Supplemental Methods

Genotyping and Imputation

STEP-BD/WTCCC/UCL

DNA for the STEP-BD and UCL samples was extracted from lymphoblastoid cell lines or whole blood at the Rutgers DNA repository. As previously described(1), all genotyping was performed at the Broad Institute of MIT and Harvard using the Affymetrix GeneChip Human Mapping 500K array and standard protocols. Genotypes were called using the Bayesian Robust Linear Model with Mahalanobis distance classifier (BRLMM) (2). Quality control was performed using PLINK v1.04 (http://pngu.mgh.harvard.edu/~purcell/plink/)(3). Individuals were excluded if they had overall call rates <85%; for excess or insufficient heterozygosity (outliers approximately three standard deviations from the mean estimated inbreeding coefficient) or for apparent relatedness. Individuals with apparent non-Caucasian ancestry were also excluded if they did not overlap with CEU samples when plotting the first two quantitative ancestry indices after merging the STEP-BD, UCL, and NIMH control samples with the HapMap phase III dataset. SNPs were excluded if they had a call rate <95%; minor allele frequency <1%, were inconsistent with Hardy-Weinberg Equilibrium at $p<1x10^{-6}$ or showed differential rates of missingness in bipolar subjects and controls(3). After this quality control, ~325,600 genotyped markers were retained for analysis, with a total genotyping rate in the final sample >99%.

Details of genotyping and quality control for the WTCCC samples are described elsewhere(4). Briefly, DNA for the WTCCC samples was extracted from whole blood and genotyped using the

Affymetrix GeneChip 500K array at Affymetrix Services Lab with standard protocols. Genotypes were called using CHIAMO(4). SNPs were excluded if they had a call rate<95% (or <99% for SNPs with MAF<5%), or were inconsistent with Hardy-Weinberg Equilibrium at $p < 5.7 \times 10^{-7}$. In all, 469,557 SNPs were originally retained for analysis. As with the STEP-BD cohort, subjects were excluded if the first two quantitative ancestry indices indicated they did not cluster with the primary Caucasian WTCCC group. For the present analysis, WTCCC genotypes were downloaded from the WTCCC website (2007-02-05 CHIAMO data freeze calls, confidence score >0.9) and further cleaned as described in Ferreira(5); after exclusion of SNPs with MAF<0.01, ~405,800 SNPs were retained, then merged with the STEP-BD SNPs to form a single data set.

Imputation was then performed for the autosomes from the combined STEP-BD/UCL/WTCCC data using the MACH software package (http://www.sph.umich.edu/csg/abecasis/MACH) (6). Imputation utilized a HapMap reference panel (release 22, 60 Caucasian-European (CEU) founders). SNPs with $r^2 > 0.8$ were retained for further analysis, yielding 1,922,309 SNPs.

MDD

Genotyping for the STAR*D cohort also utilized Affymetrix 500k platforms – half on the Affymetrix GeneChip Human Mapping 500K Array Set, half with the Affymetrix Human SNP Array 5.0. Details of genotype calling methodology and initial quality control processing are in Garriock(7). Genotypes for samples run on the Affymetrix 500K Array (n=969) were called using the BRLMM algorithm, and those analyzed on Affymetrix Array 5.0 (n=979) were called using the BRLMM-P algorithm. Further quality control was performed using PLINK v1.04, with exclusion of individuals with overall call-rates<95% or apparent relatedness and SNPs with call rate<98%,

MAF<1%, or out of Hardy-Weinberg equilibrium ($p<1x10^{-6}$). This yielded a total of 229,703 genotyped SNPs, with call rates >99%. In addition, as with the STEP-BD/UCL cohort, to minimize the risk of population stratification, the STAR*D data set was merged with the HapMap phase III dataset and the first two quantitative indices of ancestry were plotted. Those subjects who did not overlap with CEU samples were then excluded, yielding 1,273 subjects. Finally, as with STEP-BD, we imputed missing genotypes using MACH and retained SNPs with $r^2>0.8$, yielding 1,954,455 SNPs.

References

1. Sklar P, Smoller JW, Fan J, Ferreira MA, Perlis RH, Chambert K, et al. Whole-genome association study of bipolar disorder. Mol Psychiatry. 2008;13(6):558-69.
2. Rabbee N, Speed TP. A genotype calling algorithm for affymetrix SNP arrays. Bioinformatics. 2006;22(1):7-12.
3. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81(3):559-75.
4. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661-78.
5. Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet. 2008;40(9):1056-8.
6. Li Y, Abecasis G. Mach 1.0: Rapid Haplotype Reconstruction and Missing Genotype Inference. Am J Hum Genet. 2006;S79:2290.
7. Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, Jenkins GD, et al. A Genomewide Association Study of Citalopram Response in Major Depressive Disorder. Biol Psychiatry. 2009.