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.

Supplemental references

1. Rapee RM, Lyneham HJ, Schniering CA, Wuthrich VM, Abbott MA, Hudson JL, et al. The Cool Kids® Child and Adolescent Anxiety Program. Sydney: Centre for Emotional Health, Macquarie University; 2006.

2. Hudson JL, Rapee RM, Deveney C, Schniering CA, Lyneham HJ, Bovopoulos N. Cognitive-Behavioral Treatment Versus an Active Control for Children and Adolescents With Anxiety Disorders: A Randomized Trial. J Am Acad Child Adolesc Psychiatry. 2009;48(5):533-44.

3. Rapee RM, Abbott MJ, Lyneham HJ. Bibliotherapy for children with anxiety disorders using written materials for parents: A randomized controlled trial. J Consult Clin Psychol. 2006;74(3):436 - 44.

4. Lyneham HJ, Rapee RM. Evaluation of therapist-supported parent-implemented CBT for anxiety disorders in rural children. Behav Res Ther. 2006;44(9):1287-300.

5. Hudson JL, Newall C, Rapee RM, Lyneham HJ, Schniering CC, Wuthrich VM, et al. The Impact of Brief Parental Anxiety Management on Child Anxiety Treatment Outcomes: A Controlled Trial. Journal of Clinical Child and Adolescent Psychology. 2014;43(3):370-80.

6. Creswell C, Cruddace S, Gerry S, McIntosh A, Mollison J, Murray L, et al. Treatment of childhood anxiety disorder in the context of maternal anxiety disorder: A randomised controlled trial. Health Technol Assess.

7. Lyneham HJ, Abbott MJ, Wignall A, Rapee RM. The Cool Kids Anxiety Treatment Programme. Sydney MUARU, Macquarie University; 2003.

8. Thirlwall K, Cooper PJ, Karalus J, Voysey M, Willetts L, Creswell C. Treatment of child anxiety disorders via guided parent-delivered cognitive-behavioural therapy: randomised controlled trial. The British Journal of Psychiatry. 2013;203(6):436 - 44. Epub 2013/08/24.

9. Vassilopoulos SP, Banerjee R, Prantzalou C. Experimental modification of interpretation bias in socially anxious children: Changes in interpretation, anticipated interpersonal anxiety, and social anxiety symptoms. Behav Res Ther. 2009;47(12):1085-9.

10. Creswell C, Hentges F, Parkinson M, Sheffield P, Willetts L, Cooper P. Feasibility of guided cognitive behaviour therapy (CBT) self-help for childhood anxiety disorders in primary care. Mental Health in Family Medicine. 2010;7(1):49 - 57.

11. Rapee RM, Lyneham HJ, Schniering CA, Wuthrich VM, Abbott M, Hudson J, et al. Cool Kids "Chilled" Adolescent Anxiety Program2006.

12. Barrett PM, Farrell LJ, Ollendick TH, Dadds M. Long-term outcomes of an Australian universal prevention trial of anxiety and depression symptoms in children and youth: an evaluation of the friends program. Journal of Clinical Child and Adolescent Psychology. 2006;35(3):403-11.
13. Barrett P. Friends for Life Program–Group Leader's Workbook for Youth. Brisbane: Australian Academic Press; 2005.
14. Wergeland GJH, Fjermestad KW, Marin CE, Haugland BS-M, Bjaastad JF, Oeding K, et al. An effectiveness study of individual vs. group cognitive behavioral therapy for anxiety disorders in youth. Behaviour Research and Therapy. 2014;57(0):1-12.
15. Kendall PC. Treating anxiety disorders in children: results of a randomized clinical trial. J Consult Clin Psychol. 1994;62(1):100-10.
16. Schneider S, Blatter-Meunier J, Herren C, In-Albon T, Adornetto C, Meyer A, et al. The Efficacy of a Family-Based Cognitive-Behavioral Treatment for Separation Anxiety Disorder in Children Aged 8-13: A Randomized Comparison With a General Anxiety Program. J Consult Clin Psychol. 2013;81(5):932-40.
17. Schneider S, Lavallee K. Separation Anxiety Disorder. In: Essau CA, Ollendick T, editors. The Wiley-Blackwell Handbook of The Treatment of Childhood and Adolescent Anxiety Chichester: Wiley-Blackwell; 2013. p. 301-34.
18. Nauta M, Scholing A. Cognitieve gedragstherapie bij kinderen en jongeren met angststoornissen: een protocol van 12 sessies. Handleiding voor de therapeut. Groningen: Rijksuniversiteit Groningen (Klinische en Ontwikkelingspsychologie); 1998.
19. Smith P, Yule W, Perrin S, Tranah T, Dalgleish T, M. CD. Cognitive-Behavioral Therapy for PTSD in Children and Adolescents: A Preliminary Randomized Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2007;46(8):1051-61.
20. Bögels SM. Behandeling van angststoornissen bij kinderen en adolescenten: Springer; 2008.
21. Hudson JL, Keers R, Roberts S, Coleman JRI, Breen G, Arendt K, et al. Clinical Predictors of Response to Cognitive-Behavioral Therapy in Pediatric Anxiety Disorders: The Genes for Treatment (GxT) Study. J Am Acad Child Adolesc Psychiatry. 2015.
22. Shah TS, Liu JZ, Floyd JAB, Morris JA, Wirth N, Barrett JC, et al. optiCall: A robust genotype-calling algorithm for rare, low frequency and common variants. Bioinformatics. 2012.

23. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. The American Journal of Human Genetics. 2007;81(3):559-75.
24. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. arXiv preprint arXiv:14104803. 2014.
25. Weale ME. Quality control for genome-wide association studies. Methods in Molecular Biology. 2010;628:341-72.
26. Anderson CA, Pettersson FH, Clarke GM, Cardon LR, Morris AP, Zondervan KT. Data quality control in genetic case-control association studies. Nature Protocols. 2010;5(9):1564-73. Epub 2010/11/19.
27. Patterson N, Price AL, Reich D. Population Structure and Eigenanalysis. PLoS Genet. 2006;2:e190.
28. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006;38(8):904-9.
29. Yang J, Zaitlen NA, Goddard ME, Visscher PM, Price AL. Advantages and pitfalls in the application of mixed-model association methods. Nat Genet. 2014;46(2):100-6.
30. Lester KJ, Roberts S, Keers R, Jonathan R.I. Coleman, Gerome Breen, Chloe Wong, et al. The 5HTTLPR and response to psychological therapy – an update. Br J Psychiatry. In Press.
31. Visscher PM, Yang J, Goddard ME. A commentary on 'common SNPs explain a large proportion of the heritability for human height' by Yang et al. (2010). Twin research and human genetics : the official journal of the International Society for Twin Studies. 2010;13(6):517-24. Epub 2010/12/15.
32. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. Bioinformatics. 2015;31(9):1466-8. Epub 2015/01/01.
33. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460(7256):748-52.

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).

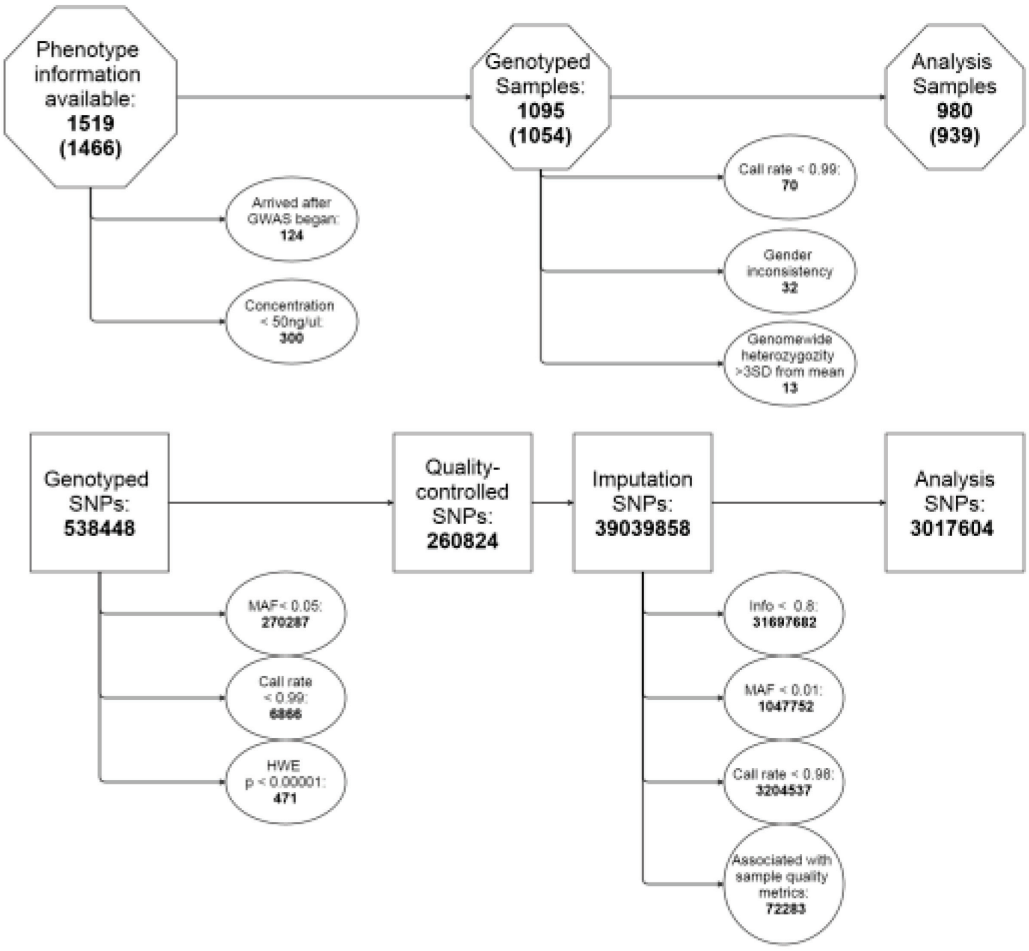

Fig. DS2(a) Samples projected on the first two principal components derived from the study samples.

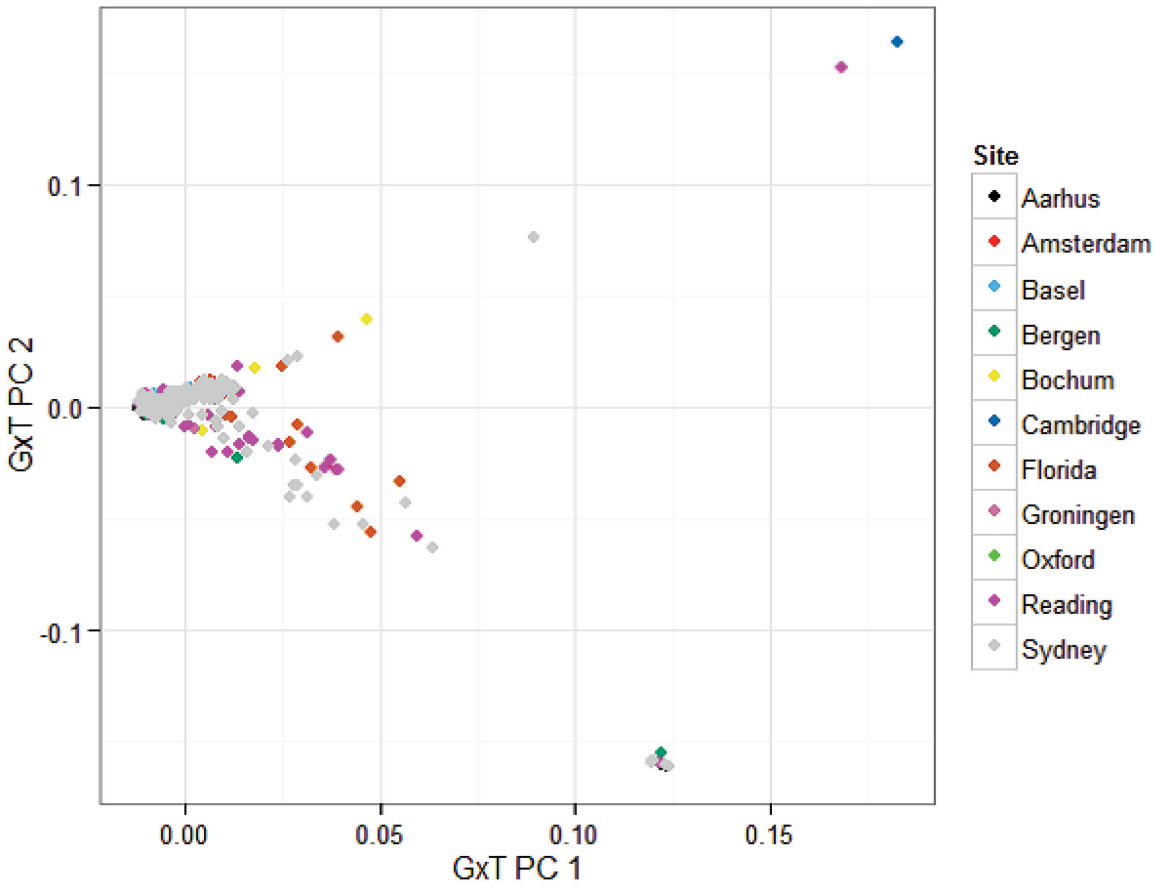

Fig. DS2(b) Samples projected on the first two principal components derived from the HapMap3 samples, showing that the majority cluster in a White Western European group (red box), with admixed samples descending down to East Asian ancestry (right), and to African ancestry (left).