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DOI
10.1192/bjp.bp.115.168229

Publication date
2016

Document Version
Final published version

Published in
British Journal of Psychiatry

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Link to publication

Citation for published version (APA):
Coleman, J. R. I., Lester, K. J., Keers, R., Roberts, S., Curtis, C., Arendt, K., Bögels, S., Cooper, P., Creswell, C., Dalgleish, T., Hartman, C. A., Heiervang, E. R., Hötzel, K., Hudson, J. L., In-Albon, T., Lavallee, K., Lyneham, H. J., Marin, C. E., Meiser-Stedman, R., ... Eley, T. C. (2016). Genome-wide association study of response to cognitive–behavioural therapy in children with anxiety disorders. *British Journal of Psychiatry*, *209*(3), 236-243. https://doi.org/10.1192/bjp.bp.115.168229

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Download date:15 Oct 2026

BJPsych | The British Journal of Psychiatry (2016)
209, 236–243. doi: 10.1192/bjp.bp.115.168229

Genome-wide association study of response to cognitive–behavioural therapy in children with anxiety disorders

Jonathan R. I. Coleman, Kathryn J. Lester, Robert Keers, Susanna Roberts, Charles Curtis, Kristian Arendt, Susan Bögels, Peter Cooper, Cathy Creswell, Tim Dalgleish, Catharina A. Hartman, Einar R. Heiervang, Katrin Hötzel, Jennifer L. Hudson, Tina In-Albon, Kristen Lavallee, Heidi J. Lyneham, Carla E. Marin, Richard Meiser-Stedman, Talia Morris, Maaike H. Nauta, Ronald M. Rapee, Silvia Schneider, Sophie C. Schneider, Wendy K. Silverman, Mikael Thastum, Kerstin Thirlwall, Polly Waite, Gro Janne Wergeland, Gerome Breen* and Thalia C. Eley*

Background
Anxiety disorders are common, and cognitive–behavioural therapy (CBT) is a first-line treatment. Candidate gene studies have suggested a genetic basis to treatment response, but findings have been inconsistent.

Aims
To perform the first genome-wide association study (GWAS) of psychological treatment response in children with anxiety disorders ($n = 980$).

Method
Presence and severity of anxiety was assessed using semi-structured interview at baseline, on completion of treatment (post-treatment), and 3 to 12 months after treatment completion (follow-up). DNA was genotyped using the Illumina Human Core Exome-12v1.0 array. Linear mixed models were used to test associations between genetic variants and response (change in symptom severity) immediately post-treatment and at 6-month follow-up.

Results
No variants passed a genome-wide significance threshold ($P = 5 \times 10^{-8}$) in either analysis. Four variants met criteria for suggestive significance ($P < 5 \times 10^{-6}$) in association with response post-treatment, and three variants in the 6-month follow-up analysis.

Conclusions
This is the first genome-wide therapygenetic study. It suggests no common variants of very high effect underlie response to CBT. Future investigations should maximise power to detect single-variant and polygenic effects by using larger, more homogeneous cohorts.

Declaration of interest
R.M.R., J.L.H. and H.J.L. are co-authors of the Cool Kids program but receive no direct payments. C. Creswell is co-author of books in the 'Overcoming' series and receives royalties. W.K.S. is author of the Anxiety Disorders Interview Schedule for Children and receives royalties. G.B. is a consultant in pre-clinical genetics for Eli Lilly.

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Anxiety disorders are the most common psychiatric disorders, with a lifetime prevalence of ~30%.[1] They are a major cause of global disability, and impose considerable economic burdens on society.[2,3] They commonly have their onset in childhood or adolescence and have been linked to the occurrence of later disorders, including depression and conduct disorder.[1,4] Adults with anxiety disorders show rates of childhood anxiety diagnoses significantly above baseline.[5] Given this potential gateway effect, and the distress caused by these disorders, there is a need to optimise and understand treatment effectiveness in childhood.

Cognitive–behavioural therapy (CBT) is a first-line treatment for anxiety disorders in the UK, with 59% remission reported immediately post-treatment.[6,7] Despite this high reported efficacy, variability exists in patient response that may be influenced in part by genetic variants. Multiple studies examining the genetics of differential response to psychological therapies (therapygenetics[8]) have been undertaken, and variants in seven genes (*5HTT/SLC6A4, TPH2, MAOA, COMT, NGF, BDNF* and *GRIK4*) have been implicated at least once in studies of CBT for anxiety disorders.[9] However, findings have proven difficult to replicate,[10] and the direction of effects found inconsistent. These problems may result from the low power of small cohort sizes, resulting in a high rate of false positives, and a narrow focus on a few genes that may have limited relevance to the phenotype.

Genome-wide association studies (GWAS) provide a hypothesis-neutral alternative, agnostic to prior assumptions of relevance and with the potential to discover novel findings at a single variant level. By analysing thousands of variants across the genome, GWAS yield more information than the candidate gene approach, allowing for the acknowledgement and control of confounds such as ancestry and the quality of genotyping. Genome-wide information can also be used to investigate associations between phenotypic change and different levels of the genetic architecture, including the effect of all variants in a given gene, and the effect of all genotyped variants across the genome. However, the explicit requirement for multiple testing correction in GWAS imposes a need for large sample sizes.

Although GWAS have not been used to study response to CBT, they have shown early promise in studying anxiety disorders. Genetic influences on the development of anxiety disorders may indicate processes underlying treatment response, and provide interesting genetic candidates.[11] A detailed review of the genetics of anxiety disorders is available elsewhere.[12] In brief, one variant, rs7309727 (*TMEM132D*), was associated with panic disorder in a cohort of European ancestry ($P = 1.1 \times 10^{-8}$, odds ratio (OR) = 1.45 (95% CI 1.20–1.72).[13] A variant in the *TMEM16B*

*These authors contributed equally to the work

gene was reported at genome-wide significance in a Japanese cohort with panic disorder, but was not significant in replication analyses.[14] Two GWAS of post-traumatic stress disorder (PTSD) have identified variants at genome-wide significance in the *TLL1* gene (rs6812849, $P = 3.13 \times 10^{-9}$, OR not reported)[15] and *PRTFDC1* (rs6482463, $P = 2.04 \times 10^{-9}$, OR = 1.47 (95% CI 1.35–1.59)).[16] However, these results require replication in larger studies; for example, variants in the *RORA* gene previously implicated in a GWAS of PTSD failed to attain significance in a larger replication effort.[17] No significant findings from the anxiety literature to date had previously been considered in candidate gene studies.[12]

To our knowledge, this is the first GWAS to examine response to psychological therapy in any disorder, and the first to examine treatment response of any kind in anxiety disorders. Participants were drawn from the Genes for Treatment (GxT) study, an international, multisite investigation of clinical, demographic and genetic predictors of response to CBT for anxiety in childhood and adolescence.[10,18] Two analyses of association between single nucleotide polymorphisms (SNPs) and response to CBT were conducted, investigating change in symptom severity between baseline and immediately post-treatment (post-treatment), and between baseline and 6 months after treatment cessation (follow-up).

Method

Study design and sample

A detailed description of the participants and the treatment programmes from which they were drawn is provided elsewhere (online supplemental material).[18] In brief, participants provided DNA for the GxT study between 2005 and 2013, at 11 sites across the USA, Australia and Western Europe. Children and adolescents (5–17 years old, 94% aged 5–13) were included if they met DSM-IV criteria[19] for a primary anxiety disorder diagnosis, with further psychiatric diagnoses made as appropriate. Exclusion criteria were significant physical or intellectual impairment, and the presence of psychotic symptoms. All participants completed a full course of individual-based CBT (with or without parental involvement), group-based CBT or guided self-help either as part of a trial or as treatment as usual within a clinical research department. All treatments were manualised and treatment protocols across all sites were comparable for core elements of CBT including teaching of coping skills, cognitive restructuring, and exposure.

Assessments were made using the Anxiety Disorders Interview Schedule for DSM-IV, Parent and Child Versions (ADIS-IV-C/P),[20] except at Bochum (Germany) and Basel (Switzerland) where the German equivalent, Kinder-DIPS,[21] was used. All participants were assessed prior to and immediately after treatment, with further assessments made at 3-, 6- or 12-month follow-up where possible. Output from the ADIS (or equivalent) was converted into Clinical Severity Ratings (CSR) on a scale of 0–8. A diagnosis was made when the child met the diagnostic criteria and received a CSR of 4 or more, usually based on a composite of parent and child report. Diagnoses were made from the ADIS for multiple anxiety disorders, and primary status allocated to the most severe, defined as the highest CSR, with ties resolved by clinical judgement (online Table DS1(b) and (c)).

To minimise differential assessment across sites, raters at Reading (UK), Oxford (UK) and Aarhus (Denmark) all received training in evaluation from the Sydney (Australia) site, and clinicians at Aarhus received additional training in the ADIS from W.K.S., principal investigator of the Florida (USA) site. As such, standardised assessments were made for at least 85% of the analysed sample (for further details see the online supplement).

Definition of the treatment response phenotype

As in previous analyses of the GxT sample, outcome was assessed across two periods: baseline to post-treatment and baseline to follow-up. Although dichotomised treatment outcomes are often used in clinical decision making in treatment response, a continuous measure of change in severity provides substantially more power for analyses.[22]

Response post-treatment was therefore defined as percentage change in CSR score between baseline and immediately following treatment. Percentage change, rather than absolute change, was used as it has been shown to better reflect clinical ratings of improvement by its successful use in pharmacogenetics GWAS.[23] For follow-up analyses, a range of time points were available; assessments taken at the 6-month time point were used, as these were the most complete ($n = 483$). Missing data at this time point was imputed using the best linear unbiased estimates from linear mixture models fitted to the GxT data as part of analyses predicting response from clinical variables alone.[18] The mixture models included the linear and quadratic effects of time as well as gender, age, primary diagnosis, treatment type and the random effects of individual and trial (for a full explanation, see Hudson *et al*[18]). This allowed us to compute response at follow-up as the percentage improvement in CSR score from baseline to 6 months after the end of treatment. Analyses were performed on residual scores generated from a linear regression of the percentage change measure adjusted for baseline severity, age, gender, treatment type, diagnosis and trial.

Both sets of residual scores were created as output variables from our previous study, which found a number of significant non-genetic influences on treatment outcome (online supplement).[18]

DNA extraction and genotyping

DNA was collected and extracted using standard protocols, from buccal swabs[24] and saliva kits (OG-500 / PrepitL2P, DNAgenotek, Kanata, Canada). Sample preparation (including concentration and quantification) prior to genotyping is described in the online supplement. Genotyping was performed on Illumina HumanCoreExome-12v1.0 microarrays (Illumina, San Diego, California, USA), using a standard protocol.[25] Samples were genotyped in two batches, and randomized by site on each microarray.

Quality control

SNPs were mapped to build version 37/hg19 of the human genome. Initial genotype calls were made with GenCall software (GenomeStudio, Illumina, San Diego, California, USA), reprocessed to remove poorly performing samples, re-clustered, and manually recalled where appropriate. Further recalling, targeted at improving the identification of rare variants (such as the exonic content of the microarray) was performed using ZCall.[26] Following recalling, the data were transferred to a multinode computing cluster, and quality control was performed following previously published protocols (online supplement).

Quality controlled data were imputed to the December 2013 release of the 1000 Genomes Project reference (for autosomes; March 2012 release for the X chromosome[27]), using the posterior-sampling method in IMPUTE2 with concurrent phasing.[28] SNPs imputed with an info metric >0.8 and a minor allele frequency (MAF) $>1\%$ were considered best-guess genotypes, and converted back to PLINK binary format using GTOOL (Freeman and Marchini, available at www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html). SNPs with a genotype probability of <0.9 were set as missing, and those present in $<98\%$ of the sample were excluded from the analysis.

Statistical analysis

Two analyses were performed, examining adjusted percentage change in CSR score from baseline to post-treatment, and from baseline to 6-month follow-up, as described above. Principal component analysis (PCA) of the genotype data was performed to attempt to control for population stratification. However, this yielded components that were not sensitive to differences in outcome. This was likely due to the quantitative nature of the phenotype, the fact that multiple covariates were controlled for in constructing the phenotype, and because participants were drawn from a variety of sites across the globe (online supplement). Accordingly, PCA was deemed unsuitable for controlling for population stratification, prompting the adoption of mixed linear modelling for the association analyses (MLMA). MLMA uses genome-wide genotype data to derive a genomic relationship matrix (GRM), which is used to control for genetic similarity between participants as a random effect.[29]

MLMA association analysis was performed in GCTA, using the *mlma-loco* option for autosomes and the *mlma* option for the X chromosome (online supplement).[30] For each SNP in the study, percentage change in CSR was regressed on the number of copies of the reference allele of the SNP (0, 1 or 2), weighted by its additive effect. A random effect of genetic similarity (from the GRM) was included as a covariate, as were fixed effects of sample concentration at genotyping, sample type (buccal swab or saliva), and ultrafiltration status (whether the sample was filtered in preparation for genotyping; online supplement). Using the assumptions of this approach, power for the GWAS was estimated using the Genetic Power Calculator.[31] The sample of 980 participants has 80% power to detect a variant explaining ~4% of variance and 1% power to detect variants explaining 1%.

Results from the association analysis were clumped according to *P*-value using PLINK.[32,33] Each clump is represented by a sentinel SNP (that with the lowest *P*-value in the clump), and contains all SNPs in linkage disequilibrium with the sentinel ($R^2 > 0.25$, within 250kb of the sentinel). One imputed sentinel SNP in the 6-month follow-up analysis was on the borderline of genome-wide significance (rs72850669, $P = 7.54 \times 10^{-8}$), and was re-genotyped *post hoc* (LGC Genomics, Teddington, UK). This showed the genotype calling of rs72850669 was unreliable (data not shown), and it was removed from the analyses.

To assess the ability of the GWAS to replicate previous findings, the association of SNPs implicated in CBT response in previous candidate gene studies was examined.[9] Exploratory secondary analyses were performed to assess the combined effects of SNPs on response (details can be found in the online supplement). The proportion of variance in CSR change across time accounted for by all the SNPs in the study was assessed with univariate genomic-relatedness-matrix restricted maximum likelihood (GREML), performed in GCTA using the GRM derived for the GWAS. Polygenic risk score profiling was used to investigate the ability of external data-sets to predict CBT response, using risk profiles from publicly available GWAS of major depressive disorder[34] and schizophrenia,[35] as well as from a meta-analysis of response to antidepressants.[36] To test the ability of the GxT data to predict response to CBT, five analyses were performed. Participants with generalised anxiety disorder, separation anxiety, social phobia and specific phobia, and those from the Reading (UK) site, were separately removed from the dataset and risk profiles derived from the remaining participants. Each profile was then used to predict outcome in the relevant set of removed participants.

Ethics

All trials and collection of samples were approved by site-specific human ethics and biosafety committees. Parents provided informed consent, children provided assent. The storage and analysis of DNA was approved by the King's College London Psychiatry, Nursing and Midwifery Research Ethics Sub-Committee.

Results

Sample and SNP exclusions are shown in online Fig. DS1. Phenotype and high-quality genotype data were available for 939 participants in the analysis post-treatment, with an additional 41 participants available for analysis at 6-month follow-up ($n = 980$). Baseline demographic information for these 980 participants is described in online Table DS1(a). The position of the samples on principal component axes derived from the HapMap reference populations suggests 92% of the sample are of White Western European ancestry.[37] A total of 260824 common SNPs passed quality control, which rose to 3017604 SNPs when imputed genotypes were added.

No SNPs were found at formal genome-wide significance for either analysis (all $P > 5 \times 10^{-8}$). In the post-treatment analysis, four independent clumps passed threshold for suggestive significance ($P < 5 \times 10^{-6}$; Table 1 and Fig. 1). Quantile–quantile plots show no departure from the chi-squared distribution of *P*-values expected under the null hypothesis, suggesting there is no underlying inflation of association statistics by uncontrolled confounds (lambda median = 0.972, Fig. 2). Three independent clumps were suggestive of significance in the 6-month follow-up analysis (Table 2 and Fig. 3), with no evidence of inflation (lambda = 1.02, Fig. 4). All clumps with $P < 1 \times 10^{-4}$ are displayed in online Table DS2.

A secondary analysis with increased power was performed restricted to nine SNPs previously associated with response to CBT in candidate gene studies (five other SNPs have been previously implicated in CBT response, but did not pass quality control). Assuming a significance threshold of 0.005455 (0.05/9), none of the nine previously associated SNPs was significant (Table 3 and online supplement). The sample had 80% power to detect an SNP accounting for 1.4% of variance at this significance threshold, suggesting any effect of these SNPs in this data-set is smaller than this.

Table 1 Independent clumps associated with cognitive–behavioural therapy response at post-treatment with $P < 5 \times 10^{-6}$

Sentinel SNP	CHR	Clump BP	Sentinel SNP *P*	Sentinel SNP MAF	Sentinel SNP information	Genes +/–100kb
rs10881475	1	108113663–108203647	2.45×10^{-6}	0.187	0.993	NTNG1, VAV3
rs11834041	12	128232721–128239057	3.50×10^{-6}	0.135	Genotyped	–
rs12464559	2	152498699–152679462	4.09×10^{-6}	0.0410	0.941	NEB, ARL5A, CACNB4
rs881301	8	38322346–38332318	4.46×10^{-6}	0.403	Genotyped	WHSC1L1, LETM2, FGFR1, C8orf86

SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair; MAF, minor allele frequency.

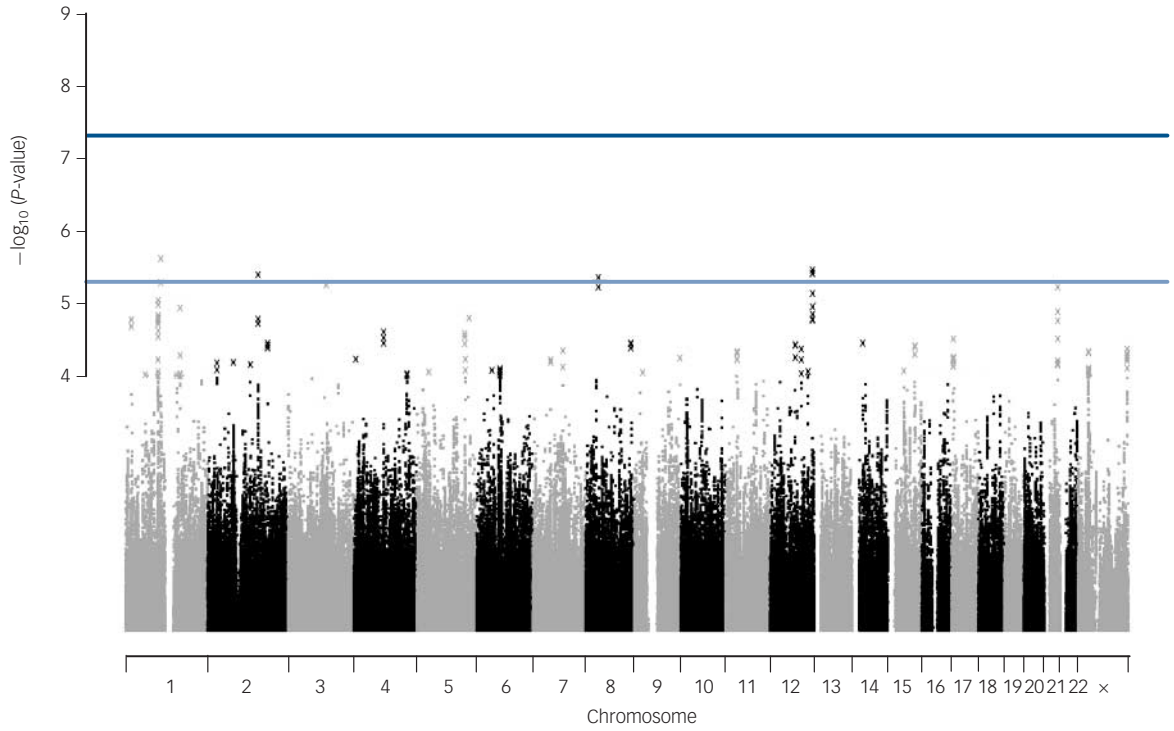

Fig. 1 Manhattan plot of genetic associations with cognitive–behavioural therapy response baseline to post-treatment.

X-axis shows the top million most associated single nucleotide polymorphisms, arranged by position on the chromosome. Lines show conventional thresholds for genome-wide significance ($P = 5 \times 10^{-8}$) and suggestive significance ($P = 5 \times 10^{-6}$).

Table 2 Independent clumps associated with cognitive–behavioural therapy response at 6-month follow-up with $P < 5 \times 10^{-6}$

Sentinel SNP	CHR	Clump BP	Sentinel SNP *P*	Sentinel SNP MAF	Sentinel SNP information	Genes +/–100kb
rs72711240	4	135657189–135695807	4.49×10^{-7}	0.0269	0.903	–
rs9875578	3	13707416–13810670	1.43×10^{-6}	0.424	0.994	FBLN2, WNT7A
rs6813264	4	146509970–146631854	4.68×10^{-6}	0.410	Genotyped	SMAD1, MMAA, C4orf51, ZNF827

SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair; MAF, minor allele frequency.

Exploratory secondary analyses (GREML, gene-wide analyses and polygenic risk score profiling) were performed. No significant estimate of SNP heritability could be obtained from GREML, and the effect of adding principal components was minimal. In the post-treatment analysis, all estimates were non-significant. In the 6-month follow-up data the highest estimate was 0.0797 (95% CI –0.194 to 0.35) without principal components. The power of univariate GREML in the sample was estimated for a range of true heritabilities.[38] Power ranged from 9 to 46% assuming true heritability between 0.2 and 0.6. To achieve 80% power within this range of heritabilities will require 1450–4450 samples (for heritabilities between 0.6 and 0.2).

Polygenic risk score profiling failed to generate predictions that were consistently significant, either for external GWAS or in the internal predictions of response.

Discussion

Main findings

We report the first genome-wide association study of psychological therapy. Although no region reached genome-wide significance, the single SNP and polygenic results are consistent with the wider literature of treatment genetics in psychiatry, given the sample size studied. Genome-wide significant variants detected in GWAS of psychiatric phenotypes have shown small effect sizes (with the exception of late-onset dementia), requiring thousands of participants to discover. The pattern of results in psychiatric genomics to date suggests that a critical number of participants (varying by disorder) are required before robust findings begin to be made. In studies of schizophrenia, this critical number was ~9000 cases.[39] Our results, although preliminary, suggest response to CBT could be a complex phenotype at the early point of this trajectory, although the critical sample size is not yet clear.

The purpose of this study was to identify genetic variants capable of predicting change in symptom severity during treatment. No common, high-effect SNPs were identified, suggesting that it is very unlikely a single variant could be used as a predictor. This also places an upper bound on expected effect sizes in studies of CBT response. This is relevant considering that neither GWAS replicated previous findings from the literature. This does not appear to be due to insufficient statistical power. For example, the *COMT* val158met polymorphism (rs6265) was reported to account for 8% of variance in CBT response in adults with panic disorder, well above the 4% of variance explained for which this GWAS was powered.[40] Failure to replicate previous findings from the candidate gene literature has proved common in psychiatric genetics, whereas GWAS is proving more

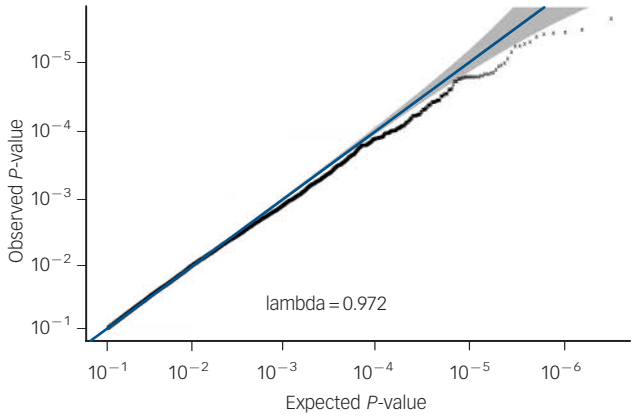

Fig. 2 Quantile–quantile plot of *P*-values (pruned for linkage disequilibrium) from genetic associations with cognitive–behavioural therapy response post-treatment.

X-axis shows spread of *P*-values expected under the null chi-squared distribution. Y-axis shows observed data. Grey region shows rough 95% confidence intervals around each point on the line x = y. Lambda median is a measure of inflation of the observed distribution of associations compared with expected null distribution. Lambda ⩽1 implies no inflation.

reliable.[35,41] The failure to replicate any published variants suggests previous assumptions of gene relevance may be erroneous, resulting from underpowered candidate gene studies that overestimated the likely effect sizes of studied variants, and that reported variants are likely to be false positives, or to have effect sizes inflated due to winner's curse.[42] Proximity to a gene does not imply an effect on gene expression, so the failure to replicate the effects of candidate SNPs does not exclude a role for candidate genes, as the SNPs assessed may not capture true functional variation.

Not all candidate variants are SNPs, and one limitation of GWAS is the difficulty of assessing structural variants not captured by the probes on microarrays. For example, we cannot comment on the previously reported role of the *MAOA*-u variable number tandem repeat in CBT response.[43] Nor could we assess the effect of the *5HTTLPR* variant of *SLC6A4*, previously associated with remission from anxiety disorders at follow-up; however, we directly genotyped this variant in this cohort, and were unable to replicate our earlier finding.[8,10]

Although small when compared with high-profile studies such as the PGC studies in schizophrenia and depression,[34,35] our sample is similar in size to studies in the depression pharmacogenetic literature.[23,44] The first of these used a multistage design ($n = 1532$) and identified several associations at nominal significance, but none remained significant after correction for multiple testing.[44] The second ($n = 706$) found one genome-wide significant locus (for response to nortryptiline treatment) and six loci at suggestive significance across four subanalyses.[23] More recent meta-analyses were unable to find genome-wide significant variants.[36] However, a significant GREML estimate of SNP-chip heritability of 42% (95% CI 6%–78%) was identified, suggesting useful information about treatment response can be obtained at the whole-genome level.[45] Future studies in psychological therapy-genetics should aim to build a cohort of sufficient size to estimate SNP-chip heritability and bivariate genetic correlations, enabling further comparison with pharmacogenetic studies. Such a cohort could act as a target data-set for polygenic risk scoring, exploring the predictive value of variants associated with potentially relevant phenotypes assessed in other GWAS.

Limitations

There are parallels between the antidepressant GWAS literature and this study, including the necessity of combining many studies to obtain sufficient participants for analysis. Herein, we examined a naturalistic clinical cohort, drawn from CBT trials or from treatment as usual. As all participants received CBT, there was no placebo group for comparison. Therefore, the results may

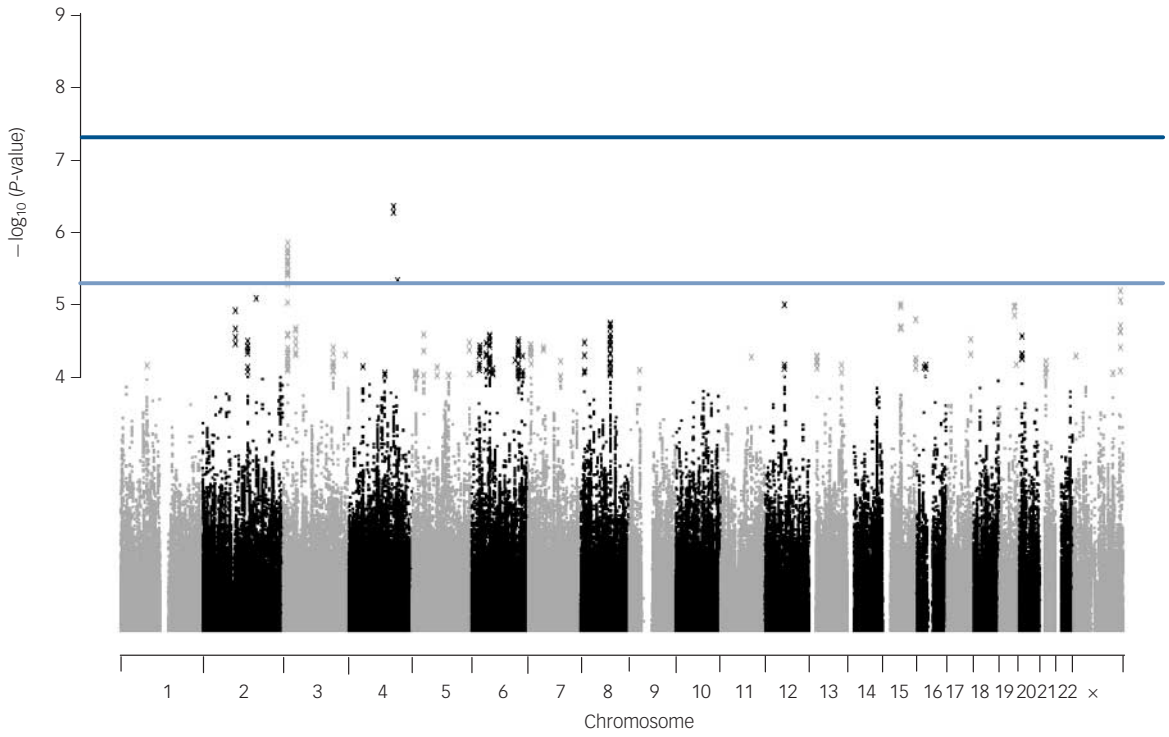

Fig. 3 Manhattan plot of genetic associations with cognitive–behavioural therapy response baseline to 6 months after treatment.

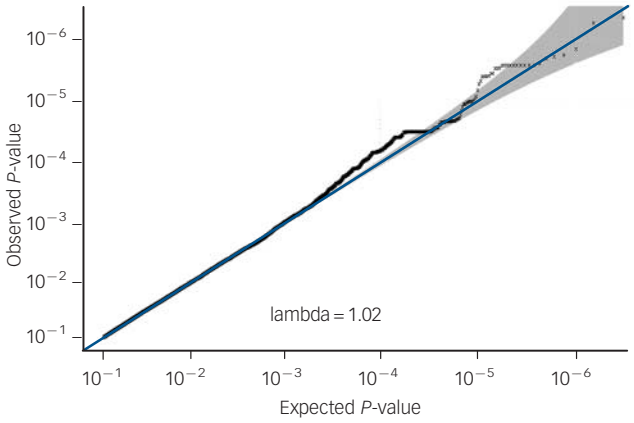

Fig. 4 Quantile–quantile plot of *P*-values from genetic associations with cognitive–behavioural therapy response baseline to 6-month follow-up, including lambda median.

reflect natural regression to the mean, rather than an effect of treatment. Theoretically, a parallel GWAS of change in severity could be performed on wait-list controls to identify associations with regression to the mean. Results from the GWAS of CBT response could be weighted by the likelihood that any given association resulted from regression to the mean. However, this would require deliberate non-treatment of thousands of wait-list controls over a period of at least 7 months for the purpose of comparison only. As CBT is effective in this age group, with significant improvement seen in treated groups relative to wait-list controls, non-treatment would raise serious ethical concerns.[7] The aim of therapygenetics is to discover predictors of differential response to treatment. These predictors need not capture a treatment effect *per se*; they may describe processes separate to treatment that nonetheless lead to better (or worse) response. Nevertheless, in the absence of a control group, this study specifically examines the association between genetic variation and change in CSR across the period of CBT treatment and follow-up, not the biological mechanism of response to CBT.

The naturalistic nature of the cohort creates heterogeneity, including differences in the details of the treatment given, the target disorder of the treatment, and several participant characteristics. The effectiveness of CBT is influenced by a variety of environmental factors. Some of these can be considered within the design, such as treatment type, diagnosis and severity. Others are less easily accounted for, including therapeutic alliance and other social influences, which may only be partly controlled for by the inclusion of trial as a covariate.[18,46] This reduces the statistical power of analyses, but should not be viewed as an argument against therapygenetics. The ability to offer personalised advice to patients about treatment could avoid considerable amounts of unnecessary distress and expense. Obtaining a set of genes able to assist in clinical prediction will require a cohort that is powerful enough to detect true variants while remaining clinically representative. Thus, a degree of heterogeneity is unavoidable in studying response to CBT, and similar difficulties in pharmacogenetic GWAS suggest this limitation applies to treatment response genomics more generally.

Combining data from trials at multiple sites necessitated compromises in study design. Participants were included if they completed treatment, but drop-out from treatment is common and likely to be related to poorer response. As such, future studies should aim to include severity data for non-completing participants. This would require appropriate modelling of the treatment period, and the proportion of the treatment process completed, before participation ceased. Similarly, combining measurements from different sites and from participants with varying diagnoses required the use of a general, widely applicable outcome measure. The ADIS fit these requirements well, but relies on clinical judgement derived from parent and child report. It may be less sensitive to the effects of CBT than a self-report measure, and be more vulnerable to site-specific biases. However, a suitable diagnosis-general self-report scale was unavailable, and standardising outcomes to combine multiple diagnosis-specific scales is likely to lead to a generalised and difficult-to-interpret result.

Future directions

This study represents the first GWAS of psychological therapy. Although no genome-wide significant findings emerged, the spread of significance in the associations captured is similar to other early general psychiatric and pharmacogenetic GWAS. The best approach in the immediate future is to increase the sample size available through combining existing cohorts in mega- and meta-analyses. Such a cohort would allow replication of the findings presented in this paper to be attempted, which currently is not possible due to the lack of an independent cohort of suitable

Table 3 Genome-wide association study *P*-values of single nucleotide polymorphisms (SNPs) previously associated with cognitive–behavioural therapy response.[12,a]

Gene	SNP	*P* (post-treatment)	*P* (follow-up)
SLC6A4	rs25531	Imputed with info <0.8	Imputed with info <0.8
HTR2A	rs6311	0.4717	0.9692
	rs6313	0.5451	0.8109
	rs6314	Imputed with info <0.8	Imputed with info <0.8
	rs7997012	Completeness after imputation <0.98	Completeness after imputation <0.98
TPH2	rs4570625	Completeness after imputation <0.98	Completeness after imputation <0.98
COMT	rs4680	0.7699	0.5956
NGF	rs6330	0.5093	0.4559
BDNF	rs6265 (val158met)	0.3408	0.9078
	rs7934165	0.5231	0.9880
	rs1519480	0.8211	0.5013
	rs11030104	0.3158	0.9675
GRIN2B	rs1019385	Imputed with info <0.8	Imputed with info <0.8
GRIK4	rs1954787	0.1315	0.1914

a. No *P*-value is significant after multiple testing correction.

size. However, individual variants are likely to have small effect sizes, so future studies should utilise higher-order approaches such as polygenic risk scoring and GREML to leverage the predictive effects of the whole genome. This would also provide an estimate of heritability, which is difficult to obtain through traditional family-based approaches. If the heritability of CBT response were around 30% (similar to that of anxiety disorders), a high-powered polygenic risk score could capture 10–15% of variance, which could be clinically useful when combined with known environmental risk factors.[47] However, creating such a score will require a sample size of at least 10 000, which would involve considerable effort to obtain.

Alternative approaches may also yield interesting findings. Response to CBT is a behavioural change following exposure to a positive environment, so epigenetic studies investigating how these exposures influence gene expression via DNA methylation will be informative.[48] Similarly, it will be useful to examine changes in gene transcript expression across treatment and in the longer term. Used in parallel to these approaches, studying specific genetic variants remains a potential method of predicting response to CBT (and understanding its biological basis) and genome-wide investigations represent the most promising avenue in which to focus the gathering momentum of therapygenetics.[49]

Jonathan R. I. Coleman, MSc, King's College London, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, UK; **Kathryn J. Lester**, DPhil, King's College London, IoPPN, MRC SGDP Centre, UK, and School of Psychology, University of Sussex, UK; **Robert Keers**, PhD, **Susanna Roberts**, MSc, King's College London, IoPPN, MRC SGDP Centre, UK; **Charles Curtis**, MSc, King's College London, IoPPN, MRC SGDP Centre, UK, and National Institute for Health Research Biomedical Research Centre, South London and Maudsley National Health Service Trust, UK; **Kristian Arendt**, PhD, Department of Psychology and Behavioural Sciences, Aarhus University, Denmark; **Susan Bögels**, PhD, Research Institute Child Development and Education, University of Amsterdam, The Netherlands; **Peter Cooper**, DPhil, School of Psychology and Clinical Language Sciences, University of Reading, UK, and Department of Psychology, Stellenbosch University, South Africa; **Cathy Creswell**, DClinPsy, PhD, School of Psychology and Clinical Language Sciences, University of Reading, UK; **Tim Dalgleish**, PhD, MRC Cognition & Brain Sciences Unit, Cambridge, UK; **Catharina A. Hartman**, PhD, Department of Psychiatry, University of Groningen, University Medical Center Groningen, The Netherlands; **Einar R. Heiervang**, PhD, Institute of Clinical Medicine, University of Oslo, Norway; **Katrin Hötzel**, PhD, Department of Psychology, Ruhr-Universität Bochum, Germany; **Jennifer L. Hudson**, PhD, Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, Australia; **Tina In-Albon**, PhD, Clinical Child and Adolescent Psychology, Universität Koblenz-Landau, Germany; **Kristen Lavallee**, PhD, Department of Psychology, University of Basel, Switzerland; **Heidi J. Lyneham**, PhD, Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, Australia; **Carla E. Marin**, PhD, Yale University, Child Study Center, New Haven, Connecticut, USA; **Richard Meiser-Stedman**, PhD, MRC Cognition & Brain Sciences Unit, Cambridge, UK; **Talia Morris**, BPsych, Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, Australia; **Maaike H. Nauta**, PhD, Department of Clinical Psychology and Experimental Psychopathology, University of Groningen, The Netherlands; **Ronald M. Rapee**, PhD, Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, Australia; **Silvia Schneider**, PhD, Department of Psychology, Ruhr-Universität Bochum, Germany; **Sophie C. Schneider**, BPsych, Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, Australia; **Wendy K. Silverman**, PhD, Yale University, Child Study Center, New Haven, Connecticut, USA; **Mikael Thastum**, PhD, Department of Psychology and Behavioural Sciences, Aarhus University, Denmark; **Kerstin Thirlwall**, DClinPsy, **Polly Waite**, DClinPsy, School of Psychology and Clinical Language Sciences, University of Reading, UK; **Gro Janne Wergeland**, MD, Department of Child and Adolescent Psychiatry, Haukeland University Hospital, Bergen, and Anxiety Disorders Research Network, Haukeland University Hospital, Norway; **Gerome Breen**, PhD, King's College London, IoPPN, MRC SGDP Centre, UK, and National Institute for Health Research Biomedical Research Centre, South London and Maudsley National Health Service Trust, UK; **Thalia C. Eley**, PhD, King's College London, IoPPN, MRC SGDP Centre, UK

Correspondence: Professor Thalia Eley, Social, Genetic and Developmental Psychiatry Centre (MRC), Institute of Psychiatry, Psychology and Neuroscience – PO80, DeCrespigny Park, Denmark Hill, London SE5 8AF, UK. Email: thalia.eley@kcl.ac.uk)

First received 14 Apr 2015, final revision 30 Sep 2015, accepted 14 Dec 2015

Funding

Combined study supported by UK Medical Research Council grant G0901874/1 to T.C.E. Individual trials support by Australian Research Council grant DP0878609 to J.L.H., R.M.R. and T.C.E.; Australian NHMRC grants to R.M.R., J.L.H. and H.J.L. (1027556), H.J.L, J.L.H and R.M.R (488505), and J.L.H and R.M.R. (382008); TrygFonden grant (7-10-1391) to M.T.; Edith og Godtfred Kirk Christiansens Fond grant (21-5675) to M.T.; Swiss National Science Foundation grant (105314-116517) to S.S., Western Norway Regional Health Authority grant to E.R.H. (911366); UK Medical Research Council Clinical Fellowship (G0802821) to R.M-S.; NIMH R01 (MH079943) to W.K.S.; UK NIHR grants to C. Creswell and P.C. (PB-PG-0110-21190) and P.C. and C. Creswell (PB-PG-0107-12042); UK Medical Research Council Grants to P.C. and C. Creswell (09-800-17), K.T., P.C. and C. Creswell (G0802326), P.W., C. Creswell and P.C. (G1002011), and C. Creswell (G0601874). Grant 09/800/17 was managed by National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership. This study presents independent research part-funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Acknowledgements

The authors would like to thank: Irma Knuistingh Neven, Marianne Bjerregaard Madsen, Lisbeth Jørgensen, Carmen Adornetto, Kristine Fonnes Griffin, Krister Fjermestad, Elisa Kulewski, Jonas Großekathöfer, Nora Dirks, Evelyn Kmelnitski, Sabrina Heuser, Adrian Boyle, Clare Dixon, Harma Moorlag, Nienke Boersma, Sanne Hogendoorn, Sue Cruddace, Marie Weber, Zoe Hughes, Kiri Clarke, Francoise Hentges, Liz White, Nynke Wagenaar, Luci Motoca, Yesenia Rodriguez, Klaudia Perreira, Erin Hedemann, Cristina Del Busto, Gillian O'Neill, Lucy Lindley, Rachel Banham, Nora Delvendahl, Hjalti Jonsson, Judith Blatter-Meunier, Chantal Herren, Odd E. Havik, Karen Krause, Anna McKinnon, Patrick Smith and Yasmin Rey; and all participants in the study.

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Data supplement to Coleman et al. Genome-wide association study of response to cognitive–behavioural therapy in children with anxiety disorders. Br J Psychiatry doi: 10.1192/bjp.bp.115.168229

Supplemental material

Site information

Unless otherwise specified, clinical trials included all primary anxiety disorder diagnoses. All sites made secondary anxiety disorder diagnoses where appropriate.

Sydney, Australia

Participants aged 6-18 were recruited from the Centre for Emotional Health, Macquarie University, Sydney. All participants completed the Cool Kids program(1), with 10-12 family sessions involving the parents (the majority of which were conducted in groups; 8% of the sample's DNA were collected retrospectively). Variations on this treatment program include a subgroup from previous randomized trials who received group, individual or phone-based CBT sessions(2, 3); participants from a guided self-help trial with phone support for children in rural Australia(4); a group from a trial with additional parental anxiety management (5); and those recruited from an ongoing randomized trial of progressive allocation to treatment (Stepped Care).

Reading and Oxford, UK

Participants aged 5-18 were recruited jointly from Reading and Oxford from eight trials at the Berkshire Child Anxiety Clinic (University of Reading) and the Oxfordshire Primary Child and Adolescent Mental Health Service. Participants received treatment in three main themes; one focusing on children with anxious mothers; a set of trials using a parent-guided self-help CBT program; and an online CBT program for adolescents.

The Mother and Child (MaCh) project(6). Children whose mother also had a current anxiety disorder completed an 8 session manual-based CBT treatment based on the Cool Kids

program(7). The mothers of these children also received extra sessions focusing on their own anxiety and on mother-child interactions.

Overcoming. Children were treated with a parent-guided self-help CBT program, comprised of the same primary components as the Cool Kids program (7, 8). This consisted of 2-4 in-person sessions and 2-4 telephone sessions. A sub-set of this group with a primary anxiety disorder diagnosis of Social Phobia also received targeted Cognitive Bias Modification Training (CBM-I,(9)). Additionally, participants with highly anxious parents (screened using DASS or by meeting ADIS criteria) were randomized to groups in a trial including additional sessions for the parents which focused on strategies for tolerating children's negative emotions. In Oxford, treatment was based on the same basic program, and delivered by primary health workers as part of a feasibility trial(10).

BRAVE. The final treatment group completed a therapist-supported online CBT program for adolescents (BRAVE), consisting of 10 sessions, half with 5 additional parent sessions and half without parent sessions.

Aarhus, Denmark

Participants aged 7-17 years were recruited from the Department of Psychology and Behavioural Sciences, Aarhus University, and all anxiety disorder diagnoses were included. Participants received CBT using the Cool Kids manual (including the adolescent version where appropriate (7, 11)). Participants came from two groups; one aged 7-17, from a trial including treatment and waitlist conditions; and another group aged 7-12 from a trial comparing efficacy of traditional group-based treatment with Cool Kids versus a guided self-help version with clinician support (bibliotherapy). In both trials only participants that received in-person CBT were included.

Bergen, Norway

Participants aged 5-13 were recruited from the child part of the "Assessment and Treatment – Anxiety in Children and Adults" study, Haukeland University Hospital, Bergen. Patients referred to outpatient mental health clinics in Western Norway, with a primary diagnosis of separation anxiety, social phobia, or generalized anxiety, received group or individual

treatment with the FRIENDS program (4th edition(12, 13)) in a randomized control trial comparing active treatment with a waitlist condition(14).

Bochum, Germany

Participants aged 5-18 were recruited from the Research and Treatment Centre for Mental Health, Ruhr-Universität Bochum. Participants received either exposure-based CBT (8-25 sessions, with sessions occurring at least every 2 weeks), the Coping Cat program (15), or a family-based version of CBT specifically designed to target separation anxiety disorder (TAFF (16, 17)). Diagnoses were provided separately for parent- and child-report. The primary diagnosis was selected as being the most severe from either reporter. If the most severe disorder reported by each was of equal severity but was a different diagnosis, the parent-reported diagnosis was selected.

Basel, Switzerland

Participants aged 5-13 (all with a primary diagnosis of Separation Anxiety Disorder) were recruited from the Faculty of Psychology, University of Basel. All participants took part in a randomized control trial comparing a family-based version of CBT specifically designed to target separation anxiety disorder (TAFF (16, 17)with Coping Cat(15)). All participants received 16 sessions over 12 weeks.

Groningen, The Netherlands

Participants aged 8 to 17 were recruited from the Department of Child and Adolescent Psychiatry, University of Groningen. All participants were treated within a randomized control trial of Coping Cat (Dutch version (18)) including 12 individual child sessions and 2 parent sessions.

Florida, USA

Participants aged 7 to 16 (including all primary anxiety disorder diagnoses except PTSD) were recruited from the Child Anxiety and Phobia Program, Florida International University, Miami. All participants received 12 to 14 hour-long sessions of individual manualized CBT. Additionally, two conditions included parental involvement focusing on different parent skills (Relationship Skills Training or Reinforcement Skills Training).

Cambridge, UK

Participants aged 8-17 were recruited from the MRC Cognition and Brain Sciences Unit, Cambridge, UK. Participants were taking part in the ASPECTS trial, which recruited individuals exposed to a recent (i.e. in the previous six months) traumatic stressor (i.e. any event that involve the threat of death, severe injury, or threat to bodily integrity, or witnessing such an event). Those that developed PTSD were randomized to a 10-week waitlist or individual PTSD-specific CBT(19), which consisted of up to 10 sessions over a 10 week period. Only participants that received treatment were included.

Amsterdam, The Netherlands

Participants aged 10-14 were recruited from the Academic Treatment Centre for Parent and Child, University of Amsterdam UvA Minds and received either 12 weeks of CBT in individual sessions or 8 weeks of CBT in group sessions, according to the Dutch protocol Discussing + Doing = Daring(20). Diagnoses were provided separately for parent- and child-report with the primary diagnosis selected from these data by the trial manager.

Assessment of treatment response

At all sites, an experienced diagnostician trained the independent assessors using observation, feedback and supervision, and clearly specified guidelines for allocating diagnoses and CSRs were used. Inter-site consistency between the two largest sites, Sydney and Reading/Oxford (hereafter referred to as Reading), was established through initial training of assessors at Reading using video-recorded assessments from Sydney. In addition, detailed guidance provided by the Sydney site was used in assessments at Reading throughout the study. The principal investigator at the Aarhus site (Mikael Thastum) was trained in Sydney, and assessors in Aarhus received additional training from the principal investigator at the Florida site (Wendy Silverman). As such, treatment response for participants at these four sites, which comprise 85% of the sample, was assessed with a consistent methodology. Within-site inter-rater reliability for the primary anxiety diagnosis ranged from 0.72-1.00, demonstrating that inter-rater agreement was high.

Clinical Severity Ratings across time (and number of participants assessed) by site are shown in Supplementary Table 1c. Overall, mean severity decreased from pre-treatment to post-treatment, and then roughly plateaued across the three follow-up assessments.

However, the results at each follow-up assessment are dependent on which sites performed the assessment; therefore, this should not be considered a general trajectory of treatment response. Similarly, although the mean CSR at each assessment varies between sites, the 95% confidence intervals of each mean overlap, suggesting mean CSRs do not vary significantly. The follow-up phenotype presented in this paper is imputed from this information, as described in the main text.

Non-genetic influences on treatment outcome

A diagnosis of specific phobia was associated with poorer response (percentage change in CSR score over time) and non-remission (CSR>4) at post-treatment, and a diagnosis of social phobia was associated with poorer outcome on both measures at post-treatment and at follow-up (both compared to a diagnosis of generalized anxiety disorder). Comorbid mood and externalizing disorders predicted poorer outcomes at both time-points, and parental psychopathology (self-reported anxious and depressive symptoms) interacted with time since treatment, showing little effect post-treatment but associated with poorer response at follow-up. For further information, see (21).

Sample preparation

DNA concentration was quantified before genotyping by fluorometry using PicoGreen (Invitrogen). Samples below 50ng/ul were concentrated using ultrafiltration and re-suspension. 3600ng of each sample (usually as 300ul at 12ng/ul, although this was adjusted as sample characteristics dictated) was dispensed using a customized Beckman FX robot, and then pipetted via a manual multichannel pipette into a 96-well filtration plate, which captured DNA fragments above 500bp (Multiwell 96-well PCR clean-up plate, Millipore). Samples were filtered under 750mBar of pressure until wells were dry. Following filtration, samples were re-suspended in 40ul of Tris-EDTA buffer with vigorous shaking, and DNA concentration re-quantified using spectroscopy (Nanodrop). Samples with concentration above 50ng/ul continued to genotyping on the Illumina Human Core Exome-12v1.0 microarray, which assays approximately 250 000 common SNPs and 250 000 exomic SNPs located across the genome.

Quality control

In addition to recalling of rare variants with ZCall, recalling was also performed in Opticall (22). The two methods were concordant for 99.78% of cases.

Quality control post-recalling was performed in PLINK (23) and PLINK2 (24), with reference to previously published protocols (25, 26). SNPs were excluded if the frequency of the minor allele was <5%, or if the frequencies of both alleles were out of Hardy-Weinberg equilibrium, with a threshold of $p<10^{-5}$. Samples and SNPs were excluded if call rate was <99%. Samples were excluded if phenotypic gender was inconsistent with X-chromosome homozygosity (F-statistic), if genome-wide heterozygosity was >3 standard deviations from the sample mean, if more than 18.75% of variants were shared by descent (pi-hat) between two samples, or if the average pi-hat of the sample differed from the mean by >6 standard deviations (Supplementary Figure 1). Reported sample gender was compared with X chromosome heterozygosity calculated from genotypes. Male samples are expected to be homozygous for X chromosome SNPs, while females are expected to be heterozygous – the standard PLINK thresholds of >0.8 and <0.2 respectively were used as guidance. Two samples were just outside these thresholds, but were retained as their phenotypic gender matched that suggested by the genotypes.

Principal component analysis (PCA) was performed in EIGENSTRAT (27, 28) on the dataset, pruned for linkage disequilibrium (25). Specifically, SNPs were compared pairwise in windows of 1500 SNPs, and one of each pair removed if $R^2 > 0.2$, and the procedure repeated after a shift of 150 SNPs (23). Initially, PCA was performed with the intention of using principal components to control for population stratification within the dataset. However, the use of quantitative phenotypes from which site differences had been regressed, combined with the fact that participants were recruited from across the globe, prevented the use of principal components for this purpose. The top 100 principal components were not associated with either phenotype beyond a level expected by chance. However, the principal components capture the different ethnicities in the sample, confirming participant self-reported ancestry. The majority (92.4%) of the sample are of White Western European descent (Supplementary Figure 2a, 2b; Supplementary Table 1). The recent development of software to perform mixed linear model association analyses in

genome-wide data provided a better alternative to control for background genetic similarity between individuals (29).

Association analyses were performed on phenotypes indicative of sample quality (sample concentration at entry into genotyping, and whether the sample was collected as a buccal swab or as saliva) as a quality control step. QQ plots were generated using R (script adapted from M. Weale, available at http://sites.google.com/site/mikeweale) and lambda-median values calculated to assess inflation. SNPs showing a lower *p*-value than expected under the null (those below thresholds $p<0.01$ and $p<0.001$, respectively) for either sample quality phenotype were excluded from the final analysis.

Statistical analysis

GWAS was performed using mixed linear model association analysis (MLMA), which derives a genomic relationship matrix (GRM) from genome-wide genotype data, and uses it to model the overall genetic contribution to phenotypic correlation between participants as a random effect. The *mlma-loco* option in GCTA was used to perform a leave-one-chromosome-out marker-excluded analysis on the autosomes, in which the GRM was produced excluding variants on the same chromosome at the SNP being tested. This prevents any effect of the variant of interest being partly captured by the GRM (which would reduce the measured effect of the variant). X-chromosome SNPs were assessed using the *mlma* option and a GRM produced from all autosomes. The X chromosome results were then merged with the autosomal data.

The ability of the GWAS to replicate previous findings was explored. Variants previously implicated in CBT response in mood disorders were examined, as well as further variants in *HTR2A* that have been linked to anxiety disorders more generally (see Table 2). Fourteen SNPs were identified, of which nine passed quality control in the GWAS, none of which was nominally associated with either phenotype (all $p>0.05$). Other variants, such as VNTRs in *SLC6A4* (STin2) and *MAOA* cannot be captured by GWAS. This is also true of the *SLC6A4* 5HTTLPR, which was explored elsewhere (30). In addition to individual assessment, the effect of the SNPs as a set in a linear regression in PLINK was examined. This regression used the same phenotypes and covariates as the main GWAS analyses, but used 10 PCs to control

for further confounds. The effect of the set was not significant (p=1). However, population stratification was not controlled for in this analysis, as it is not currently possible to include a set-based test in the MLMA-GWAS, so it is possible the results of the set-based test were population-confounded.

The GRM produced in the main analysis from all autosomes was used to perform univariate genomic-relatedness-matrix restricted maximum likelihood (GREML) estimation. GREML estimates the heritability captured by the SNPs investigated within the study; this is a fraction of the total heritability in the phenotype, as genotyping will not capture the full effect of variants in imperfect linkage disequilibrium with genotyped SNPs (31). GREML was performed with iterative inclusion of zero to twenty principal components.

Polygenic risk score profiling (implemented in PRSice (32)) was used to investigate the predictive power of the dataset. For each dataset, SNP positions were converted to hg19 where necessary and SNPs not present in the GxT GWAS discarded. The remaining SNPs were clumped by the top p-value using PLINK, such that no SNP that remained was in linkage disequilibrium (r^2>0.1, distance <250kb) with a more significant SNP (33). Risk profiles were created in PLINK, using SNPs with external GWAS p ranging from 0.0001 to 0.5, in increments of 0.00005. Risk was weighted by multiplying risk allele number by beta or log(OR), depending on the dataset. The proportion of variance (adjusted R^2) was calculated from a linear regression of score on outcome for each p-value threshold.

Leave-one-out polygenic risk score profile analyses was performed to test prediction within the dataset. In separate analyses, participants with GAD, separation anxiety disorder, social phobia and specific phobias were secondarily excluded from the data, and MLMA analysis performed on the remaining participants. Profile scores were calculated using the method described above, and the resulting profiles used to predict response in the excluded individuals. The same technique was also used to predict response in participants from Reading, using a profile derived from the participants at other sites.

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Table DS1(a) Demographic details for the 980 participants included in the follow-up GWAS

Site	**N**	**% Female**	**Mean Age (95% CI)**	**White Western European ancestry (N, %)**
Reading	229	55.02	9.57 (6.02-13.12)	208 (91%)
Sydney	467	53.10	9.42 (5.56-13.28)	435 (93%)
Oxford	14	57.14	9.21 (6.37-12.06)	14 (100%)
Florida	25	48.00	9.24 (4.95-13.53)	13 (52%)
Aarhus	96	59.38	11.12 (5.98-16.27)	93 (97%)
Amsterdam	3	0.00	12.67 (9.61-15.72)	3 (100%)
Groningen	25	56.00	11.64 (5.62-17.66)	24 (96%)
Bochum	37	56.76	11.22 (5.72-16.72)	34 (92%)
Basel	38	52.63	8.42 (4.19-12.65)	38 (100%)
Bergen	36	61.11	11.44 (7.38-15.51)	35 (97%)
Cambridge	10	70.00	13.4 (8.79-18.01)	10 (100%)
Total	980	54.69	9.82 (5.39-14.25)	906 (92%)

Table DS1(b) Treatment and diagnosis of the 980 participants included in the follow-up GWAS

Site	Treatment			Primary Anxiety Diagnosis				
	Individual CBT	Group CBT	Guided Self-Help	SAD	Social Phobia	Specific Phobia	GAD	Other Anxiety Disorder
Reading	103	0	126	57	48	40	67	17
Sydney	24	382	61	64	92	31	247	33
Oxford	0	0	14	5	6	1	1	1
Florida	25	0	0	9	5	3	6	2
Aarhus	1	95	0	25	13	16	27	15
Amsterdam	1	2	0	1	1	1	0	0
Groningen	25	0	0	5	11	3	4	2
Bochum	37	0	0	9	11	13	3	0
Basel	38	0	0	38	0	0	0	1
Bergen	20	16	0	11	16	0	9	0
Cambridge	10	0	0	0	0	0	0	10
Total	284	495	201	224	203	108	364	81

Table DS1(c) Mean Clinical Severity Rating and 95% confidence intervals for the participants split by site and assessment

Site	Severity by assessment									
	Pre		Post		3 months		Six months		12 months	
	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N
Reading	5.64 (4.07-7.21)	229	2.69 (-2.05-7.44)	227	-	-	1.90 (-2.65-6.45)	143	2.11 (-2.70-6.91)	76
Sydney	6.33 (4.57-8.09)	467	3.21 (-0.33-6.75)	432	2.85 (-1.54-7.25)	41	2.78 (-0.63-6.19)	324	2.76 (-1.29-6.81)	46
Oxford	5.64 (3.79-7.50)	14	2.36 (-2.64-7.36)	14	-	-	0.00 (0.00-0.00)	2	-	-
Florida	6.84 (4.34-9.34)	25	2.72 (-0.84-6.27)	25	-	-	-	-	5.50 (2.04-8.96)	4
Aarhus	6.45 (3.97-8.93)	96	2.71 (-2.64-8.06)	96	1.97 (-3.19-7.14)	92	-	-	1.40 (1.07-1.72)	7
Amsterdam	5.00 (3.00-7.00)	3	5.00 (-3.72-13.72)	3	-	-	-	-	-	-
Groningen	6.24 (4.48-8.00)	25	2.75 (-0.37-5.87)	25	0.43 (-2.51-3.38)	23	-	-	-	-
Bochum	6.86 (4.65-9.08)	37	2.00 (-2.40-6.40)	34	1.63 (1.33-1.93)	17	1.57 (-2.63-5.78)	14	1.52 (1.23-1.81)	21
Basel	5.92 (4.42-7.42)	38	2.18 (-0.37-4.73)	38	-	-	-	-	4.67 (2.36-6.98)	3
Bergen	6.81 (4.42-9.19)	36	4.80 (0.25-9.35)	35	-	-	-	-	3.58 (-1.50-8.65)	33
Cambridge	6.40 (4.05-8.75)	10	2.24 (-0.41-4.89)	10	-	-	-	-	-	-
Total	6.20 (4.20-8.20)	980	2.96 (-1.28-7.20)	939	1.94 (-2.72-6.61)	173	2.47 (-1.43-6.37)	483	2.54 (-1.98-7.07)	190

Table DS2 Clumps with association *p*-value < $1x10^{-4}$ in the GWAS, extending Tables 1 and 2

a) Independent clumps associated with CBT response post-treatment with *p*<$1x10^{-4}$						
Sentinel SNP	**CHR**	**Clump BP**	**Sentinel SNP *p***	**Sentinel SNP MAF**	**Sentinel SNP Info**	**Genes +/- 100kb**
rs10881475	1	108113663-108203647	$2.45x10^{-6}$	0.187	0.993	NTNG1, VAV3
rs11834041	12	128232821-128239057	$3.50x10^{-6}$	0.135	Genotyped	-
rs12464559	2	152498699-152679462	$4.09x10^{-6}$	0.0410	0.941	NEB, ARL5A, CACNB4
rs881301	8	38322346-38332318	$4.46x10^{-6}$	0.403	Genotyped	WHSC1L1, LETM2, FGFR1, C8orf86
rs16823934	3	115335684-115340900	$5.62x10^{-6}$	0.238	Genotyped	GAP43
rs460214	21	39962001-40059734	$6.01x10^{-6}$	0.269	0.988	ERG
rs11581859	1	99095611-99393710	$9.18x10^{-6}$	0.218	0.981	SNX7, LPPR5
rs3856211	1	166021956-166047333	$1.18x10^{-5}$	0.394	Genotyped	FAM78B
rs12188300	5	158829527-158848071	$1.61x10^{-5}$	0.0801	Genotyped	IL12B
rs2095842	1	18283857-18297688	$1.71x10^{-5}$	0.231	Genotyped	-
rs2619372	4	90710099-90779823	$2.53x10^{-5}$	0.279	0.994	SNCA, MMRN1
rs4705334	5	145822073-145904225	$2.64x10^{-5}$	0.166	Genotyped	TCERG1, GPR151, PPP2R2B

rs143282317	17	5136668-5327973	$3.15x10^{-5}$	0.0160	0.926	USP6, ZNF594, SCIMP, RABEP1, NUP88, RPAIN, C1QBP, DHX33, MIS12, NLRP1
rs12548760	8	136791557-136900947	$3.60x10^{-5}$	0.470	0.979	-
rs727675	14	31693539-31949029	$3.60x10^{-5}$	0.419	Genotyped	HECTD1, HEATR5A, DTD2, GPR33, NUBPL
rs17667668	2	181500273-181626750	$3.61x10^{-5}$	0.299	0.990	SCHLAP1
rs111988532	12	76161146-76174818	$3.79x10^{-5}$	0.0100	0.855	-
rs3922930	15	81610902-81664087	$3.92x10^{-5}$	0.248	0.982	IL16, STARD5, TMC3
rs10777556	12	94309145-94316320	$4.32x10^{-5}$	0.0530	Genotyped	CRADD
rs6627537	X	151284910-151339003	$4.32x10^{-5}$	0.146	0.988	MAGEA10-MAGEA5, GABRA3
rs11770698	7	90201382-90608207	$4.55x10^{-5}$	0.382	0.987	CDK14
rs78885728	11	34720279-35015437	$4.73x10^{-5}$	0.0700	0.969	EHF, APIP, PDHX
rs2506818	X	33768102-34099788	$4.74x10^{-5}$	0.201	0.975	FAM47A
rs34141319	9	139146916-139148344	$5.81x10^{-5}$	0.139	Genotyped	LHX3, QSOX2, GPSM1
rs2079169	4	7684641-7685529	$5.95x10^{-5}$	0.389	Genotyped	SORCS2, AFAP1

rs17106850	5	146905987-146920247	$6.02x10^{-5}$	0.169	0.998	DPYSL3, JAKMIP2
rs73127355	7	53180775-53653377	$6.04x10^{-5}$	0.0200	0.930	POM121L12
rs433156	2	77589901-77627119	$6.59x10^{-5}$	0.368	Genotyped	LRRTM4
rs35048888	2	28683174-28689459	$6.72x10^{-5}$	0.498	0.992	FOSL2, PLB1
rs148631369	2	128804780-128929492	$7.06x10^{-5}$	0.0110	0.927	SAP130, UGGT1, HS6ST1
rs6900853	6	71618855-71729332	$8.14x10^{-5}$	0.306	Genotyped	SMAP1, B3GAT2
rs35884480	6	46519020-46632594	$8.49x10^{-5}$	0.0587	Genotyped	RCAN2, CYP39A1 , SLC25A27, TDRD6, PLA2G7, ANKRD66
rs143836403	15	48728634-48941542	$8.66x10^{-5}$	0.0820	0.951	DUT, FBN1, CEP152
rs4766728	12	114711649-114725149	$8.88x10^{-5}$	0.152	0.988	TBX5
rs7734294	5	36689181-36768602	$9.01x10^{-5}$	0.197	Genotyped	SLC1A3
rs1336336	9	26759980-26918113	$9.17x10^{-5}$	0.474	Genotyped	CAAP1, PLAA, IFT74, LRRC19
rs6536613	4	162668979-162729203	$9.47x10^{-5}$	0.0230	0.931	FSTL5
rs12410507	1	60899849-61041875	$9.72x10^{-5}$	0.177	0.978	-
rs59085393	1	156374432-156390617	$9.88x10^{-5}$	0.0390	0.949	CCT3, RHBG, MEF2D

b) Independent clumps associated with CBT response at six-month follow-up with $p<1x10^{-4}$						
Sentinel SNP	**CHR**	**Clump BP**	**Sentinel SNP *p***	**Sentinel SNP MAF**	**Sentinel SNP Info**	**Genes +/- 100kb**
rs72711240	4	135657189-135695807	$4.49x10^{-7}$	0.0269	0.903	-
rs9875578	3	13707416 - 13810670	$1.43x10^{-6}$	0.424	0.994	FBLN2, WNT7A
rs6813264	4	146509970-146631854	$4.68x10^{-6}$	0.410	Genotyped	SMAD1, MMAA, C4orf51, ZNF827
rs12850751	X	145130635-145161195	$6.64x10^{-6}$	0.0655	0.952	-
rs13432654	2	162300286-162411997	$8.40x10^{-6}$	0.0939	Genotyped	PSMD14, TBR1, SLC4A10
rs76635837	15	53613961-53636281	$1.00x10^{-5}$	0.0376	0.956	-
rs1795708	12	58750680-58836631	$1.04x10^{-5}$	0.344	Genotyped	-
rs7257625	19	46468703-46474428	$1.05x10^{-5}$	0.189	Genotyped	FOXA3, IRF2BP1, MYPOP, NANOS2, NOVA2, CCDC61, PGLYRP1, IGFL4
rs17025778	2	98637504-98701594	$1.23x10^{-5}$	0.0821	Genotyped	TMEM131, VWA3B
rs56090036	15	99052579-99054173	$1.65x10^{-5}$	0.0457	0.931	FAM169B
rs111589871	8	89764480-90195838	$1.87x10^{-5}$	0.0459	0.955	-

rs73060838	3	37982687-38221526	$2.18x10^{-5}$	0.0487	0.970	CTDSPL, VILL, PLCD1, DLEC1, ACAA1, MYD88, OXSR1, SLC22A13
rs11949603	5	36361696-36383780	$2.67x10^{-5}$	0.307	0.994	RANBP3L
rs7766941	6	54310901-54702870	$2.70x10^{-5}$	0.339	0.991	T1NAG, FAM83B
rs6133736	20	9627908-9726640	$2.79x10^{-5}$	0.133	0.968	PAK7
rs55776604	17	73362147-73411596	$3.11x10^{-5}$	0.0532	0.965	MRPS7, MIF4GD, SLC25A19, GRB2, KIAA0195, CASKIN2
rs10484917	6	142038521-142110406	$3.14x10^{-5}$	0.122	0.978	-
rs61470941	2	136393157-136747085	$3.24x10^{-5}$	0.0958	0.984	R3HDM1, UBXN4, LCT, MCM6, DARS
rs11784693	8	11527910-11832769	$3.40x10^{-5}$	0.291	Genotyped	GATA4, NEIL2, FDFT1, CTSB, DEFB136, DEFB135, DEFB134, DEFB130
rs13163544	5	174069668-174126415	$3.44x10^{-5}$	0.426	Genotyped	MSX2
rs9472259	6	44291641-	$3.50x10^{-5}$	0.327	0.989	SLC29A1,

		44355423				HSP90AB1, SLC35B2, NFKBIE, TMEM151B, TCTE1, AARS2, SPATS1, CDC5L
rs6971364	7	8417400-8453313	$3.69x10^{-5}$	0.438	0.993	NXPH1
rs2690112	6	25288549-25328790	$3.81x10^{-5}$	0.372	0.985	LRRC16A
rs1486171	7	46172701-46211646	$3.97x10^{-5}$	0.392	0.996	-
rs6804426	3	151676820-151780935	$4.00x10^{-5}$	0.224	0.988	SUCNR1
rs13237987	7	9842272-9875208	$4.83x10^{-5}$	0.278	0.994	-
rs4686487	3	188341678	$5.03x10^{-5}$	0.199	Genotyped	LPP
rs114726046	6	24058226-24083141	$5.16x10^{-5}$	0.0130	0.819	NRSN1, DCDC2
rs11155986	6	154875787-154953972	$5.21x10^{-5}$	0.244	Genotyped	CNKSR3
rs4770433	13	23892555-23916736	$5.27x10^{-5}$	0.439	Genotyped	SGCG, SACS
rs12855797	X	10723386	$5.28x10^{-5}$	0.125	Genotyped	MID1
rs7131178	11	93322831-93473333	$5.46x10^{-5}$	0.181	Genotyped	SMCO4, CP295, TAF1D, c11orf54, MED17, VSTM5
rs202245865	6	132282553-132336972	$6.03x10^{-5}$	0.00980	0.828	ENPP1, CTGF
rs7784698	7	98253847-	$6.17x10^{-5}$	0.0608	0.993	NPTX2

		98311136				
rs56118623	21	19063114-19085866	$6.21x10^{-5}$	0.0906	0.946	CXADR, BTG3, c21orf91
rs12985380	19	51850290-51869346	$6.91x10^{-5}$	0.475	Genotyped	SIGLECL1, IGLON5, VSIG10L, ETFB, CLDND2, NKG7, LI2, c19orf84, SIGLEC10, SIGLEC8
rs4417554	16	27028555-27034201	$6.97x10^{-5}$	0.417	0.983	c16orf82
rs875104	13	97981705-98028784	$7.04x10^{-5}$	0.115	0.980	MBNL2, RAP2A
rs1279690	1	81066500-81154515	$7.13x10^{-5}$	0.300	Genotyped	-
rs115613292	4	43199190-43330931	$7.40x10^{-5}$	0.170	0.979	-
rs6453323	5	76726202-76877496	$7.42x10^{-5}$	0.364	Genotyped	PDE8B, WDR41, OTP
rs8047148	16	22255898-22377003	$7.45x10^{-5}$	0.225	Genotyped	VWA3A, EEF2K, POLR3E, CDR2
rs321505	6	64381461-64741820	$7.91x10^{-5}$	0.407	0.996	PTP4A1, PHF3, EYS
rs9393387	6	23274466-23320458	$8.11x10^{-5}$	0.497	Genotyped	-
rs17289116	9	32454368-32546117	$8.33x10^{-5}$	0.206	0.977	ACO1, DDX58, TOPORS, NDUFB6
rs6862501	5	12611030-12778499	$8.72x10^{-5}$	0.155	0.973	-

rs2343115	4	109070672-109111726	$8.99x10^{-5}$	0.462	Genotyped	LEF1
rs6608068	X	122425522-122503729	$9.08x10^{-5}$	0.184	Genotyped	GRIA3
rs75403290	5	175607631-175839232	$9.33x10^{-5}$	0.0203	0.910	FAM153B, SIMC1, KIAA1191, ARL10, NOP16, CLTB, FAF2
rs62312236	4	108955150-109017528	$9.58x10^{-5}$	0.0594	0.984	CYP2U1, HADH, LEF1
rs26571	5	111189290-111668828	$9.70x10^{-5}$	0.0428	0.958	NREP, EPB41L4A

Fig. DS1 Exclusion of samples (top) and single nucleotide polymorphisms (bottom).

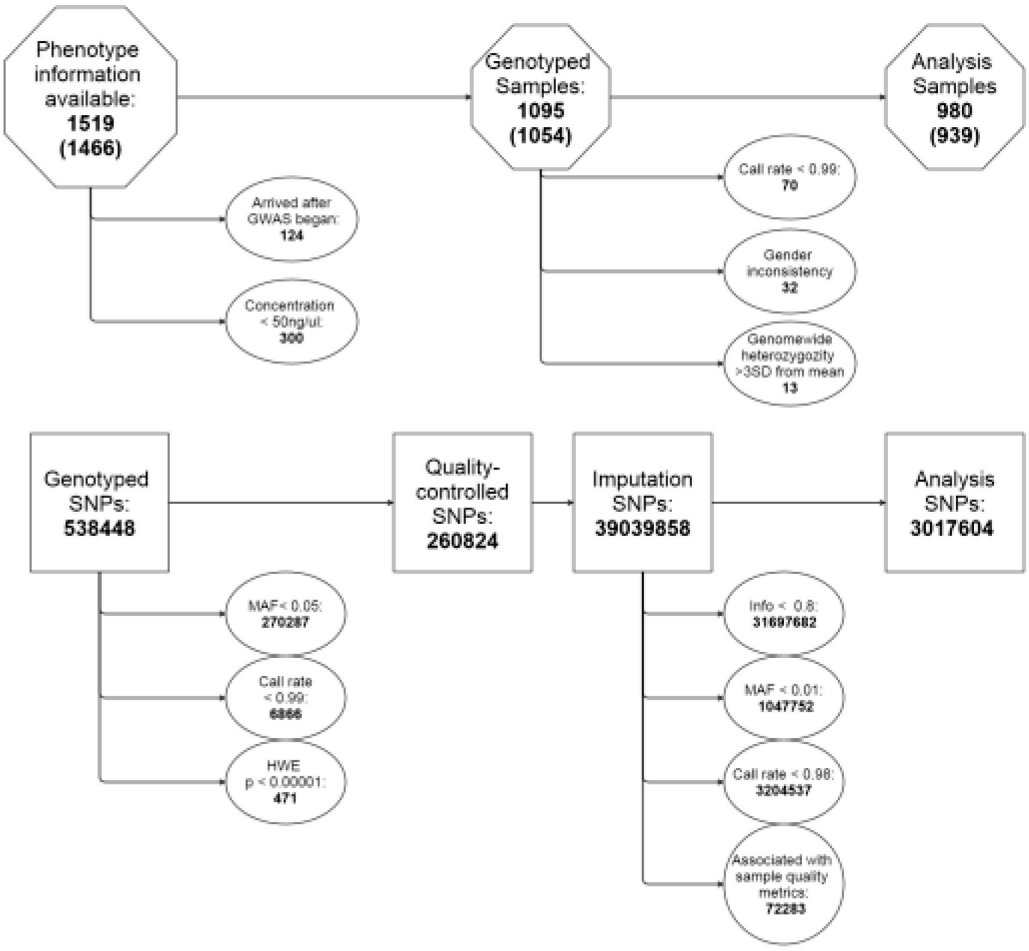


Fig. DS2(a) Samples projected on the first two principal components derived from the study samples.

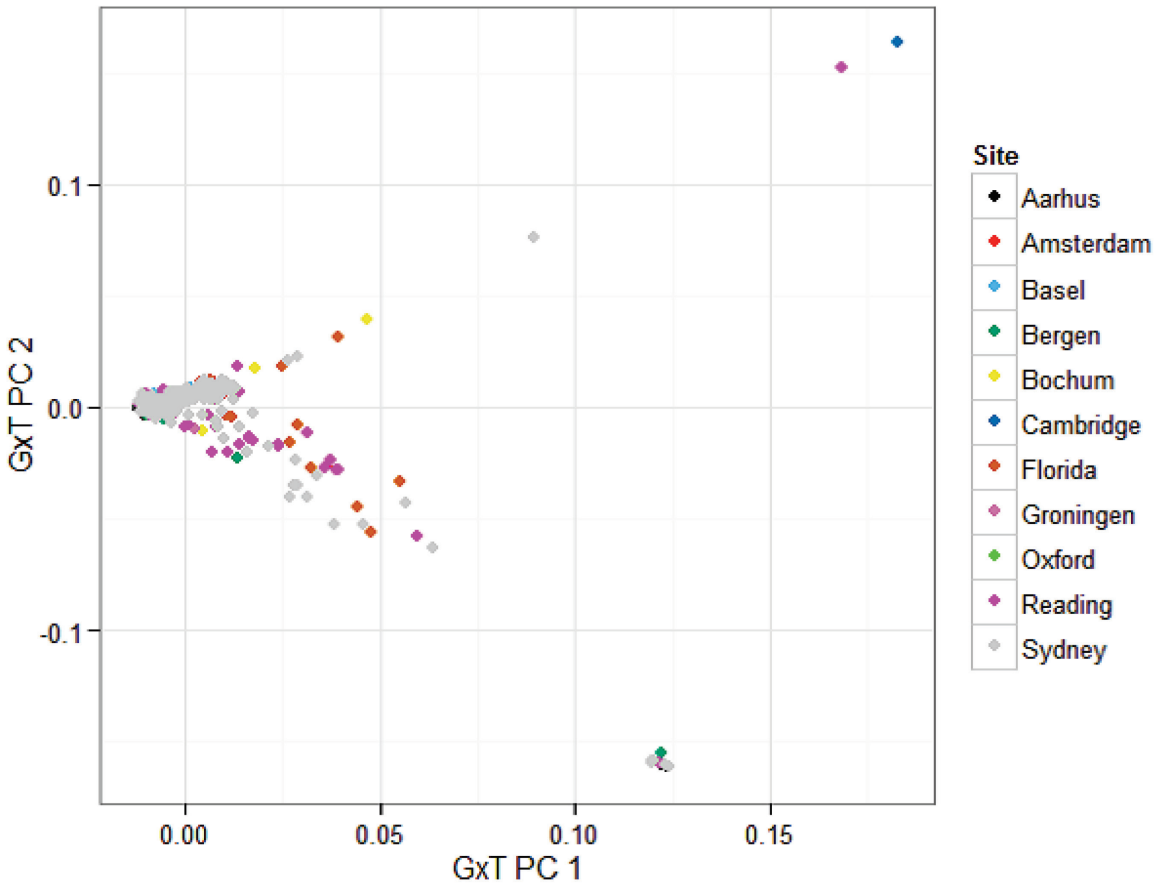
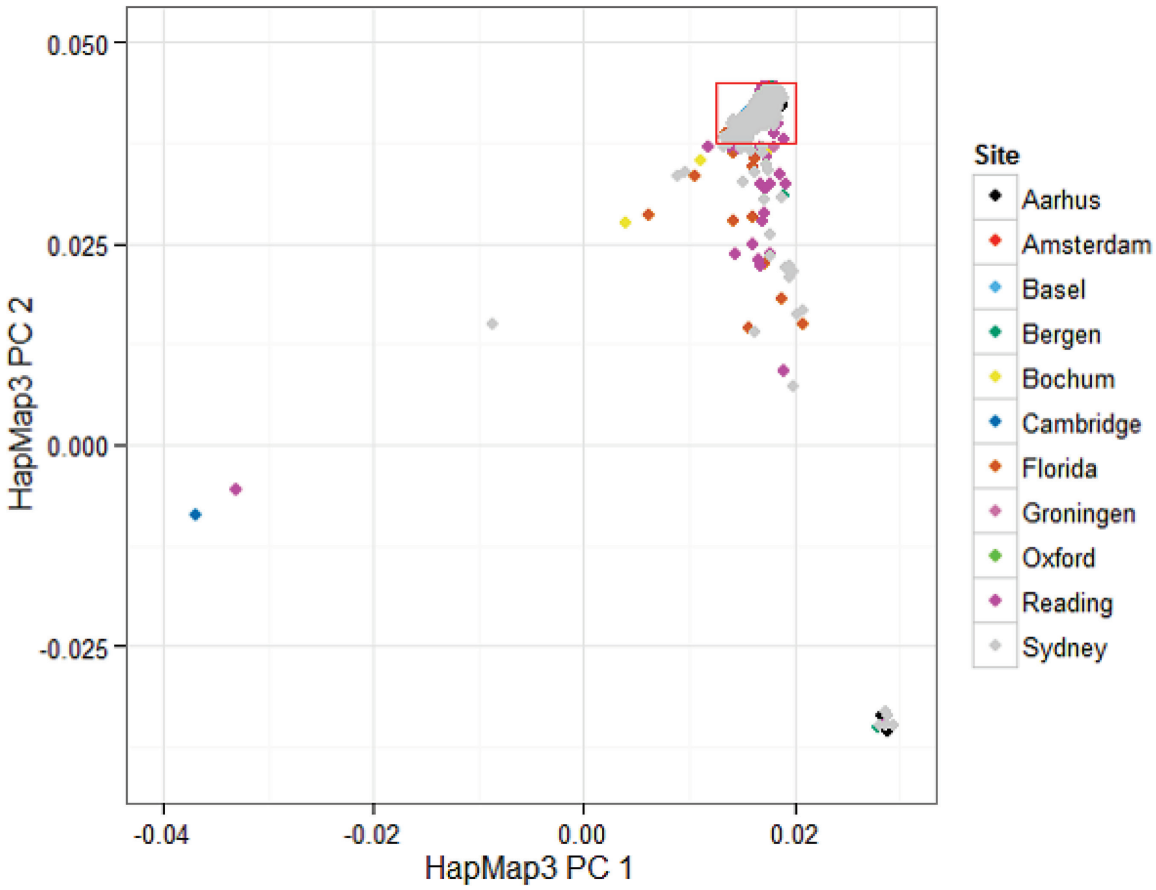


Fig. DS2(b) Samples projected on the first two principal components derived from the HapMap3 samples, showing that the majority cluster in a White Western European group (red box), with admixed samples descending down to East Asian ancestry (right), and to African ancestry (left).



Genome-wide association study of response to cognitive–behavioural therapy in children with anxiety disorders

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BJP 2016, 209:236-243.
Access the most recent version at DOI: 10.1192/bjp.bp.115.168229

Supplementary Material Supplementary material can be found at: http://bjp.rcpsych.org/content/suppl/2016/03/14/bjp.bp.115.168229.DC1

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