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CORRECTION

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

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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

$$FDR_{SCZ\&BD}(p_1, p_2) = \pi_0 F_0(p_1, p_2) / F(p_1, p_2) + \pi_1 F_1(p_1, p_2) / F(p_1, p_2) + \pi_2 F_2(p_1, p_2) / F(p_1, p_2), \quad (6)$$

where π_0 is the *a priori* proportion of SNPs null for both SCZ and BD simultaneously and $F_0(p_1, p_2)$ is the joint null cdf, π_1 is the *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 π_2 is the *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 (6). This can be seen as follows. Estimate the conjunction FDR by

$$FDR_{SCZ\&BD} = \max \{ FDR_{SCZ|BD}, FDR_{BD|SCZ} \} \quad (7)$$

where $FDR_{SCZ|BD}$ and $FDR_{BD|SCZ}$ (the estimated conditional FDRs described above) are conservative (upwardly biased) estimates of Eq. [5]. Thus, Eq (7) is a conservative estimate of $\max \{ p_1 / F(p_1 | p_2), p_2 / F(p_2 | p_1) \} = \max \{ p_1 F_2(p_2) / F(p_1, p_2), p_2 F_1(p_1) / F(p_1, p_2) \}$, with $F_1(p_1)$ and $F_2(p_2)$ the marginal non-null cdfs of SNPs for SCZ and BD, respectively. For enriched samples, p-values will tend to be smaller than predicted from the uniform distribution, so that



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Table 3. Conjunction FDR; pleiotropic loci in SCZ and BD (SCZ&BD).

locus	SNP	neighbor gene	Chr	A1	A2	conjfdr BD&SCZ	z-score BD	z-score SCZ
1	rs2252865	<i>RERE</i>	1p36.23	T	C	0.030	3.696	3.494
2	rs4650608	<i>IFI44</i>	1p31.1	T	C	0.043	3.289	3.711
4	rs11205362	<i>PRP3</i>	1q21.1	G	A	0.033	3.404	3.262
8	rs9834970	<i>TRANK1</i>	3p22.2	C	T	0.027	3.470	3.965
9	rs4687657	<i>ITIH4†</i>	3p21.1	G	T	0.028	3.787	3.781
11	rs3134942	<i>NOTCH4†</i>	6p21.3	G	T	0.048	3.251	3.571
15	rs3757440	<i>MAD1L1</i>	7p22	A	G	0.031	3.490	3.425
20	rs10883757	<i>TRIM8</i>	10q24.3	C	T	0.040	3.261	3.046
22	rs1006737	<i>CACNA1C†</i>	12p13.3	A	G	0.022	4.553	4.137
26	rs961196	<i>TTC7B</i>	14q32.11	C	T	0.044	3.618	2.960
28	rs12708772	<i>SHISA9</i>	16p13.12	C	T	0.044	3.294	2.955
31	rs1800359	<i>ZNF276</i>	16q24.3	A	G	0.035	3.329	3.165
33	rs159788	<i>BC039673</i>	20p13	G	A	0.034	3.411	-3.232
35	rs381523	<i>PPM1F</i>	22q11.22	A	G	0.045	3.220	3.166

Independent complex or single gene loci ($r^2 < 0.2$) with SNP(s) with a conjunctive FDR (conjFDR) < 0.05 in schizophrenia (SCZ) and bipolar disorder (BD). All SNPs with a conjFDR value < 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.

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$F_1(p_1) \geq p_1$ and $F_2(p_2) \geq p_2$. Then

$$\begin{aligned} & \max\{p_1 F_2(p_2)/F(p_1, p_2), p_2 F_1(p_1)/F(p_1, p_2)\} \\ & \geq [\pi_0 + \pi_1 + \pi_2] \max\{p_1 F_2(p_2)/F(p_1, p_2), p_2 F_1(p_1)/F(p_1, p_2)\} \\ & \geq [\pi_0 p_1 p_2 + \pi_1 p_2 F_1(p_1) + \pi_2 p_1 F_2(p_2)]/F(p_1, p_2). \end{aligned}$$

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 ($-\log_{10}(\text{FDR}) > 1.3$) with schizophrenia and bipolar disorder considered jointly are listed in Table 3 (after pruning), together with the corresponding z-scores and minor alleles. The z-scores were calculated from the p-values and the direction of effect was determined by the risk allele.

Incorrect mathematical definition of the conjunction FDR in the ‘Conditional and Conjunction Local False Discovery Rate’ section of the S1 Text.

There are also errors under the sub-heading ‘Conditional and Conjunction Local False Discovery Rate’ in the S1 Text. Please view the correct S1 Text here, with updates to the text in red.

Supporting Information

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

S1 Text. Supporting statistical methods.
(DOC)

Reference

1. Andreassen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelseo JR, et al. (2013) Improved Detection of Common Variants Associated with Schizophrenia and Bipolar Disorder Using Pleiotropy-Informed Conditional False Discovery Rate. PLoS Genet 9(4): e1003455. doi:[10.1371/journal.pgen.1003455](https://doi.org/10.1371/journal.pgen.1003455) PMID: [23637625](https://pubmed.ncbi.nlm.nih.gov/23637625/)