Title
Correction: Improved Detection of Common Variants Associated with Schizophrenia and Bipolar Disorder Using Pleiotropy-Informed Conditional False Discovery Rate.

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Correction: Improved Detection of Common Variants Associated with Schizophrenia and Bipolar Disorder Using Pleiotropy-Informed Conditional False Discovery Rate


Incorrect mathematical definition of the conjunction FDR in the section ‘Conjunction statistics—test of association with both phenotypes’

Under the sub-heading of ‘Conjunction statistics—test of association with both phenotypes’ in the ‘Materials and Methods’ section of the manuscript, there are errors in the mathematical definition of the conjunction FDR. The authors have provided an updated version here with corrections to the text in bold:

In order to identify which of the SNPs were associated with schizophrenia and bipolar disorder we used a conjunction FDR procedure similar to that described for p-value statistics in Nichols et al. [45]. This minimizes the effect of a single phenotype driving the common association signal. Conjunction FDR is defined as the posterior probability that a given SNP is null for either phenotype or both phenotypes simultaneously when the p-values for both phenotypes are as small or smaller than the observed p-values. Formally, conjunction FDR is given by

\[
\text{FDR}_{\text{SCZ&BD}}(p_1, p_2) = \frac{\pi_0 F_0(p_1, p_2) + \pi_1 F_1(p_1, p_2) + \pi_2 F_2(p_1, p_2)}{F(p_1, p_2)},
\]

where \(\pi_0\) is the \textit{a priori} proportion of SNPs null for both SCZ and BD simultaneously and \(F_0(p_1, p_2)\) is the joint null cdf, \(\pi_1\) is the \textit{a priori} proportion of SNPs non-null for SCZ and null for BD with \(F_1(p_1, p_2)\) the joint cdf of these SNPs, and \(\pi_2\) is the \textit{a priori} proportion of SNPs non-null for BD and null for SCZ, with joint cdf \(F_2(p_1, p_2)\). \(F(p_1, p_2)\) is the joint overall mixture cdf for all SCZ and BD SNPs.

Conditional empirical cdfs provide a model-free method to obtain conservative estimates of Eq (5). This can be seen as follows. Estimate the conjunction FDR by

\[
\text{FDR}_{\text{SCZ&BD}} = \max \left\{ \text{FDR}_{\text{SCZ|BD}}, \text{FDR}_{\text{BD|SCZ}} \right\},
\]

where \(\text{FDR}_{\text{SCZ|BD}}\) and \(\text{FDR}_{\text{BD|SCZ}}\) (the estimated conditional FDRs described above) are conservative (upwardly biased) estimates of Eq. [5]. Thus, Eq (7) is a conservative estimate of max \(\frac{p_1}{F(p_1|p_2)}\) p-values will tend to be smaller than predicted from the uniform distribution, so that
F₁(p₁) ≥ p₁ and F₂(p₂) ≥ p₂. Then

\[
\max \{ p₁F₂(p₂)/F(p₁, p₂), p₂F₁(p₁)/F(p₁, p₂) \} \\
≥ \left[ \pi_0 + \pi_1 + \pi_2 \right] \max \{ p₁F₂(p₂)/F(p₁, p₂), p₂F₁(p₁)/F(p₁, p₂) \} \\
≥ \left[ \pi_0 p₁ p₂ + \pi_1 p₂ F₁(p₁) + \pi_2 p₁ F₂(p₂) \right] / F(p₁, p₂).
\]

Under the assumption that SNPs are independent if one or both are null, reasonable for disjoint samples, this last quantity is precisely the conjunction FDR given in Eq (6). Thus, Eq (7) is a conservative model-free estimate of the conjunction FDR. We present a complementary model-based approach to estimating conjunction FDR in the S1 Text.

We assigned the conjunction FDR values by interpolation into a bi-directional two-dimensional look-up table (S3 Fig). All SNPs with conjunction FDR < 0.05 (bidirectional association, i.e. association with SCZ given association with BD (condFDR < 0.05) and association with BD given association with SCZ (condFDR < 0.05)) are listed and sorted in each LD block. We defined the most significant SNP in each LD block based on the minimum conjFDR. All independent loci are listed consecutively, and the same locus number are used as in the condFDR < 0.05 results (Table 1). Chromosome (Chr). Z-scores for each pleiotropic locus are provided, with minor allele (A1) and major allele (A2). All data were first corrected for genomic inflation. †Same locus identified in previous BD or SCZ genome-wide association studies.

Supporting Information

S3 Fig. Conjunction FDR bi-directional 2-D Look-up table.

(DOC)
S1 Text. Supporting statistical methods.
(DOC)

Reference