Variants in the ankyrin-G and L-type voltage-gated calcium channel genes are associated with bipolar disorder

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1. BACKGROUND

Recent genome-wide association studies (GWAS) have identified genetic variants that show consistent association with common, complex diseases, such as type II diabetes, prostate cancer and Crohn’s disease.

In many cases, a critical component for success involved combining results and data across multiple, smaller studies, to provide adequate power to detect common variants of modest relative risk.

Given that a single study will often not be sufficient, here we present the results of combining two previously published and one new (n = 2,365) GWAS of bipolar disorder (BD).

2. METHODS

We combined individual genotyping data from two published GWAS of BD, the WTCCC and STEP-UCL studies, and a previously unpublished dataset (ED-DUB-DUB-STEP2) ––

3. RESULTS

Analysis of the new ED-DUB-DUB-STEP2 samples identified fourteen chromosomal regions associated at P < 5 × 10⁻⁶. No region exceeded our threshold for genome-wide significance of 5 × 10⁻⁸. However, one of these regions spanned the CACNA1C association previously-identified in the WTCCC + STEP-UCL analysis (Figure 2).

For the combined analysis of the WTCCC, STEP-UCL and ED-DUB-DUB-STEP2 studies, the most significant association was for SNP rs10994336, with P = 9.1 × 10⁻⁹. This SNP resides within a 195 kb region of multiple associated SNPs in the ankyrin-G gene (ANK3) on chromosome 10q21. Two additional regions were associated with BD at P < 10⁻⁶, chromosomes 12p13 and 15q14 (Figure 3).

4. CONCLUSIONS

We present evidence that allelic variants in ANK3 and CACNA1C confer risk to BD in three independent datasets. Ankyrin-G links integral membrane proteins, particularly voltage-dependent sodium channels, to the cytoskeleton in axonal initial segments. On the other hand, L-type calcium channels mediate a variety of calcium-dependent processes. We present evidence that allelic variants in the ankyrin-G and L-type voltage-gated calcium channel genes (ANK3 and CACNA1C) confer risk to BD in three independent datasets. The primary association analysis was a logistic regression of previously unpublished dataset (ED-DUB-DUB-STEP2) ––

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