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


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 × 10⁻⁸) in either analysis. Four variants met criteria for suggestive significance (P < 5 × 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 therapy genetic 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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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 (rs60812849, \( P = 3.13 \times 10^{-9} \), OR not reported)15 and PRTFDC1 (rs64822463, \( P = 2.04 \times 10^{-9} \), 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 criteria19 for a primary anxiety disorder diagnosis, with 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 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.23 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.20 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 chromosome27), 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.

### 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.29

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 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.

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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 (buffalo 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 (R² > 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 (LG 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.3 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 outcome. This was done by using risk profiles from publicly available GWAS of major depressive disorder34 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 positions 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>
<thead>
<tr>
<th>Sentinel SNP</th>
<th>CHR</th>
<th>Clump BP</th>
<th>Sentinel SNP P</th>
<th>Sentinel SNP MAF</th>
<th>Sentinel SNP information</th>
<th>Genes +/-100kb</th>
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<tr>
<td>rs10881475</td>
<td>1</td>
<td>108113663–108203647</td>
<td>2.45 $\times 10^{-6}$</td>
<td>0.187</td>
<td>0.993</td>
<td>NTNG1, VAV3</td>
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<tr>
<td>rs11834041</td>
<td>12</td>
<td>128202721–128299507</td>
<td>3.50 $\times 10^{-6}$</td>
<td>0.135</td>
<td>Genotyped</td>
<td>–</td>
</tr>
<tr>
<td>rs124464559</td>
<td>2</td>
<td>152498699–152679462</td>
<td>4.09 $\times 10^{-6}$</td>
<td>0.0410</td>
<td>0.941</td>
<td>NEB, ARL5A, CACNB4</td>
</tr>
<tr>
<td>rs6813301</td>
<td>8</td>
<td>38322346–38332318</td>
<td>4.46 $\times 10^{-6}$</td>
<td>0.403</td>
<td>Genotyped</td>
<td>WHSC1L1, LETM2, FGFR1, C8orf86</td>
</tr>
</tbody>
</table>

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. 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. 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. Failure to replicate previous findings from the candidate gene literature has proved common in psychiatric genetics, whereas GWAS is proving more.
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 SHTTLPR 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
reflect natural variation 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. The aim of therapygenetics is to discover predictors of differential treatment effects 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. 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 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. |  |
|---|---|---|---|
| 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 |
| NFG | rs6330 | 0.5093 | 0.4559 |
| BDNF | rs265 (val158met) | 0.3048 | 0.9078 |
| | rs7934165 | 0.5231 | 0.9880 |
| | rs1519480 | 0.8211 | 0.5013 |
| | rs11030104 | 0.3188 | 0.9475 |
| 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 GEMRE 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 necessarily those of the NHS, the NIHR or the Department of Health.

Acknowledgements


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8


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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 \texttt{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 \texttt{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 \textit{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 \textit{SLC6A4} (STin2) and \textit{MAOA} cannot be captured by GWAS. This is also true of the \textit{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 $<250$kb) 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.
Supplemental references


<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>% Female</th>
<th>Mean Age (95% CI)</th>
<th>White Western European ancestry (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading</td>
<td>229</td>
<td>55.02</td>
<td>9.57 (6.02-13.12)</td>
<td>208 (91%)</td>
</tr>
<tr>
<td>Sydney</td>
<td>467</td>
<td>53.10</td>
<td>9.42 (5.56-13.28)</td>
<td>435 (93%)</td>
</tr>
<tr>
<td>Oxford</td>
<td>14</td>
<td>57.14</td>
<td>9.21 (6.37-12.06)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>Florida</td>
<td>25</td>
<td>48.00</td>
<td>9.24 (4.95-13.53)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Aarhus</td>
<td>96</td>
<td>59.38</td>
<td>11.12 (5.98-16.27)</td>
<td>93 (97%)</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>3</td>
<td>0.00</td>
<td>12.67 (9.61-15.72)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Groningen</td>
<td>25</td>
<td>56.00</td>
<td>11.64 (5.62-17.66)</td>
<td>24 (96%)</td>
</tr>
<tr>
<td>Bochum</td>
<td>37</td>
<td>56.76</td>
<td>11.22 (5.72-16.72)</td>
<td>34 (92%)</td>
</tr>
<tr>
<td>Basel</td>
<td>38</td>
<td>52.63</td>
<td>8.42 (4.19-12.65)</td>
<td>38 (100%)</td>
</tr>
<tr>
<td>Bergen</td>
<td>36</td>
<td>61.11</td>
<td>11.44 (7.38-15.51)</td>
<td>35 (97%)</td>
</tr>
<tr>
<td>Cambridge</td>
<td>10</td>
<td>70.00</td>
<td>13.4 (8.79-18.01)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>980</td>
<td>54.69</td>
<td>9.82 (5.39-14.25)</td>
<td>906 (92%)</td>
</tr>
</tbody>
</table>
Table DS1(b) Treatment and diagnosis of the 980 participants included in the follow-up GWAS

<table>
<thead>
<tr>
<th>Site</th>
<th>Treatment</th>
<th>Primary Anxiety Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individual CBT</td>
<td>Group CBT</td>
</tr>
<tr>
<td>Reading</td>
<td>103</td>
<td>0</td>
</tr>
<tr>
<td>Sydney</td>
<td>24</td>
<td>382</td>
</tr>
<tr>
<td>Oxford</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Florida</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Aarhus</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Groningen</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Bochum</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Basel</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Bergen</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Cambridge</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>495</td>
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Table DS1(c) Mean Clinical Severity Rating and 95% confidence intervals for the participants split by site and assessment

<table>
<thead>
<tr>
<th>Site</th>
<th>Severity by assessment</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>3 months</td>
<td>Six months</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (N)</td>
<td>Mean (N)</td>
<td>Mean (N)</td>
<td>Mean (N)</td>
<td>Mean (N)</td>
<td>Mean (N)</td>
</tr>
<tr>
<td>Reading</td>
<td>5.64 (4.07-7.21) (229)</td>
<td>2.69 (-2.05-7.44) (227)</td>
<td>-</td>
<td>1.90 (-2.65-6.45) (143)</td>
<td>2.11 (-2.70-6.91) (76)</td>
<td></td>
</tr>
<tr>
<td>Sydney</td>
<td>6.33 (4.57-8.09) (467)</td>
<td>3.21 (-0.33-6.75) (432)</td>
<td>2.85 (-1.54-7.25) (41)</td>
<td>2.78 (-0.63-6.19) (324)</td>
<td>2.76 (-1.29-6.81) (46)</td>
<td></td>
</tr>
<tr>
<td>Oxford</td>
<td>5.64 (3.79-7.50) (14)</td>
<td>2.36 (-2.64-7.36) (14)</td>
<td>-</td>
<td>0.00 (0.00-0.00) (2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Florida</td>
<td>6.84 (4.34-9.34) (25)</td>
<td>2.72 (-0.84-6.27) (25)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.50 (2.04-8.96) (4)</td>
</tr>
<tr>
<td>Aarhus</td>
<td>6.45 (3.97-8.93) (96)</td>
<td>2.71 (-2.64-8.06) (96)</td>
<td>1.97 (-3.19-7.14) (92)</td>
<td>-</td>
<td>-</td>
<td>1.40 (1.07-1.72) (7)</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>5.00 (3.00-7.00) (3)</td>
<td>5.00 (-3.72-13.72) (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Groningen</td>
<td>6.24 (4.48-8.00) (25)</td>
<td>2.75 (-0.37-5.87) (25)</td>
<td>0.43 (-2.51-3.38) (23)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bochum</td>
<td>6.86 (4.65-9.08) (37)</td>
<td>2.00 (-2.40-6.40) (34)</td>
<td>1.63 (1.33-1.93) (17)</td>
<td>1.57 (-2.63-5.78) (14)</td>
<td>1.52 (1.23-1.81) (21)</td>
<td></td>
</tr>
<tr>
<td>Basel</td>
<td>5.92 (4.42-7.42) (38)</td>
<td>2.18 (-0.37-4.73) (38)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.67 (2.36-6.98) (3)</td>
</tr>
<tr>
<td>Bergen</td>
<td>6.81 (4.42-9.19) (36)</td>
<td>4.80 (0.25-9.35) (35)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.58 (-1.50-8.65) (33)</td>
</tr>
<tr>
<td>Cambridge</td>
<td>6.40 (4.05-8.75) (10)</td>
<td>2.24 (-0.41-4.89) (10)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>6.20 (4.20-8.20) (980)</td>
<td>2.96 (-1.28-7.20) (939)</td>
<td>1.94 (-2.72-6.61) (173)</td>
<td>2.47 (-1.43-6.37) (483)</td>
<td>2.54 (-1.98-7.07) (190)</td>
<td></td>
</tr>
</tbody>
</table>
Table DS2 Clumps with association $p$-value $<1\times10^{-4}$ in the GWAS, extending Tables 1 and 2

### a) Independent clumps associated with CBT response post-treatment with $p<1\times10^{-4}$

<table>
<thead>
<tr>
<th>Sentinel SNP</th>
<th>CHR</th>
<th>Clump BP</th>
<th>Sentinel SNP $p$</th>
<th>Sentinel SNP MAF</th>
<th>Sentinel SNP Info</th>
<th>Genes +/- 100kb</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10881475</td>
<td>1</td>
<td>108113663-108203647</td>
<td>2.45x10$^{-6}$</td>
<td>0.187</td>
<td>0.993</td>
<td>NTNG1, VAV3</td>
</tr>
<tr>
<td>rs11834041</td>
<td>12</td>
<td>128232821-128239057</td>
<td>3.50x10$^{-6}$</td>
<td>0.135</td>
<td>Genotyped</td>
<td>-</td>
</tr>
<tr>
<td>rs12464559</td>
<td>2</td>
<td>152498699-152679462</td>
<td>4.09x10$^{-6}$</td>
<td>0.0410</td>
<td>0.941</td>
<td>NEB, ARL5A, CACNB4</td>
</tr>
<tr>
<td>rs881301</td>
<td>8</td>
<td>38322346-38332318</td>
<td>4.46x10$^{-6}$</td>
<td>0.403</td>
<td>Genotyped</td>
<td>WHSC1L1, LETM2, FGFR1, C8orf86</td>
</tr>
<tr>
<td>rs16823934</td>
<td>3</td>
<td>115335684-115340900</td>
<td>5.62x10$^{-6}$</td>
<td>0.238</td>
<td>Genotyped</td>
<td>GAP43</td>
</tr>
<tr>
<td>rs460214</td>
<td>21</td>
<td>39962001-40059734</td>
<td>6.01x10$^{-6}$</td>
<td>0.269</td>
<td>0.988</td>
<td>ERG</td>
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<tr>
<td>rs11581859</td>
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<td>99095611-99393710</td>
<td>9.18x10$^{-6}$</td>
<td>0.218</td>
<td>0.981</td>
<td>SNX7, LPPR5</td>
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<tr>
<td>rs3856211</td>
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<td>1.18x10$^{-5}$</td>
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<tr>
<td>rs12188300</td>
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<td>158829527-158848071</td>
<td>1.61x10$^{-5}$</td>
<td>0.0801</td>
<td>Genotyped</td>
<td>IL12B</td>
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<tr>
<td>rs2095842</td>
<td>1</td>
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<td>1.71x10$^{-5}$</td>
<td>0.231</td>
<td>Genotyped</td>
<td>-</td>
</tr>
<tr>
<td>rs2619372</td>
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<td>2.53x10$^{-5}$</td>
<td>0.279</td>
<td>0.994</td>
<td>SNCA, MMRN1</td>
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<tr>
<td>rs4705334</td>
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<tr>
<td>Genotype ID</td>
<td>Chromosome</td>
<td>Position</td>
<td>P-value</td>
<td>Quality</td>
<td>Genotypes</td>
<td>Genes</td>
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<td>rs143282317</td>
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<td>$3.15 \times 10^{-5}$</td>
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<td>0.926</td>
<td>USP6, ZNF594, SCIMP, RABEP1, NUP88, RPAIN, C1QBP, DHX33, MIS12, NLRP1</td>
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<tr>
<td>rs12548760</td>
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<td>$3.60 \times 10^{-5}$</td>
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<tr>
<td>rs727675</td>
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<td>31693539-31949029</td>
<td>$3.60 \times 10^{-5}$</td>
<td>0.419</td>
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<td>HECTD1, HEATR5A, DTD2, GPR33, NUBPL</td>
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<tr>
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<td>181500273-181626750</td>
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<td>0.990</td>
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<tr>
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<td>0.988</td>
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<tr>
<td>rs11770698</td>
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<td>0.975</td>
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<tr>
<td>rs34141319</td>
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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
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
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