Supplementary Online Content


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eAppendix. Psychiatric Genomics Consortium Bipolar Group Members and Affiliations

This supplementary material has been provided by the authors to give readers additional information about their work.
eFigure 1. Threshold for Study Entry Is Related to Gene Size

A

Required # SNPs <0.05 to satisfy a global 5% error rate

B

required # SNPs to satisfy 5% error rates

eFigure 1A shows the derivation of a regression equation to determine the empirical p value threshold for each gene entered into the pathway analysis. Four GWAS studies were simulated using 10,000 SNPs.
replications per study and permuting case and control status. The number of times that SNPs from a particular gene were found to reach a nominal p value of ≤.05 in 3 out of 4 GWAS datasets was found to be directly related to the maximum number of SNPs tested in that gene in any GWAS (an indirect measure of gene size). The relationship between maximum number of SNPs tested in a gene and the number of SNPs at nominal p ≤.05 necessary to achieve an empirical p ≤.05 is given by the regression line. eFigure 1B provides an expansion of that relationship to more precisely define the threshold for smaller genes.
eFigures 2-7. These figures show the Canonical Pathway Diagrams for each of the selected pathways, as designated in Ingenuity Systems. The shaded molecules in each diagram indicate the specific genes, or gene-families, tagged by genes in the list of 226 in the Box of the present report.

**eFigure 2. Corticotropin-Releasing Hormone Signaling**

![Corticotropin-Releasing Hormone Signaling Diagram](image-url)
eFigure 3. Cardiac β-Adrenergic Signaling

Cardiac β-adrenergic Signaling
**eFigure 4. Phospholipase C Signaling**
eFigure 5. Glutamate Receptor Signaling
eFigure 6. Endothelin 1 Signaling
eFigure 7. Cardiac Hypertrophy Signaling
**eTable.** Characteristics of 25 Genes Included in Simulation to Determine the Relationship Between Gene Size and Empirical $P$ Value

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<tr>
<th>Gene</th>
<th>GAIN</th>
<th>STEP</th>
<th>Wellcome</th>
<th>German</th>
<th>GENE_SIZE(bp)</th>
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<th>Maximum # of SNPs among 4 GWAS</th>
<th>the required # of SNPs &lt;0.05 for a global 5% FPE</th>
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eBox. Summary of Steps in Pathway Analysis

1) We derived a list of 966 genes with 2 SNPs at $p < 0.05$ in 3 out of four GWAS datasets ($N = 5253$ cases and 6874 controls).

2) We used 10,000 permutations of phenotype in the four GWAS datasets in order to extract 226 genes from the 966 that were each empirically significant at $p < 0.05$.

3) We ran the 226 genes through an Ingenuity pathway analysis and obtained 16 pathways.

4) We ran the 16 pathways in a separate GWAS dataset (PGC2, an independent set of several thousand cases and controls). 6/16 pathways showed $p < 0.05$ and FDR$< 0.05$.

5) We compared gene-level results from a multicenter gene expression analysis ($N = 919$ genes) with the gene-level results from our own analysis ($N = 226$ genes), observing an overlap of 9 genes, three of which were among the genes driving the pathway results (chi-square $p < 0.005$).
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