. If genetic variant i belongs to multiple annotation categories, the variances parameters of those annotations with be added together in an additive manner.

Similarly, in the full model, index q runs across genes $\{G_1, G_2, \ldots, G_{Ng}\}$, while the parameter $\sigma^2_{G,q}$ represents the contribution of q-th gene. In the baseline model SNPs from all genes are forced to have the same effect size variance parameter σ^2_G. The parameters $\Sigma^2_{A,0}$ and $\Sigma^2_{G,0}$ allow for non-zero variance σ^2_i for genetic variants that do not belong to any functional category or gene. In order to simplify the notation in the rest of this Supplementary Note we introduce a fake annotation category A_0 and a "gene" G_0 which both contain all SNPs. We also note that $\sigma^2_{base,i}$ model can be described by $\sigma^2_{full,i}$ model assuming $N_g = 1$, allowing us to derive all formulas just for $\sigma^2_{full,i}$. We'll use σ^2_i notation without specifying $base$ or $full$ subscripts to highligh the fact that formulas derived below are applicable both the base as well as to the full models.

On a technical note, GSA-MiXeR implementation allows G_q to iterate over gene-sets rather than over individual genes. The software also supports non-additive interaction of overlapping annotations or gene-sets, replacing the additive model:

$$\sum_{p=0}^{N_a} [i \in A_p] \sigma^2_{A,p} \quad \text{and} \quad \sum_{q=0}^{N_g} [i \in G_q] \sigma^2_{G,q} \ ,$$

with a "smooth-max" model defined by:

$$\left(\sum_{p=0}^{N_a} [i \in A_a] \sigma^{2p_a}_{A,p}\right)^{1/p_a} \quad \text{and} \quad \left(\sum_{q=0}^{N_G} [i \in G_g] \sigma^{2p_g}_{G,q}\right)^{1/p_g} \ ,$$

where the parameters p_a and p_g controls the "smooth-max" behavior for overlapping annotations and gene-sets, respectively. Note that the p_a and p_g parameters of the GSA-MiXeR are unrelated to the p notation used here to index annotation categories in the above formulas. By default, GSA-MiXeR implementation will use an additive model across overlapping annotations ($p_a = 1$) and across gene-sets ($p_g = 1$). Setting these parameters to e.g. $p_a = 5$ will closely resemble a model where only a single annotation with the largest variance parameter σ^2_a (the largest among all annotations containing variant i) will contribute to σ^2_i. Equivalently, setting $p_g = 5$ will trigger similar logic for overlapping gene-sets.

Log-likelihood computation ("full" z-score model)

To infer parameters of the GSA-MiXeR model we use z-scores (z_j) from GWAS summary statistics, where the index $j = 1, \ldots, M$ runs over GWAS tag SNPs (imputed or genotyped). Note that the set of GWAS tag SNPs is not necessarily the same as the

set of genetic variants used in modeling additive genetic effects β_i, with $i = 1, \ldots, \bar{M}$. In the GSA-MiXeR implementation, the set of genetic variants is formed by SNPs of the Haplotype Reference Consortia (HRC) reference panel, while a subset of HRC SNPs that are also present in GWAS summary statistics is used as a set of tag SNPs. Further details about QC procedures applied to HRC and GWAS variants for filtering low-quality SNPs are described in the Online Methods section of the manuscript. The following equations related additive effects of allele substitution β_i to z-scores from GWAS summary statistics.

Let $\hat{\beta}'_j$ be GWAS estimate of the marginal effect size for j-th tag SNP, assessed via univariate linear regression, and z_j be the corresponding z-score, $z_j = \hat{\beta}'_j / \hat{se}(\beta'_j)$. Then

$$\begin{aligned} z_j &= \delta_j + \epsilon_j, \\ \delta_j &= \sum_{i=1}^{\bar{M}} a_{ij}\beta_i, \ \textit{where } a_{ij} = \sqrt{N_j H_i} r_{ij}, \\ \epsilon_j &\sim \mathcal{N}(0, \sigma_0^2) \ , \end{aligned} \tag{2}$$

where N_j is the number of subjects with non-missing genotype information on j-th variant; $H_i = 2f_i(1-f_i)$ is the heterozygosity of i-th variant; $r_{ij} = corr(\mathbf{v_i}, \mathbf{v_j})$ is an LD allele count correlation between genotype vectors $\mathbf{v_i}$, and $\mathbf{v_j}$ (two column-vectors running across individuals, containing dosages g_i and g_j, respectively), parameter σ_0^2 accounts for non-polygenic inflation in GWAS z-scores, and ϵ_j denotes a normally distributed residual.

In the absence of covariates, the least square estimate $\hat{\beta}'_j$ can be expressed as

$$\hat{\beta}'_j = \frac{\mathbf{v_j^T y}}{\mathbf{v_j^T v_j}} = \beta_j + \sum_{i \neq j} \hat{\xi}_{ij}\beta_i + \frac{\mathbf{v_j^T e}}{\mathbf{v_j^T v_j}} = \sum_i \sqrt{\frac{H_i}{H_j}} r_{ij}\beta_i + \frac{\epsilon_j}{\sqrt{H_j N_j}} \ ,$$

where $\hat{\xi}_{ij} = \mathbf{v_i^T v_j} / \mathbf{v_j^T v_j} = \hat{\zeta}_{ij} / \hat{\zeta}_{jj}$, with $\hat{\zeta}_{ij} = \mathbf{v_i^T v_j}/N$ being an estimate of the covariance between i-th and j-th variants:

$$\hat{\zeta}_{ij} \simeq \sqrt{2f_i(1-f_i)}\sqrt{2f_j(1-f_j)} r_{ij} \ .$$

Here, the symbol "$\simeq$" denotes asymptotic equality as $n \to \infty$. Then using $\hat{se}(\beta'_j) = 1/\sqrt{H_j N_j}$ result in Eq. (2).

Let $\theta = \{\pi_1, \sigma_i^2, \sigma_0^2\}$ be the vector of parameters of the GSA-MiXeR model, where we simplify notation allowing each SNP to have its own σ_i^2 (but as described above, σ_i^2 is, in turn, parametrized as in Eq. (1)). We now introduce the latent variables $u_i \in \{0, 1\}$ given by a Bernoulli distribution, $p(u_i) = Bern(u_i|\pi_1)$, so that the full probabilistic

model can be written as follows:

$$
\begin{aligned}
&p(z_j, \vec{\beta}, \vec{u}|\theta) = p(z_j|\vec{\beta}, \theta) \cdot p(\vec{\beta}|\vec{u}, \theta) \cdot p(\vec{u}|\theta)) \ , \\
&p(z_j|\beta_1, \ldots, \beta_M, \theta) = N\Big(z_j \Big| \sum_{i=1}^{M} a_{ij}\beta_i, \sigma_0^2\Big) \ , \\
&p(\beta_i|u_i = 0, \theta) = N(\beta_i|0, 0) \ , \quad p(\beta_i|u_i = 1, \theta) = N(\beta_i|0, \sigma_i^2) \ , \\
&p(u_i|\theta) = Bern(u_i|\pi_1) \ .
\end{aligned}
$$

A tricky part here is that z_j may depend on multiple β_i. After observing $\vec{z} = (z_1, \ldots, z_M)^T$, we are aiming to do inference on θ by the maximum likelihood:

$$
p(\vec{z}|\theta) = \prod_j \int_u \int_\beta p(z_j, \vec{\beta}, \vec{u}, \theta) du d\beta \to \max_\theta
$$

In GSA-MiXeR, we approximate the above integral by drawing $K = 20,000$ samples from $p(u_i)$ for each latent variable u_i. For j-th variant and k-th sampling iteration, let U_{jk} be the set of variants with $u_i = 1$. For each realization of latent variables the distribution over $p(z_j|U_{jk}, \theta)$ became normal zero-mean distribution with a simple analytical formula for its variance:

$$
\begin{aligned}
&p(z_j|U_{jk}, \theta) = N(z_j|0, \Sigma_{jk}^2) \ , \\
&\Sigma_{jk}^2 = \sigma_0^2 + \sum_{i \in U_{jk}} a_{ij}\sigma_i^2 \ .
\end{aligned}
$$

We would like to point out that in practice it is impossible to store all elements of the a_{ij} matrix ($a_{ij} = \sqrt{N_j H_i} r_{ij}$) due to its size. Nevertheless, most of its elements are close to zero, and in GSA-MiXeR we use a sparse matrix (Compressed Sparse Row (CSR) format with delta-encoding and small integer compression) to store all a_{ij} with $r_{ij}^2 \geq r_{min}^2$, by default $r_{min}^2 = 0.01$, considering all pairs of variants within each chromosome regardless of the distance between them, but neglecting potential correlations between different chromosomes. However, the truncated parts of the LD structure (with $r_{min}^2 < 0.01$) may result in slightly inflated σ_0^2 parameter estimates. To reduce this effect, GSA-MiXeR computes partial LD scores $\tilde{L}_j = \sum_{i:\ r_{ij}^2 < r_{min}^2} a_{ij}^2$ and allow them to contribute to Σ_{jk}^2 under the assumptions of an infinitesimal model with a new variance parameter σ_{0L}^2 to be estimated from the data:

$$
\Sigma_{jk}^2 = \sigma_0^2 + \tilde{L}_j \sigma_{0L}^2 + \sum_{i \in U_{jk}} a_{ij}\sigma_i^2 \ .
$$

To clarify how this works, let's consider an infinitesimal model with $\pi_1 = 1$ (all additive genetic effects have non-zero variance) and $\sigma_i^2 = \sigma_\beta^2$ (equal variance across all genetic variants). Under these assumptions we can use the above formulas with $u_i = 1$ across all variants to derive $p(z_j|\theta) = N(z_j|0, \sigma_0^2 + \sum_i a_{ij}^2 \sigma_\beta^2)$. In this formula $L_j = \sum_i a_{ij}^2 = \sum_i N_j H_i r_{ij}^2$ plays a role of LD score, with a linear relationship between $E(z^2)$ and L_j under the assumptions of an infinitesimal model. In GSA-MiXeR, partial LD scores $\tilde{L}_j$ are, by default, computed across variants with $0.0001 \leq r_{ij}^2 < 0.01$, and the user

has the option to constraint σ^2_{0L} to 0, or let GSA MiXeR fit σ^2_{0L} parameter from the data. By default, σ^2_{0L} is set to zero, and this setting was used throughout all analyses in this work.

The final expression for log-likelihood in GSA-MiXeR is as follows:

$$\log L = \sum_j w_j \log p_j = \sum_j w_j \log \left(\frac{1}{K} \sum_k q(z_j; 0, \sigma^2_0 + \tilde{L}_j \sigma^2_{0L} + \sum_{i \in U_{jk}} a_{ij} \sigma^2_i) \right) , \quad (3)$$

where weights w_j are induced by random-pruning technique to avoid over-counting contribution from large LD blocks, and $q(z; 0, s^2) = \phi(z; 0, s^2) = \frac{1}{\sqrt{2\pi}s} e^{-z^2/2s^2}$ stands for the probability density function of centered normal distribution, except for z-scores that are very large. For large z-scores that exceed certain threshold $|z_j| \geq z_{max}$, the log-likelihood is computed based on right-censoring, i.e., with $q(z_j; 0, s^2) = 2\Phi(-z_{max}; 0, s^2) = erfc\left(\frac{z_{max}}{\sqrt{2}s}\right)$. A typical value for z_{max} is 5.45, which corresponds to conventional genome-wide significance threshold $\alpha = 5 \times 10^{-8}$.

Log-likelihood gradients

To maximize log-likelihood with regards to parameters θ, GSA-MiXeR employs the Adam algorithm, a stochastic gradient-based optimization, which requires a gradient of the log-likelihood with regard to all parameters. By inspecting Eq. (3) we observe that it is trivial to compute gradients with regards to σ^2_0, σ^2_{0L}, and σ^2_i:

$$\begin{aligned} \frac{\partial \log L}{\partial \sigma^2_i} &= \sum_j \frac{w_j}{K p_j} \sum_{k:\ i \in U_{jk}} q'_{jk} a^2_{ij} , \\ \frac{\partial \log L}{\partial \sigma^2_0} &= \sum_j \frac{w_j}{K p_j} \sum_k q'_{jk} , \\ \frac{\partial \log L}{\partial \sigma^2_{0L}} &= \sum_j \frac{w_j \tilde{L}_j}{K p_j} \sum_k q'_{jk} , \end{aligned} \quad (4)$$

where

$$\begin{aligned} q_{jk} &= q(z_j; 0, s^2), \quad \text{with} \quad s^2 = \sigma^2_0 + \tilde{L}_j \sigma^2_{0L} + \sum_{i \in U_{jk}} a_{ij} \sigma^2_i , \\ q'_{jk} &= \frac{\partial \phi(z_j; 0, s^2)}{\partial s^2} = \frac{z^2 - s^2}{2s^4} q_{jk} \ \text{ when } \ |z_j| < z_{max} , \ \text{ otherwise} \\ q'_{jk} &= \frac{\partial 2\Phi(-z_{max}; 0, s^2)}{\partial s^2} = \frac{z_{max} e^{\frac{z^2_{max}}{2s^2}}}{\sqrt{2\pi} s^3} = \frac{z_{max}}{s^2} \phi(z_{max}; 0, s^2) . \end{aligned}$$

Generally, s^2 in the above formulas should appear as s^2_{jk}, i.e., indexed by j and k; the indices that were omitted in the formulas above in favor of less heavy notation. When implemented in GSA-MiXeR software, these formulas result in a numeric vector with length $M + 2$, where the two last elements correspond to the σ^2_0 and σ^2_{0L} gradients, and the remaining elements corresponding to M gradients, i.e., one for each genetic

variant, with M typically being around 10^7. Interestingly, the joint computation of all these derivatives takes approximately the same time as computing the log-likelihood function, because for each σ_i^2 the gradient only depends on a smaller set of GWAS tag SNPs that are in LD with i. Another good analogy of this is the backpropagation of errors in neural networks, which also takes a similar time as computing a forward pass over the neural network.

To conclude the computation of log-likelihood gradients we need to consider all parameters of the GSA-MiXeR model that needs to be optimized. These parameters are as follows:

- π_1 - the polygenicity parameter;
- σ_i^2 - the variance parameter of each SNP, which in turn depend on S and ℓ (parameters of effect size distribution with regards to allele frequency and LD), $\sigma_{A,p}^2$ (a set of variance parameters, one for each annotation category) and $\sigma_{G,q}^2$ (a set of variance parameters, one for each gene);
- σ_0^2 - inflation parameter;
- σ_{0L}^2 - inflation capturing the truncated parts of the LD matrix.

To avoid having boundaries on these parameters during optimization, we further parametrize π_1 using the logistic function, $\pi_1(x) = \frac{e^x}{1+e^x}$, with x here being the actual parameter used during optimization; all non-negative variance parameters are further parametrized with an exponential function, $\sigma^2(A,p) = e^{x_p}$ and $\sigma^2(G,q) = e^{y_q}$; parameters S and ℓ are unbounded, and thus are used directly during optimization.

Now, we further re-parametrize σ_i^2 as follows, to reduce collinearity among parameters:

$$\sigma_i^2 = \frac{\sigma_\beta^2}{\pi_1}\Big(\sum_{p=0}^{N_a}[i \in A_p]e^{p_a x_p}\Big)^{\frac{1}{p_a}}\Big(\sum_{q=0}^{N_g}[i \in G_q]e^{p_g y_q}\Big)^{\frac{1}{p_g}}\frac{H_i^S}{\frac{1}{\bar{M}}\sum_t H_t^S}\frac{L_i^\ell}{\frac{1}{\bar{M}}\sum_t L_t^\ell}\,, \qquad (5)$$

where $t = 1, \ldots, \bar{M}$ runs across all SNPs. The above formula differs from Eq. (1) only by a factor $\frac{\sigma_\beta^2}{\pi_1}\frac{1}{\frac{1}{\bar{M}}\sum_t H_t^S}\frac{1}{\frac{1}{\bar{M}}\sum_t L_t^\ell}$ that is the same for all SNPs, thus it does not change the relative effect size distribution across genetic variants. Here we introduced a global σ_β^2 parameter which allows for simultaneously adjusting all σ_i^2 up or down, which plays a role if one fits the GSA-MiXeR model with constrained variance parameters for annotation categories and genes. Further, we divided all σ_i^2 by the polygenicty parameter π_1, making sure that the polygenicity parameter itself does not affect heritability estimate $h^2 = \sum_i \pi_i H_i \sigma_i^2$. Finally, we normalize the formula by mean H_i^S over genetic variants, and also by mean L_i^ℓ over genetic variants, so that changes in S and ℓ parameters also have a minimal effect on the heritability estimate. The idea behind the parametrization of Eq. (5) is that the heritability estimate $h^2 = \sum_i \pi_i H_i \sigma_i^2$ has a substantial impact on log-likelihood, and fine-tuning of other parameters that control intricate aspects of the genetic architecture is more robust when total heritability is constrained to a given value.

Now everything is set to finalize gradient computation.

The π_1 parameter is treated specially, in a sense that $\frac{\partial \log L}{\partial \pi_1}$ is estimated numerically using finite difference

$$\frac{\log L(x+\Delta x) - \log L(x-\Delta x)}{2x},$$

where step Δx changes adaptively depending on the iteration, and is set to the value used in the Adam algorithm.

We already derived gradients for σ_0^2 and σ_{0L}^2, except for the parametrization $\sigma_0^2(x)$ which uses an exponential function, $\sigma_0^2(x) = e^x$, so we need to use corresponding gradient with regards to x, i.e., $\frac{\partial \log L}{\partial x} = \frac{\partial \log L}{\partial \sigma_0^2} \times \frac{\partial \sigma_0^2(x)}{\partial x} = \sigma_0^2 \frac{\partial \log L}{\partial \sigma_0^2}$, and similarly for σ_{0L}^2.

All of the remaining parameters $(S, \ell, \sigma_\beta^2(x), \sigma_{A,p}^2(x_p), \sigma_{G,q}^2(y_q))$ enter into the log-likelihood only via σ_i^2, thus we will now derive $\frac{\partial \sigma_i^2}{\partial S}$, $\frac{\partial \sigma_i^2}{\partial \ell}$, $\frac{\partial \sigma_i^2}{\partial x}$, $\frac{\partial \sigma_i^2}{\partial x_p}$, $\frac{\partial \sigma_i^2}{\partial y_q}$, and then calculate the final gradient as follows:

$$\frac{\partial \log L}{\partial S} = \sum_i \frac{\partial \log L}{\partial \sigma_i^2} \frac{\partial \sigma_i^2}{\partial S},$$

and similarly for all other parameters.

Starting with $\frac{\partial \log L}{\partial S}$ and $\frac{\partial \log L}{\partial \ell}$, let us introduce shorthand notations $T(S) = \sum_t H_t^S / \bar{M}$ and $T(\ell) = \sum_t L_t^\ell / \bar{M}$. Then

$$\Big(\frac{H_i^S}{T(S)}\Big)' = \frac{\frac{\partial H_i^S}{\partial S} T(S) - H_i^S T'(S)}{T^2(S)} = \frac{H_i^S}{T(S)} \frac{(\log H_i) T(S) - \big(\sum_t (\log H_t) H_t^S / M\big)}{T(S)}.$$

Hence

$$\frac{\partial \sigma_i^2}{S} = \sigma_i^2 \frac{T(S) \log H_i - \big(\sum_t (\log H_t) H_t^S / \bar{M}\big)}{T(S)},$$

and similarly

$$\frac{\partial \sigma_i^2}{\ell} = \sigma_i^2 \frac{T(\ell) \log L_i - \big(\sum_t (\log L_t) L_t^\ell / \bar{M}\big)}{T(L)}.$$

Note that both $T(S)$, $T(\ell)$ as well as $\sum_t (\log H_t) H_t^S$ and $\sum_t (\log L_t) L_t^\ell$ are independent of i, thus computation of these derivatives takes linear time with regards to the number of variants M.

Turning to $\sigma_{A,p}^2$ and $\sigma_{G,q}^2$, which are in turn parameterized by exponential functions $\sigma_{A,p}^2(x_p) = e^{x_p}$ and $\sigma_{G,q}^2(y_q) = e^{y_q}$, let us first consider a "smooth-max" function $F(x_1, \ldots, x_N) = \Big(\sum_{u=1}^N e^{p x_u}\Big)^{\frac{1}{p}}$ and explore the derivative $\frac{\partial F}{\partial x_t}$:

$$\frac{\partial F(x_1, \ldots, x_N)}{x_t} = \frac{1}{p}\big(\sum_u e^{p x_u}\big)^{\frac{1}{p}-1} p e^{p x_t} = F(x_1, \ldots, x_N)^{1-p} e^{p x_t} = F(x_1, \ldots, x_N) \frac{e^{p x_t}}{\sum_u e^{p x_u}}.$$

As such,

$$\frac{\partial \sigma_i^2}{\partial x_p} = \sigma_i^2 \frac{[i \in A_p] e^{p_a x_p}}{\sum_u [i \in A_u] e^{p_a x_u}} = \sigma_i^2 \frac{[i \in A_p] \sigma_{A,p}^{2p}}{\sum_u [i \in A_u] \sigma_{A,u}^{2p_a}}.$$

In matrix form, $\frac{\partial \sigma_i^2}{x_p}$ follows the same sparsity structure as $[i \in A_p]$ matrix with $\bar{M}$ rows (one row per SNP) and N_a columns (one column per annotation), with each row of this matrix being multiplied by $\sigma_i^2 / \sum_u [i \in A_u] \sigma_{A,u}^{2p_a}$ value (note this value only depends on i, but not on annotation p), and each column is multiplied by $\sigma_{A,p}^{2p_a}$ (a value that only depends on annotation p, but not on i). Such row-wise and column-wise multiplications can be efficiently implemented using matrix-matrix products with a diagonal matrix. Also, note that the "smooth-max" function, being also a $||x||_p$ p-norm, scales linearly with regard to the scale of its argument, so we are free to re-scale σ_u^2 by dividing it by its mean to ensure numeric stability even with single precision float-point numbers.

Similarly to $\frac{\partial \sigma_i^2}{\partial x_p}$, for the genes we can derive that

$$\frac{\partial \sigma_i^2}{\partial y_q} = \sigma_i^2 \frac{[i \in G_q] \sigma_{G,q}^{2p}}{\sum_u [i \in G_u] \sigma_{G,u}^{2p_g}} \ .$$

And finally, for the σ_β^2 that is also parametrized by an exponential function $\sigma_\beta^2(x) = e^x$, we have $\frac{\partial \sigma_i^2}{\partial x} = \sigma_i^2$. This concludes all pieces needed for efficient gradient computation of the log-likelihood function with regard to the parameters of the GSA-MiXeR model.

Hessian matrix of the log-likelihood function

From equations Eq. (1) (heritability model) and Eq. (3) (log-likelihood function) one can derive formulas for computing the Hessian matrix of the log-likelihood function with respect to all $\sigma_{G,q}^2$ parameters ($q = 1, \ldots, N_g$), i.e. the $\left\{ \frac{\partial^2 \log L}{\partial \sigma_{G,q1}^2 \partial \sigma_{G,q2}^2} \right\}$ matrix. The formulas for $\frac{\partial^2 \log L}{\partial \sigma_{A,p1}^2 \partial \sigma_{A,p2}^2}$, i.e. the Hessian matrix with respect to $\sigma_{A,p}^2$ parameters, are largely equvalent, as $\sigma_{A,p}^2$ and $\sigma_{G,q}^2$ in Eq. (1) appear a similar way. Below we show how under relevant conditions the GSA-MiXeR log-likelihood function can be re-written as

$$\log L = \sum_j w_j \log q(z_j; 0, B_j^2), \text{ where } B_j^2 = \sigma_0^2 + \sum_{q=0}^{N_g} v_{jq} \sigma_{G,q}^2, \tag{6}$$

and terms v_{jq} are defined as follows: $v_{jq} = \sum_{i=1}^{\bar{M}} [i \in G_q] a_{ij} \Big(\sum_{p=0}^{N_a} [i \in A_p] \sigma_{A,p}^2 \Big) H_i^S L_i^\ell$. The v_{jq} elements do not depend on the $\sigma_{G,q}^2$ parameters, thus after differentiation one obtains the following expression for the elements of the Hessian matrix:

$$\frac{\partial^2 \log L}{\partial \sigma_{G,q1}^2 \partial \sigma_{G,q2}^2} = \sum_j w_j \frac{v_{jq_1} v_{jq_2} (B_j^2 - 2 z_j^2)}{2 B_j^6} \tag{7}$$

Eq. (7) is valid both for the off-diagonal ($q_1 \neq q_2$) and the diagonal ($q_1 = q_2$) elements.

The matrix $V = \{v_{jq}\}$ can be computed efficiently as a matrix-matrix multiplication of two sparse matrices: matrix $\{a_{ij}\}$ which has same sparsity structure as the LD matrix, and $\{[i \in G_q] S_i\}$ matrix annotating SNPs to genes, which is highly sparse each gene contains only a small number of SNPs. The term $S_i = \Big(\sum_{p=0}^{N_a} [i \in A_p] \sigma_{A,p}^2 \Big) H_i^S L_i^\ell$

that is part of the $[i \in G_q]S_i$ expression indicates that all elements in i-th row of the $\{[i \in G_q]\}$ matrix need to be multiplied by S_i - an operation which can be achieved as matrix-matrix multiplicaton of a diagonal matrix made of S_i elements (i.e. $diag(S_i)$), and the sparse matrix $\{[i \in G_q]\}$. Similarly, the Hessian matrix defined by Eq. (7) can be computed by matrix-matrix multiplication $V'TV$, where V' is a matrix transpose of V, and $T = \text{diag}(w_j \frac{B_j^2 - 2z_j^2}{2B_j^6})$ is a diagonal matrix.

The above computations did not account for covariance in the errors of $\sigma^2_{G,q}$ and $\sigma^2_{A,p}$ estimates, i.e. we ignored the $\frac{\partial^2 \log L}{\partial \sigma^2_{G,q} \partial \sigma^2_{A,p}}$ term of the Hessian matrix. Additionally, the formulas were derrived specifically for the base and the full GSA-MiXeR models as configured in our main and exploratory analyses, applying $\pi_1 = 1$ assumption (so that the log-likelihood expression was accurate already with a single sampling iteration, $K = 1$), $\sigma^2_{0L} = 0$ (for the parameter which captures inflation due to the truncation of the LD matrix), disable "right-censoring" feature (or, equivalently, assume a large enough value of the z_{max} parameter), and use $p_a = 1$ and $p_g = 1$ parameters (additive contribution from overlaping genes and functional annotations, without modeling "smooth-max" model). We also introduced the $S_i = \Big(\sum_{p=0}^{N_a}[i \in A_p]\sigma^2_{A,p}\Big) H_i^S L_i^\ell$ term so that the heritability model can be expressed as $\sigma_i^2 = S_i \Big(\sum_{q=0}^{N_g}[i \in G_q]\sigma^2_{G,q}\Big)$; subsequently, the log-likelihood function can be written as follows:

$$\log L = \sum_j w_j \log p_j = \sum_j w_j \log q\Big(z_j; 0, \sigma_0^2 + \sum_{i=1}^{\bar{M}} \sum_{q=0}^{N_g} [i \in G_q] a_{ij} S_i \sigma^2_{G,q}\Big) \ ,$$

where $q(z; 0, s^2) = \phi(z; 0, s^2) = \frac{1}{\sqrt{2\pi}s} e^{-z^2/2s^2}$ stands for the probability density function of centered normal distribution. Final formulas for the Hessian matrix (Eq. (7)) are derived from the above $\log L$ expression by applying standard differentiation rules.

Standard errors exceeding 5 times the respective point estimate were capped at this value, in order to limit the detrimental effect of erroneously large SE estimates of individual genes on the gene-sets. Hessian-based SEs are derived from the Taylor series expansion of the log-likelihood function around the MLE point, thus from a theoretical standpoint they are only valid locally, i.e. when SEs are "small enough"; to this end, capping SEs at no more than 5-times the point estimate as per our empirical heuristic is unlikely to make them worse. Second, hessian-based SEs are only valid in the interior of the parameter space and may fail next to its boundary - which may happen in the case of the GSA-MiXeR model if the σ_g^2 parameter estimate for a particular gene is approaching zero. Our real-data analysis is unlikely to be affected by either of these issues, as we are already filtering genes on positive AIC values, which implies sufficient curvature of the log-likelihood around the MLE point and justify hessian-based SEs estimation.

Gaussian approximation ("fast" z-score model)

In this section we will assume $\beta_i \sim (1 - \pi_i)N(0, 0) + \pi_i N(0, \sigma_i^2)$, allowing for π_i to vary across SNPs, in addition to varying σ_i^2 across SNPs as modeled previously.

Lemma. Raw moments of $E\beta_i^2$ and $E\beta_i^4$ are as follows:

$$\begin{aligned} E\beta_i^2 &= \pi_i\sigma_i^2 \ , \\ E\beta_i^4 &= 3\pi_i\sigma_i^4 \ . \end{aligned} \tag{8}$$

Let X_i be a set of independent random variables, and $Y = \sum_i \pi_i X_i$ be mixture distribution. Then all raw moments EY^n are given by a linear combination $\sum_i \pi_i EX_i^n$. This trivial fact follows directly from the definition of the expectation operator: $EY^n = \int_{-\infty}^{\infty} x^n dF_Y(x) = \int_{-\infty}^{\infty} x^n \sum_i \pi_i dF_{X_i}(x) = \sum_i \pi_i EX_i^n$. ■

Lemma. Let $\delta_j = \sum_i a_{ij}\beta_j$, where $a_{ij} = \sqrt{N_j}\sqrt{H_i}r_{ij}$. Then raw moments of $E\delta_j^2$ and $E\delta_j^4$ are as follows:

$$\begin{aligned} E\delta_j^2 &= \sum_i a_{ij}^2 E\beta_i^2 = \sum_i a_{ij}^2 \pi_i\sigma_i^2 \ , \\ E\delta_j^4 - 3(E\delta_j^2)^2 &= \sum_i a_{ij}^4 \Big(E\beta_i^4 - 3(E\beta_i^2)^2 \Big) = \sum_i 3a_{ij}^4 \pi_i(1-\pi_i)\sigma_i^4 \ . \end{aligned} \tag{9}$$

The first equation $E\delta_j^2 = \sum_i a_{ij}^2 E\beta_i^2$ is simply because β_i are independent zero-mean random variables.

Let A_i and B_i be some arbitrary expressions. Then $(\sum_i B_i)^2 = \sum_i B_i^2 + 2\sum_{i<j} B_i B_j$, and $(\sum_i A_i)^4 = \sum_i A_i^4 + 6\sum_{i<j} A_i^2 A_j^2 + \cdots$, where omitted terms contain at least one odd power of A_i. Consequently, if A_i are independent zero-mean random variables, then $E[(\sum_i A_i)^4] = E[\sum_i A_i^4 + 6\sum_{i<j} A_i^2 A_j^2] = \sum_i E[A_i^4] + 6\sum_{i<j} E[A_i^2]E[A_j^2]$, where the square brakets in $E[x]$ notation define the argument of the expectancy operator in cases when Ex notation becames ambiguous. Using the above expression for $(\sum_i B_i)^2$ with $B_i = E[A_i^2]$, we get $2\sum_{i<j} E[A_i^2]E[A_j^2] = (\sum_i E[A_i^2])^2 - \sum_i (E[A_i^2])^2$. Therefore,

$$E[(\sum_i A_i)^4] = \sum_i E[A_i^4] + 3\Big((\sum_i E[A_i^2])^2 - \sum_i (E[A_i^2])^2 \Big) \ .$$

Replacing $(\sum_i E[A_i^2])$ with $E[(\sum A_i)^2]$, we get

$$E[(\sum_i A_i)^4] - \Big(E[(\sum A_i)^2] \Big)^2 = \sum_i \Big(E[A_i^4] - 3(E[A_i^2])^2 \Big) \ .$$

Using expression $A_i = a_{ij}\beta_i$, we get

$$E\delta_j^4 - 3(E\delta_j^2)^2 = \sum_i a_i^4 \Big(E\beta_i^4 - 3(E\beta_i^2)^2 \Big) \ . \quad ■$$

Lemma. Let A and B be two numeric values, $\tilde{\delta}_j = p_0 N(0,0) + p_1 N(0,s^2)$ so that

$$p_0 = \frac{B}{B+3A^2} \ , \quad p_1 = \frac{3A^2}{B+3A^2} \ , \quad s^2 = \frac{B+3A^2}{3A} \ . \tag{10}$$

Then, by trivial computation, $E\tilde{\delta}_j^2 = A$, and $E\tilde{\delta}_j^4 - 3(E\tilde{\delta}_j^2)^2 = B$. ■

Substituting $A_j \equiv E\delta_j^2 = \sum_i a_{ij}^2 \pi_i\sigma_i^2$ and $B_j \equiv E\delta_j^4 - 3(E\delta_j^2)^2 = \sum_i 3a_{ij}^4 \pi_i(1-\pi_i)\sigma_i^4$ into Eq. (10) yields explicit formulas defining p_{j0}, p_{j1} and s_j^2 for the distribution $\tilde{\delta}_j =$

$p_{0j}N(0,0) + p_{1j}N(0, s_j^2)$ which approximates true distribution for $\delta_j = \sum_i a_{ij}\beta_i$, in a sense that $E\delta_j^2 = E\tilde{\delta}_j^2$ and $E\delta_j^4 = E\tilde{\delta}_j^4$. From these expressions, one can derive explicit formulas for computation of the gradients $\frac{\partial p(z_j)}{\partial \pi_i}$ and $\frac{\partial p(z_j)}{\partial \sigma_i^2}$.

The log-likelihood optimization in GSA-MiXeR utilizes the Adam algorithm defined in (1), with specific details of its application explained in Online Methods section.

Algorithm 1: Adam algorithm for GSA-MiXeR inference

Input: $\alpha_1, \ldots, \alpha_N$: Stepsize for each epoch
Input: $\beta_1, \beta_2 \in [0, 1)$: Exponential decay rates for the moment estimates
Input: $f(\theta, X)$: Stochastic objective function with parameters θ on batch X
Input: θ_0: Initial parameter vector
$m_0 \leftarrow 0$ (Initialize 1st moment vector)
$v_0 \leftarrow 0$ (Initialize 2nd moment vector)
$\leftarrow 0$ (Initialize timestep)
for n ***in*** $1, \ldots, N$ **do**
  for X ***in*** $shuffle(X_1, \ldots, X_{22})$ **do**
    $t \leftarrow t + 1$
    $g_t \leftarrow \nabla_\theta f_t(\theta_{t-1}, X)$ (Get gradients w.r.t. stochastic objective at time t)
    $m_t \leftarrow \beta_1 \cdot m_{t-1} + (1 - \beta_1) \cdot g_t$ (Update biased 1st moment estimate)
    $v_t \leftarrow \beta_2 \cdot v_{t-1} + (1 - \beta_2) \cdot g_t^2$ (Update biased 2nd raw moment estimate)
    $\hat{m}_t \leftarrow m_t / (1 - \beta_1^t)$ (Compute bias-corrected 1st moment estimate)
    $\hat{v}_t \leftarrow v_t / (1 - \beta_2^t)$ (Compute bias-corrected 2nd raw moment estimate)
    $\theta_t \rightarrow \theta_{t-1} - \alpha_n \cdot \hat{m}_t / (\sqrt{\hat{v}_t} + \epsilon)$ (Update parameters)
  end
end
Result: θ_t (Resulting parameters)

Simulations with pre-defined levels of fold enrichment

Let G and g be two regions in a genome, and g be a subset of G. For example, G can be the set of all genes, while g be a subset of genes. Let H_G and H_g be the total heterozigosity (i.e. $2p(1-p)$ where p is minor allele frequency) combined across all causal variants in regions G and g, respectively.

Let effect size variance for causal SNPs in $G \backslash g$ (i.e. set difference "G minus g") be σ_G^2, while effect size variance for SNPs in g be $(\sigma_G^2 + \sigma_g^2)$. Let's also assume that there are no causal variants outside G. Then, the total heritability of a trait simulated according to the above model is $h^2 = H_G\sigma_G^2 + H_g\sigma_g^2$. Under the null model (no enrichment) we let σ_{null}^2 be the effect size variance for causal variants in G. Then the heritability under the null model is $h^2 = H_G\sigma_{null}^2$.

Heritability within the region g can be expressed as $h^2(g) = H_g(\sigma_g^2 + \sigma_G^2)$ (under full model) or $H^2(g) = H_g\sigma_{null}^2$ (under null model). Therefore, fold enrichment of heritability is expected to be $f(g) = (\sigma_g^2 + \sigma_G^2)/\sigma_{null}^2$.

Using the above equations, and assuming that H_g, H_G, h^2 and $f(g)$ are known param-

eters one can derive that

$$\begin{aligned} \sigma_G^2 &= h^2 \frac{H_G - f(g)H_g}{H_G(H_G - H_g)} \\ \sigma_G^2 + \sigma_g^2 &= h^2 f(g)/H_G, \end{aligned} \tag{11}$$

(under a constraint that $f(g)$ does not exceed H_G/H_g ratio). We will use the above formulas to simulate a trait with pre-defined heritability and fold enrichment in a region g over a wider region G. Note the ratio has the following formula:

$$\frac{\sigma_G^2 + \sigma_g^2}{\sigma_G^2} = f(g)\frac{H_G - H_g}{H_G - f(g)H_g}$$

Finally, $h^2(g) = H_g(\sigma_g^2 + \sigma_G^2) = h^2 f(g)H_g/H_G$. This last formula can be applied also to individual genes within g, which can be written as $\sum_i H_i\beta_i^2$ across causal SNPs. After drawing β_i from normal distribution we can re-scale β_i by a constant factor to achieve the expected $h^2(g)$.

Extended authors list: *Mapping genomic loci implicates genes and synaptic biology in schizophrenia*, Nature, 2022.

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