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Online supplement

WTCCC bipolar lifetime presence of definite psychosis

This refers to presence of clear delusions and/or hallucinations on at least one occasion during a person's lifetime. Where Bipolar Affective Disorder Dimension Scale (BADDS)[24] psychosis dimension (P) ratings were available ($n = 1226$), a score of P = 0 was scored as psychosis absent ($n = 215$). P > 9 was scored as psychosis definitely present ($n = 840$). P = 1–9 inclusive was scored as unknown (missing, $n = 171$). Cases with insufficient available clinical information were scored as missing data. Where only OPCRIT[22] data were available, psychosis was scored present if at least one psychosis symptom was endorsed as being present. The OPCRIT items considered for the psychosis measure are items 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77. Interrater reliability for BADDS P dimension and OPCRIT items was assessed using joint ratings of 20 cases with a range of mood disorder diagnoses. The intra-class correlation for BADDS P was 0.91 and mean overall kappa statistic for OPCRIT items ranged from 0.81 to 0.99.

Quality control

The WTCCC bipolar disorder data set comprised 469 557 single nucleotide polymorphisms (SNPs) distributed across the genome. All individual SNP genotypes were obtained through the same analysis pipeline. Briefly, we used polymorphisms that had a minor allele frequency of at least 1% in the bipolar disorder and control data-sets and met stringent levels of genotyping quality. The large number of genotypes scored in a study such as this requires the use of generic approaches to quality control, allowing SNPs to be excluded where the quality of genotyping is in question. We used the following quality filter for inclusion of SNPs.

(a) Call rate (i.e. the proportion of genotypes that could be scored confidently, out of all the genotypes that were attempted for that SNP) > 97% in the bipolar disorder and control data sets.

(b) Hardy–Weinberg P > 0.00001 in the bipolar disorder data-set.

(c) Hardy–Weinberg P > 0.001 in the control data-set.

Using these stringent quality filters, 377 742 autosomal SNPs were selected for analysis.

Robustness of results to method of analysis

To ensure our results were robust to changes in the precise method of analysis, we reanalysed the data by the following.

- Varying the International Schizophrenia Consortium[15] discovery sample *P*-value threshold. Thresholds of $P < 0.05$, < 0.2 and < 0.5 gave the WTCCC schizoaffective bipolar disorder sample *v.* non-schizoaffective subset comparisons of $P = 0.020$, 0.00096 and 0.00059 respectively.
- Using only the SNPs that met the most stringent quality filters,[20] and thus limiting the effect of missing genotypes, the results were unchanged.
- Taking into account principal components derived from the genotype data with EIGENSTRAT.[39,40] We note that the principal components will reflect population stratification, but also any polygenic effect in the data. To minimise the possibility of overadjusting our WTCCC analyses for polygenic effects, we use the WTCCC control samples[16] to derive principal components, then project these onto the cases. Adjusting the WTCCC bipolar disorder data by 0, 4 and 10 principal components gave schizoaffective *v.* non-schizoaffective comparisons of $P = 0.00059$, 0.040 and 0.037 respectively. Adjusting the replication data by 0, 4 and 10 principal components gave schizoaffective *v.* non-schizoaffective comparisons of $P = 0.007$, 0.025 and 0.022 respectively.

A note about interpretation of polygenic scores

We note that there is continuing discussion (unpublished) about the interpretation of polygenic scores in terms of the precise number of variants involved. Such discussions do not have any impact on the interpretation of the results of this manuscript because the current analyses depend on showing a difference between two bipolar disorder samples, not on the number of risk alleles involved. Although the polygenic analysis is compatible with hundreds or thousands of genes being implicated, some have argued that it could still be due to an effect from linkage disequilibrium, with genes already showing stronger evidence of allelic association with schizophrenia. Thus the polygenic score effect could be duplicating/reconfirming the evidence for a smaller set of susceptibility genes. As mentioned, even if this were the case, there is no effect on the interpretation of the current analyses.