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Genetic variation in the endocannabinoid system and response to cognitive behaviour therapy for child anxiety disorders

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Abstract

Extinction learning is an important mechanism in the successful psychological treatment of anxiety. Individual differences in response and relapse following Cognitive Behaviour Therapy may in part be explained by variability in the ease with which fears are extinguished or the vulnerability of these fears to re-emerge. Given the role of the endocannabinoid system in fear extinction, this study investigates whether genetic variation in the endocannabinoid system explains individual differences in response to CBT. Children (N = 1309) with a primary anxiety disorder diagnosis were recruited. We investigated the relationship between variation in the CNR1, CNR2 and FAAH genes and change in primary anxiety disorder severity between pre- and post-treatment and during the follow-up period in the full sample and a subset with fear-based anxiety disorder diagnoses. Change in symptom severity during active treatment was nominally associated ($p < .05$) with two SNPs. During the follow-up period, five SNPs were nominally associated with a poorer treatment response (rs806365 (CNR1); rs2501431 *(*CNR2); rs2070956 (CNR2); rs7769940 (CNR1); rs2209172 (FAAH)) and one with a more favourable response (rs6928813 (CNR1)). Within the fear-based subset, the effect of rs806365 survived multiple testing corrections ($p < .0016$). We found very limited evidence for an association between variants in endocannabinoid system genes and treatment response once multiple testing corrections were applied. Larger, more homogenous cohorts are needed to allow us to identify variants of small but statistically significant effect and to estimate effect sizes for these variants with greater precision in order to determine their potential clinical utility.

Keywords: Anxiety, Endocannabinoids, Fear extinction, Cognitive Behaviour Therapy, Children

Introduction

Childhood anxiety disorders are very common [Kessler et al 2005] and are associated with a wide range of impairments [Asendorpf et al 2008; Erath et al 2007; Kim-Cohen et al 2003]. Response to Cognitive Behaviour Therapy (CBT) varies substantially between patients [James et al 2013]. Identifying predictors of response is important given the potential for clinicians to identify children and adolescents at risk for poorer outcomes before treatment begins and to help inform the development of more efficacious therapies. Recent years have seen a growing interest in the genetic prediction of response to psychological therapy, a field known as therapygenetics [Lester et al 2013]. Yet to receive attention is the endocannabinoid (ECB) system, despite a growing literature implicating endocannabinoids in the pathogenesis of anxiety and fear, fear extinction, and emotional processing [Hillard et al 2012; Lafenetre et al 2007; Mechoulam et al 2013; Ruehle et al 2012].

Extinction learning is assumed to be an important component of CBT, in which individuals are repeatedly exposed to their feared object, situation or anxiety-provoking thought in the absence of any aversive consequences. Over successive exposures, the patient learns that their feared object is not predictive of an aversive outcome and anxiety is reduced [Craske et al 2014]. However, extinguished fears are vulnerable to recovery and can re-emerge with the passage of time, which creates limitations on the potential durability and effectiveness of CBT [Arch et al 2009; Craske et al 2008]. This is because extinction is a new learning process that involves the encoding of a new competing memory, but which does not replace the original fear memory, leaving it potentially ready to re-emerge [Bouton 2002]. A feature of anxiety disorders both in adult and child samples is their tendency to recur even following initially successful treatment with relapse rates reported to approximate 20-30% in child and adolescent samples[Gearing et al 2013; Piacentini et al 2014]. Surprisingly little is known about predictors of relapse. One possibility is that individual differences in the ease with which fears are extinguished and/or vulnerability of extinguished fears to re-emerge may in part explain inter-individual variation in initial response and risk of relapse following CBT.

The ECB system comprises of cannabinoid receptors (CB1 and CB2), the endogenous endocannabinoids (anandamide (AEA) and 2-arachidonoylglycerol (2-AG)), and the catabolic enzymes for endocannabinoid degradation (fatty acid amide hydrolase (FAAH) for AEA and monoacylglycerol lipase (MAGL) for 2-AG). Considerable research supports the hypothesis

that endogenous endocannabinoid signalling regulates anxiety. There is also suggestive evidence that targeting components of the ECB system via activation of CB1 receptors or by manipulating FAAH activity may produce anxiolytic effects [Gunduz-Cinar et al 2013; Kathuria et al 2003; Lafenetre et al 2007]. Pertinent to our understanding of the factors influencing treatment response is research in adults demonstrating the role of the ECB system in fear extinction [Gunduz-Cinar et al 2013]. Failure to effectively extinguish fear when cues that previously predicted threat are no longer present can lead to the maintenance of fear and has been proposed as an important mechanism in the etiology of anxiety disorders [Hofmann 2008].

Animal research has shown that genetic deletion and pharmacological blockade of CB1 receptors impedes extinction [Lafenetre et al 2007; Marsicano et al 2002]. In contrast, enhancing cannabinoid neurotransmission using either anandamide reuptake inhibitors, which alter FAAH activity or direct CB1 agonists facilitates fear extinction [Bitencourt et al 2008; Chhatwal et al 2005; Pamplona et al 2006]. The ECB system may be particularly important for the consolidation and retention of extinction memories [Suzuki et al 2008] thus attenuating the spontaneous recovery of conditioned fear responding. Two studies, one [Rabinak et al 2013], which administered tetrahydrocannabinol (THC) pre-extinction, and a second [Das et al 2013] that administered cannabidiol after extinction learning found consolidation of extinction learning to be enhanced in human participants. However, a third study [Klumpers et al 2012], which also administered THC did not detect an effect of THC on consolidation of fear extinction. Several studies have also shown that administration of cannabinoid system modulators, such as THC, modulates the neural substrates (amygdala, ventromedial prefrontal cortex, hippocampus) involved in extinction learning, extinction memory recall [Rabinak et al 2014] and the processing of emotional stimuli [Bossong et al 2013; Fusar-Poli et al 2009; Phan et al 2008]. Given these findings, cannabinoid-based pharmacotherapy and augmentation of existing treatments has been proposed as a promising avenue for the development of novel treatments for anxiety disorders [Domschke et al 2008b; Fitzgerald et al 2014; Graham et al 2011], although as of yet the evidence for efficacy remains unclear [Whiting et al 2015].

Recent research has investigated the effects of genetic variability in human endocannabinoid signalling for fear extinction. Numerous single nucleotide polymorphisms (SNPs) have been identified in CNR1 and CNR2, the genes that encode for cannabinoid

receptor 1 and 2 respectively and in FAAH, the gene that encodes for the FAAH protein, the primary regulator of AEA signalling in the brain [Cravatt et al 2001]. Variation in rs2180619, a SNP in the promoter region of CNR1 has been associated with fear extinction. G allele carriers demonstrated robust extinction of fear evidenced by a reduction in fear-potentiated startle relative to AA homozygote carriers who failed to extinguish fear [Heitland et al 2012]. A small number of variants in CNR1 (e.g. rs1049353; rs806368) and CNR2 (rs2501431) have been investigated in the context of emotional processing of socially relevant stimuli [Chakrabarti et al 2006; Domschke et al 2008a] and in predicting antidepressant treatment response in patients with Major Depression [Domschke et al 2008a; Mitjans et al 2012; Mitjans et al 2013].

Research in mice has shown that FAAH inhibitors facilitate extinction by augmenting AEA signalling in the amygdala. Similarly, healthy carriers of the low-expressing A allele at rs324420, which leads to reduced expression of FAAH and elevated levels of AEA showed reduced amygdala activity [Hariri et al 2009]. Furthermore, low expressing A allele carriers showed more rapid habituation of amygdala responses to threatening stimuli relative to CC homozygotes [Gunduz-Cinar et al 2013]. They also reported lower scores on a personality measure of stress reactivity [Gunduz-Cinar et al 2013]. A recent study showed persuasive convergent effects of FAAH variation in both humans and mice. Human A allele carriers showed enhanced fear extinction indexed by reduced skin conductance response to the extinguished cue and lower levels of trait anxiety. Mice carrying the A allele demonstrated reduced freezing behaviour on presentation of the extinguished cue and decreased anxiety in response to two measures of anxiety-like behaviours that involved placing the mice in conflict situations (elevated plus maze test and novelty induced hypophagia test) [Dincheva et al 2015]. These findings suggest that variation in FAAH may be an important moderator of anxiety-related behaviours and is a plausible candidate for involvement in determining for whom psychological treatments involving exposure components will be most effective.

In the current study, we tested the association between polymorphisms of the CNR1, CNR2 and FAAH genes and response to CBT in children and adolescents with an anxiety disorder diagnosis. To our knowledge, this is the first study to investigate genetic variation in the endocannabinoid system and response to a psychological treatment. We began by testing our hypotheses in a large sample of children (N = 1309) experiencing the full range of anxiety disorder diagnoses and who had received a course of CBT in order to maximise

power to detect genetic effects. However, one possibility is that extinction learning may be implicated more or less in the mechanisms of treatments for different disorders. For example, extinction learning may be of greater relevance for the successful treatment of predominantly fear based disorders such as specific phobias and to a lesser extent for distress based disorders like generalised anxiety disorder [Borkovec et al 2001]. Thus, in secondary analyses, we tested our hypotheses in a subset of the sample (N = 749) that had received a fear-based anxiety disorder diagnosis (e.g. specific phobia, social phobia, separation anxiety disorder, panic disorder). Theses analyses were informed by research using genetic and phenotypic data to determine the structure of psychopathology [Clark et al 2006; Lahey et al 2004; Watson et al 2008] and which suggests that emotional disorders can be decomposed into distress disorders (e.g. major depression, generalised anxiety disorder, posttraumatic stress disorder); fear disorders (e.g. phobias, panic disorder) and the bipolar disorders [Watson et al 2008].

We tested two hypotheses. Firstly, that genetic variation in CNR1, CNR2 and FAAH would be significantly associated with change in symptom severity from baseline to post-treatment reflecting the influence of genetic variation in the ECB system during the active treatment period. One possibility is that any effect of ECB genes on early symptom change may reflect the role of the ECB system in the extinction of fear. Second, we examined whether ECB genetic variation was associated with change in symptom severity from post-treatment to follow-up reflecting the influence of ECB genetic variation on maintenance of treatment gains. While for some, this will reflect a period in which they continue to consolidate the gains made during treatment, for others this may reflect a period in which they begin experiencing a relapse of symptoms. One possibility is that any effect of ECB genes on symptom change and specifically the continuance of treatment gains during the follow-up period may reflect the role of the ECB system in the maintenance of extinction memories.

Materials and Methods

Participants

Participants were recruited for the Genes for Treatment Study (G×T) study, a multi-site international collaboration designed to identify clinical, demographic and genetic predictors of outcome following CBT for anxiety disorders in children and adolescents [Hudson et al 2015]. The sample comprised 1309 individuals for whom treatment response

data was available at the post and/or follow-up time points and genotype data was available for one or more SNPs. Participants were 5 – 17 years of age (89.6% aged 5-12 years, mean age: 9.81 years, 52% female) and met DSM-IV criteria for primary diagnosis of an anxiety disorder. Exclusion criteria comprised significant physical or intellectual impairment, psychoses and concurrent treatment. Participants completed a course of CBT as part of a trial or as treatment as usual at one of eleven sites: Sydney, Australia (n = 641); Reading and Oxford, UK (n = 302 and n = 15); Aarhus, Denmark (n = 123); Bergen, Norway (n = 39); Groningen, the Netherlands (n = 36); Bochum, Germany (n = 52); Florida, US (n = 38); and Basel, Switzerland (n = 47), Cambridge, UK (n = 12) and Amsterdam, the Netherlands (n = 4). All treatments were manualised and treatment protocols across sites were comparable for core elements of CBT including teaching of coping skills, cognitive restructuring and exposure. Three broad groups of treatment modality were given: individual CBT (27.4%), group based CBT (52.8%) and parent-supported guided self-help CBT (19.9%). Follow-up data was collected at three (n = 231), 6 (n = 675) or 12-months (n = 250) after cessation of treatment. Further sample characteristics for the full sample are given in Table I and site-specific trial information is given in the supplementary information accompanying this article. Sample characteristics for the subset with a fear-based diagnosis (excluding GAD, OCD, PTSD, ADNOS) are given in Table SI in the supplementary materials.

Measures

Diagnoses were made using the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV-C/P)[Silverman et al 1996] at all sites except for Bochum and Basel where the German equivalent Kinder-DIPS was used [Schneider et al 2009]. Clinical Severity Ratings (CSRs) ranged from 0 to 8 and were based on composite parent and child reports (see Hudson et al., 2015, for further details). Treatment response was assessed as change in primary diagnosis severity from pre-treatment to post-treatment and from post-treatment to follow-up. A diagnosis was assigned when the child met diagnostic criteria and received a CSR of 4 or greater. Primary diagnoses included Generalised Anxiety Disorder (GAD; 37.7%), Separation Anxiety Disorder (SAD; 21.7%), Social Anxiety Disorder (21.3%), Specific Phobia (11.4%), or Panic Disorder, Obsessive Compulsive Disorder, Post Traumatic Stress Disorder,

Selective Mutism[1] or Anxiety Disorders Not Otherwise Specified (other anxiety disorders; 7.9%).

Genotyping

DNA was collected using buccal swabs or Oragene saliva samples (DNA Genotek, Ottawa, Canada). Buccal swab DNA was extracted using established procedures designed to maximise the purity and yield of the sample [Freeman et al 2003]. DNA from saliva samples was extracted using Prep-it.L2P according to the manufacturers protocol (DNA Genotek). Sample preparation prior to genotyping is described elsewhere [Coleman et al 2016]. In brief, samples were subjected to ultrafiltration and resuspension to increase DNA concentration and included in genotyping if the resulting concentration exceeded 50ng/ul.

Genotypes for 7 CNR1 polymorphisms (rs2180619; rs1049353; rs806368; rs806371; rs1535255; rs806369), 1 CNR2 polymorphism (rs2501431) and 1 FAAH polymorphisms (rs324420) drawn from the candidate gene literature on fear extinction, emotional processing and response to antidepressant treatment were genotyped by LGC Genomics (Hoddesdon, UK) using validated arrays with KASP technology or were obtained from the Illumina Core Exome-12v1.0 microarray. Four additional markers, which were genotyped using both platforms showed an average of 98% consensus on genotype calls.

For the subset of the sample with array data (n = 980) additional genotypes were available for 123 CNR1 polymorphisms, 159 CNR2 polymorphisms, and 318 FAAH polymorphisms. Array data was included in all analyses to provide LD context for multiple testing corrections and to provide more accurate gene-based tests of association.

Quality control and imputation procedures for those samples with microarray data are provided in full elsewhere [Coleman et al 2016]. Briefly, common variants (minor allele frequency > 5%) were included in the analyses if they were genotyped in >99% of samples and if they did not deviate substantially from Hardy-Weinberg equilibrium (HWE test *p*-value>10^{-5}). SNPs were included if they could be imputed to the December 2013 release of the 1000 Genomes Project reference [1000GenomesConsortium 2012] with > 90% completeness, and an info metric of > 0.8 (a value ranging between 0 and 1 which indicates

[1] In cases with primary selective mutism, a diagnosis of severe social phobia was also given. The selective mutism was considered by the clinician to be primary, the most interfering.

the certainty with which the SNP has been imputed). Using these cut-offs, data was available for 127 CNR1 SNPs, 160 CNR2 SNPs and 318 FAAH SNPs. Gene coverage estimated using directly genotyped and imputed SNPs meeting criteria for inclusion was 11.5%, 19.8% and 28.9% for CNR1, CNR2 and FAAH genes respectively. For each gene, analysed variants were entered as tagging SNPs in the Tagger utility of Haploview [Barrett et al 2005]. All common variants (MAF >= 0.05) within and +/- 100kb of the gene boundaries (as listed in HapMap release II+III) were in linkage disequilibrium ($r^2 > 0.8$) with at least one tagging SNP. This indicates good coverage of all linkage regions across the genes studied. To account for patterns of linkage disequilibrium (LD) between SNPs, LD based clumping was performed for each analysis to reduce the SNP set to a smaller number of clumps of correlated SNPs.

Ethical Approval

Each site had trial-specific Human Ethics and Biosafety Committee approval for the collection of biological samples with the research conducted in accordance with the Declaration of Helsinki. In all instances parents provided written informed consent, children assent. The storage and analysis of DNA was approved by the King's College London Psychiatry, Nursing and Midwifery Research Ethics Sub-Committee.

Analyses

Two outcome measures were considered in our primary analyses. First, the change in severity (CSR score) of the primary anxiety diagnosis from baseline to post-treatment, reflecting the active treatment period. Second, the change in severity of the primary anxiety diagnosis from post-treatment to follow-up time points, reflecting a period of consolidation or risk for relapse.

Linear mixed effects models were performed to investigate the effect of ECB polymorphisms on change in severity (CSR score) of the primary anxiety disorder diagnosis. All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote. To make use of all available post baseline measurements and provide estimates in the presence of missing data, the effects of predictors of response were estimated using mixed models fitted with full maximum likelihood. All models included either the fixed effects of baseline severity (CSR of the primary anxiety disorder diagnosis at baseline, centred at the mean) or post-treatment

severity (CSR of the primary anxiety disorder diagnosis at post-treatment, centred at the mean), age (centred at the mean) and gender. Analyses investigating post to follow-up change also included the linear and quadratic effects of time to account for the curvilinear slope of treatment response across this period. All models included the random effects of individual to account for correlations between repeated measures from the same individual. We also included a higher order random effect of trial to account for between trial differences in outcome. As each trial was conducted at a single site, this random effect also accounted for between-site differences.

In all analyses, the beta values of variables predicting a more favourable response to treatment or continued gains during the follow-up period (i.e. greater reduction in severity) are negative, while variables predicting a less favourable response are positive. Analyses were performed in STATA version 12.0.

All analyses (baseline to post-treatment change, post-treatment to follow-up change, fear-based diagnoses subset ((N = 749), gene-based association tests) consider data from all available SNPs including both directly genotyped SNPs available on the entire sample (N = 1309) and the additional SNPs available for the subset of the sample with array data (n = 980). N's are given for each sentinel SNP in the corresponding table for each analysis.

Results from the initial association analyses were clumped based on patterns of LD according to *p*-value using PLINK [Purcell et al 2007], thus reducing the SNP set to a smaller number of correlated SNPs. Each independent clump was 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). To correct for multiple testing, revised significance thresholds were calculated based on the number of independent clumps identified for each analysis.

Gene-based tests for association with response were performed using VEGAS modified to use the hg19 genome build [Liu et al 2010]. Gene boundaries were defined as the longest transcript of the gene listed in the UCSC Genome Browser and variants considered +/- 100kb from each end. Linkage disequilibrium patterns were calculated from the genotyped data.

Power calculations

Power calculations indicated that with a sample size of 980, we had 80% power to detect a variant with a minor allele frequency of 0.05 capturing 1.6% of variance with a corrected alpha level of 0.017. For variants explaining 0.1%, 0.5% and 1% of the variance we had 1.6%, 18% and 50% power respectively.

Results

Clinical outcomes in the full sample were comparable to previously reported estimates [Hudson et al 2015; Hudson et al 2013; James et al 2013]. Following treatment, 58% of the sample was free of their primary anxiety disorder diagnosis with this rate rising to 67% by follow-up. Symptom severity reduced significantly between baseline (6.22) and post-treatment (2.97, $t(1256) = 54.57$, $p < .0001$) and post-treatment and follow-up time points (2.42, $t(1256) = 9.40$, $p < .0001$). We initially explored the effects of clinical (baseline severity; primary diagnosis; treatment type) and demographic factors (age; gender) on change in symptom severity between baseline and post-treatment. Findings were broadly similar to those reported for the full sample [Hudson et al 2015]. Individuals with Social Anxiety Disorder, Specific Phobias or Separation Anxiety Disorder showed a significantly poorer response to treatment compared to those with Generalised Anxiety Disorder ($\beta = 0.24$, $p < .0001$; $\beta = 0.11$, $p = .005$ and $\beta = 0.06$, $p = .044$ respectively. Higher severity at baseline was associated with significantly poorer response to treatment ($\beta = 0.30$, $p < .0001$). However, treatment response did not differ according to sex, age or treatment type (all p values > .05). For change in symptom severity between post-treatment and follow-up time points, individuals with Specific Phobias showed a significantly poorer treatment response compared to those with Generalised Anxiety Disorder ($\beta = 0.15$, $p = .011$). Higher severity at post-treatment was also associated with significantly poorer response during the follow-up period ($\beta = 0.19$, $p < .0001$). Response during the follow-up period did not differ according to sex, age or treatment type (all p values > .05). A highly similar pattern of results was observed when the sample was restricted to those with a fear-based anxiety disorder diagnosis only.

Change in symptom severity from baseline to post-treatment: analyses using the entire sample (N = 1309)

Thirty independent clumps were identified based on patterns of LD and were used to calculate adjusted *p*-values for multiple testing corrections ($p < .0017$). Each independent clump was 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). Two independent clumps were nominally associated with response ($p < .05$). An increasing number of copies of the minor allele of rs12133557 was associated with a more favourable treatment response (i.e. greater reductions in severity) across the treatment period. In contrast, the minor allele of the sentinel SNP rs6454676 (with this clump including the directly genotyped rs1535255) was associated with a poorer treatment response ((i.e. smaller reductions in severity or an increase in severity associated with increasing number of copies of the minor allele, see Table II). However, neither of these effects survived multiple testing corrections at $p < .0017$. The remaining SNPs all had *p* values exceeding 0.05. Analyses restricted to a subset that identified as having four White European grandparents (n = 916) are available in the supplementary materials. Gene based association tests were non-significant (CNR1: $p = .172$; CNR2: $p = .202$; FAAH: $p = .846$).

Change in symptom severity from baseline to post-treatment: fear-based anxiety disorder diagnosis subset (N = 749)

Twenty-nine independent clumps were identified based on patterns of LD and were used to calculate adjusted *p*-values for multiple testing corrections ($p < .0017$). Two independent clumps were nominally associated with response ($p < .05$) with an increasing number of copies of the minor allele of the sentinel SNP rs6454676 (with this clump including the directly genotyped rs1535255) associated with a poorer treatment response (see Table III). The minor allele of rs12133557 was associated with a more favourable treatment response across the treatment period. However, neither of these effects survived multiple testing corrections. Gene based tests on this subset were non-significant (CNR1: $p = .129$; CNR2: $p = .148$; FAAH: $p = .694$).

Change in symptom severity from post-treatment to follow-up

Thirty independent clumps were identified and were used to calculate adjusted *p*-values for multiple testing corrections ($p < .0017$). Of these, five independent clumps were associated with a poorer response (i.e. smaller reductions in severity or an increase in

severity associated with an increasing number of copies of the minor allele) during the follow-up period at a nominal *p* value of < .05 (sentinel SNPs: rs806365; rs2501431; rs2070956; rs7769940; rs2209172) while one independent clump (sentinel SNP: rs6928813) predicted a more favourable response (i.e. greater reductions in severity associated with increasing number of copies of minor allele). All clumps with $p < .05$ are displayed in Table II. However, none of the suggestively significant clumps survived multiple testing correction ($p < .0017$) with rs806365 having the lowest *p* value at $p = .004$. Analyses restricted to a subset that identified as having four White European grandparents are available in the supplementary materials. Gene based association tests on the full sample were all non-significant (CNR1: $p = .360$; CNR2: $p = .092$; FAAH: $p = .745$).

Change in symptom severity from baseline to post-treatment: fear-based anxiety disorder diagnosis subset

Thirty-one independent clumps were identified and were used to calculate adjusted *p*-values for multiple testing corrections ($p < .0016$). Of these, three independent clumps were associated with a poorer response (i.e. smaller reductions in severity or an increase in severity associated with increasing number of copies of the minor allele) during the follow-up period at a nominal *p* value of < .05 (sentinel SNPs: rs806365; rs7769940; rs2501431, see Table III). These same SNPs were nominally significant in the analyses using the entire dataset. However, the effects were stronger when examined in the subset of participants with fear-based disorders, with the effect for rs806365 surviving multiple testing corrections ($p = .0011$). Gene based tests on this subset were non-significant (CNR1: $p = .620$ CNR2: $p = .053$; FAAH: $p = .335$).

Discussion

Given the potential role of the ECB system in fear extinction and the maintenance of extinction memories, this study investigated whether genetic variation in the CNR1, CNR2 and FAAH genes was associated with response to CBT in children and adolescents with an anxiety disorder. In our analyses, two SNPs (rs12133557 and rs6454676) were nominally associated ($p < .05$) with change in symptom severity in both the entire sample and the subset with fear based diagnoses. An increasing number of copies of the minor allele of rs12133557 was associated with a more favourable response during the active treatment

period. In contrast, an increasing number of copies of the minor allele of rs6454676 were associated with a poorer response during the active treatment period. However, these effects did not survive stringent multiple testing correction in either the entire sample or subset restricted to fear-based diagnoses only. Furthermore, we hypothesised that individual differences in the continuation of treatment gains during the follow-up period may be associated with genetic variation in ECB genes. Six independent clumps were nominally associated ($p < .05$) with change in symptom severity over the follow-up period in the entire sample, five where an increasing number of copies of the minor allele was associated with a poorer response (sentinel SNPs: rs806365; rs2501431; rs2070956; rs7769940; rs2209172), and one with a more favourable response (sentinel SNP: rs6928813). Again, none of these effects survived multiple testing corrections. Three of these same sentinel SNPs were also nominally associated with response in the fear-based subset (rs806365; rs7769940; rs2501431). The effect size of these SNPs was larger in the fear-based subset with the effect of rs806365 remaining significant after multiple testing corrections were applied. Gene based tests of association were all non-significant. In summary, our findings suggest only very limited evidence for a role of genetic variation in the ECB system in predicting individual differences in response to CBT for anxiety disorders in children and adolescents. Where these effects do exist they are very small and appear to have greater predictive power when examined in a sample restricted to fear-based anxiety diagnoses only.

The strongest finding in our analyses was for SNP rs806365, which was nominally associated with a poorer response during the follow-up period in the full sample ($p = .004$) and remained significantly associated after multiple testing correction in the fear-based anxiety diagnosis subset ($p = .0011$). While not previously investigated with respect to anxiety linked traits or fear extinction, this locus has shown preliminary evidence of association with insulin resistance, risk for Type 2 diabetes and coronary heart disease [de Miguel-Yanes et al 2011]. Of greater relevance is research suggesting that variation at this locus may be associated with differential response to smoking cessation treatments and thus it could be hypothesised, sensitivity to environmental influences such as treatment regimens. For example, male carriers of one or more minor T alleles had increased rates of abstinence to treatment with buproprion (a norepinephrine and dopamine reuptake inhibitor) and transdermal (patch) nicotine replacement therapy but significantly decreased

odds of abstinence in response to nicotine nasal spray replacement therapy [Lee et al 2012]. In the present study, with each additional T allele, participants showed a significantly poorer response (a smaller reduction in severity) to treatment across the follow-up period. This may indicate that T allele carriers are less sensitive to any continuing effects of CBT beyond the initial treatment period and ultimately may be placed at a greater risk of relapse. One possible mechanism worthy of further investigation is that this SNP (and the ECB system more broadly) may be involved in the maintenance of extinction memories beyond the active treatment period. While not possible in this study, it would be of interest to observe whether T allele carriers are at an increased risk of relapse with a longer follow-up assessment period perhaps as a consequence of increased risk for spontaneous recovery of conditioned fear responding.

None of the SNPs previously studied in candidate gene studies of laboratory based fear extinction [Dincheva et al 2015; Heitland et al 2012], emotional processing [Chakrabarti et al 2006; Domschke et al 2008a; Gunduz-Cinar et al 2013; Hariri et al 2009] or response to antidepressant treatment [Domschke et al 2008a; Mitjans et al 2012; Mitjans et al 2013], on which data was available in this study, approached significance in either analysis. The only exception was rs2501431, a SNP in CNR2 that was previously studied in relation to response to treatment with citalopram in a small sample of outpatients with depression [Mitjans et al 2012]. In this earlier study, variation in rs2501431 was not associated with symptom change in response to citalopram, but overall AA homozygotes reported more severe depression across the entire treatment period. In the present study, GG homozygotes showed a less favourable response (a smaller reduction in severity) during the follow-up period, albeit only at a nominal level of significance. Unlike prior research, there was no significant difference in severity of anxiety at baseline or mean severity across the treatment and follow-up period as a function of rs2501431 genotype. Differences in phenotype, sample type, treatment approach and sample size may explain the inconsistency in direction of effects seen across this study and that of Mitjans and colleagues [Mitjans et al 2012].

There are several explanations, which may in part account for the lack of convincing significant findings in this study despite encouraging experimental work for a role of genetic variation in ECB genes in fear extinction learning and emotional processing. Firstly, the CBT protocols given to participants, while strongly underpinned by the principles of extinction through exposure, also comprised a number of cognitive elements including teaching of

coping skills and cognitive restructuring. Inevitably, this creates a far noisier analogue of the fear extinction paradigms used in the laboratory environment, which may have reduced the ability to detect significant effects. Furthermore, previous associations between variation in CNR1 and FAAH and fear extinction have been observed in response to short-term experimentally conditioned fears in adults and not to clinical levels of anxiety in children and adolescents. Nonetheless, stronger effects may have been observed on response to a purer exposure-based treatment or with a sample that was less heterogeneous with regard to anxiety diagnosis and treatment modality. In particular, the present sample and our initial analyses included the full range of anxiety disorder diagnoses. One possibility is that extinction learning may be implicated more or less in the mechanisms of treatments for different disorders. For example, extinction learning may be of greater relevance for the successful treatment of predominantly fear based disorders such as specific phobias and to a lesser extent for distress based disorders like generalised anxiety disorder [Borkovec et al 2001]. A secondary analysis performed in the subset of the sample restricted to those with a fear-based anxiety diagnosis provides suggestive evidence that this may be the case. The magnitude of effects was somewhat stronger in this restricted sample with the effect of rs806365 remaining significant even after multiple testing corrections were applied (see Table III). Further research should also establish a role for the ECB system in fear extinction in children and adolescents given that all of the experimental and treatment research to date has been with adult samples.

Secondly, any effects of ECB genetic variation on the maintenance of treatment gains, or conversely relapse of symptoms, may require a longer follow-up period to emerge (90% of the current sample had a follow-up period of 6 months or less). The change in symptom severity over the follow-up period was smaller and less variable than that seen during the active treatment phase with 47% of participants showing no change in symptom severity from post-treatment to follow-up. Only a minority of participants (17%) showed any worsening of symptoms over the follow-up period. Thus, analyses of the follow-up period were limited by the reduced variance in response.

A more general limitation of the present study is that it took a candidate gene approach. However, this limitation was mitigated by the inclusion of array data on a subset of the sample providing more comprehensive coverage of the genes under investigation and LD context for the calculation of multiple testing corrections. Nonetheless within psychiatric

genetics broadly, and the therapygenetics literature to date, candidate gene studies have often failed to replicate, have typically reported very small effect sizes and are sensitive to publication bias [Duncan et al 2011; Lester et al 2013]. Nominating candidate genes for investigation requires knowledge of the pathophysiology of the phenotype under investigation and the putative mechanisms through which CBT may act. Psychological treatment response is a complex trait and while extinction learning is an important process underpinning CBT, the etiology of treatment response is multifactorial. Thus it is very unlikely that any single genetic polymorphism within the ECB system, or more generally, will explain a sufficiently large amount of variance in response to be clinically meaningful. To date, the strongest evidence for a role of the ECB system in fear extinction has come from animal studies employing genetic deletion and pharmacological modulation designs [Lafenetre et al 2007]. Such studies are more likely to show large and pervasive effects in comparison to human genetic association studies, where the biological effect of an individual variant in vivo is likely to be very small. Despite being by far the largest therapygenetics study to date, the present study was powered to detect a variant capturing 1.6% of variance in treatment response with 80% power but had only 1.5% power to detect a variant of very small effect size explaining 0.1% of variance. If the true effect of rs806365 lies closer to the effect size of 0.0029% observed (in the full sample), then this would require a sample of 5435 to detect these effects at $\alpha = .0017$ with 80% power. Notwithstanding the huge expense and effort that would be required to assemble samples of this magnitude, such a small effect on its own is extremely unlikely to be of any clinical utility.

Given the challenges of candidate gene studies, it will become increasingly important for the therapygenetics field to work collaboratively to assemble large datasets that can be used to both study the mechanisms underlying CBT response and which will allow us to exploit hypothesis-free whole genome based approaches. These methods have the potential to identify novel and unexpected variants associated with treatment response [Coleman et al 2016]. In conjunction with statistical approaches such as polygenic risk scoring, genome wide approaches allow the opportunity to move beyond single variant approaches to methods which aggregate across a large number of markers in order to capture a greater and ultimately clinically significant proportion of the variance in outcome [Keers et al 2016; Krapohl et al 2015]. An interesting avenue for further research is to investigate epigenetic and gene expression predictors and correlates of psychological treatment response, as these

approaches may allow us to get closer to the biological mechanisms of CBT response. This work while in its infancy has shown early promise [Perroud et al 2013; Roberts et al 2015; Roberts et al 2014; Yehuda et al 2015]. Of relevance, a recent study investigating gene expression change in response to exposure-based CBT for anxiety disorders reported that an increase in DALGB gene expression (diacylglycerol lipase beta gene), which is involved in the biosynthesis of 2-AG (an endogenous endocannabinoid), was associated with greater reductions in severity while a reduction in DALGB expression corresponded with lower reductions in severity [Roberts et al in preparation]. This finding is consistent with research showing that increased levels of 2-AG (an endogenous endocannabinoid) are associated with anxiolytic effects [Gunduz-Cinar et al 2013].

In summary, this is the first study to investigate the role of genetic variation in the endocannabinoid system and response to psychological therapy for anxiety disorders. A small number of genetic variants were nominally associated with individual differences in treatment response during the active treatment and follow-up period. Only one of these effects remained significant after multiple testing corrections and in a sample restricted to those with a fear-based anxiety disorder diagnosis. The ECB system remains a plausible target for involvement in response to psychological therapies underpinned by the principles of extinction learning. However, the effect of any single variant is likely to be very small given the complexity and multitude of mechanisms underpinning response to psychological treatments. The use of larger samples with greater statistical power and more homogeneous samples which reduce noise in the data would allow us to estimate the effect size of any variant with greater precision. Notwithstanding this, there are potentially large benefits for patients and wider society in knowing more about what determines who responds well to psychological therapies, and why. Thus, therapygenetics remains an important area for further research.

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Conflict of Interest

Rapee, and Hudson are authors of the Cool Kids program, but receive no direct payments. Creswell was joint author of book used in treatment within the Overcoming trial and receives royalties from sales of the books. Silverman is an author of the Anxiety Disorders Interview Schedule for Children from which she receives royalties. Schneider is an author of the Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter (Kinder-DIPS for DSM-IV-TR) from which she receives royalties. Breen is a consultant in pre-clinical genetics for Eli Lilly. All other authors declare no financial interests.

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Table I: Sample characteristics by site for the full sample

Characteristic	Sydney	Reading	Aarhus	Bergen	Bochum	Basel	Groningen	Oxford	Florida	Cambridge	Amsterdam	Total
N	**641**	**302**	**123**	**39**	**52**	**47**	**36**	**15**	**38**	**12**	**4**	**1309**
Gender Female n (%)	317 (49.5)	165 (54.6)	70 (56.9)	24 (61.5)	30 (57.7)	26 (55.3)	17 (47.2)	9 (60.0)	18 (47.4)	8 (66.7)	0 (0)	684 (52.3)
Age: mean (SD)	9.41 (1.91)	9.59 (1.71)	11.02 (2.40)	11.46 (1.96)	11.15 (2.58)	8.49 (2.07)	11.89 (3.11)	9.00 (1.60)	9.61 (2.26)	12.58 (2.83)	12.00 (1.83)	9.81 (2.16)
Severity primary diagnosis: mean (SD)	6.36 (0.88)	5.62 (0.79)	6.53 (1.22)	6.72 (1.28)	6.77 (1.13)	5.98 (0.77)	6.19 (0.95)	5.60 (0.91)	6.82 (1.14)	6.33 (1.15)	5.75 (1.71)	6.22 (1.00)
Primary diagnosis: n (%)												
GAD	339 (52.8)	93 (30.8)	31 (25.2)	10 (25.6)	5 (9.6)	0 (0)	7 (19.4)	1 (6.7)	8 (21.1)	0 (0)	0 (0)	494 (37.7)
SoAD	136 (21.2)	62 (20.5)	18 (14.6)	17 (43.6)	15 (28.8)	0 (0)	14 (38.9)	6 (40.0)	10 (26.3)	0 (0)	1 (25.0)	279 (21.3)
SP	51 (8.0)	49 (16.2)	19 (15.4)	0 (0)	17 (32.7)	0 (0)	6 (16.7)	1 (6.7)	5 (13.2)	0 (0)	1 (25.0)	149 (11.4)
SAD	74 (11.5)	77 (25.5)	37 (30.1)	12 (30.8)	13 (25.0)	47 (100)	6 (16.7)	6 (40.0)	10 (26.3)	0 (0)	2 (50.0)	284 (21.7)
Other AD[a]	41 (6.4)	21 (7.0)	18 (14.6)	0 (0)	2 (3.8)	0 (0)	3 (8.3)	1 (6.7)	5 (13.2)	12 (100)	0 (0)	103 (7.9)
CBT treatment: n (%)												
Individual based	20 (3.1)	128 (52.4)	2 (1.6)	22 (56.4)	52 (100)	47 (100)	36 (100)	0 (0)	38 (100)	12 (100)	1 (25.0)	358 (27.4)
Group-based	550 (85.8)	0 (0)	121 (98.4)	17 (43.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (75.0)	691 (52.8)
Guided self-help	71 (11.1)	174 (57.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	15 (100)	0 (0)	0 (0)	0 (0)	260 (19.9)

[a] Other anxiety disorders include Panic Disorder, Obsessive Compulsive Disorder, Post Traumatic Stress Disorder, Selective Mutism and Anxiety Disorders Not Otherwise Specified

Table II: Independent clumps nominally associated ($p < .05$) with treatment response between a.) baseline and post-treatment and b.) post-treatment and follow-up

a.) **Change in symptom severity from baseline to post-treatment**									
SNP	**Gene**	**Clump BP**	**Minor allele**	**MAF**	**Info**	**β**	**95% CI**	***p***	**n**[a]
rs12133557	CNR2	24191219 - 24223859	T	0.098	0.978	-0.07	-0.14 – -0.01	0.02	925
rs6454676	CNR1	88860482- 88885426	A	0.104	0.977	0.07	0.002 – 0.13	.042	926
b.) **Change in symptom severity from post-treatment to follow-up**									
Sentinel SNP	**Gene**	**Clump BP**	**Minor allele**	**MAF**	**Info**	**β**	**95% CI**	***p***	**n**
rs806365	CNR1	88843390 - 88845949	T	0.408	Genotyped (microarray)	0.11	0.04 – 0.18	.004	702
rs2501431	CNR2	24108683 - 24206032	G	0.423	Genotyped (LGC)	0.09	0.03 –0.16	.007	874
rs2070956	CNR2	24191219 - 24223859	C	0.101	0.995	0.14	0.02 – 0.26	.021	698
rs6928813	CNR1	88860482 - 88885426	G	0.180	Genotyped (microarray)	-0.11	-0.20 – -0.01	.033	702
rs7769940	CNR1	88947649 - 88973751	T	0.209	Genotyped (microarray)	0.10	0.01 – 0.19	.034	702
rs2209172	FAAH	46938837 - 46978946	T	0.206	Genotyped (microarray)	0.09	0.00 – 0.18	.044	702

Note: All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote

Regression weights (***β***) significantly less than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a greater reduction in symptom severity across the active treatment or follow-up period. Values significantly greater than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a poorer reduction in symptom severity.

[a] n reflects total number of cases included in regression analysis for the sentinel SNP.

Table III: Independent clumps nominally associated ($p < .05$) with treatment response between a.) baseline and post-treatment and b.) post-treatment and follow-up in the subset of the sample with fear-based anxiety disorder diagnoses (n = 749)

	a.) **Change in symptom severity from baseline to post-treatment**								
Sentinel SNP	**Gene**	**Clump BP**	**Minor allele**	**MAF**	**Info**	**β**	**95% CI**	***p***	**n**[a]
rs12133557	CNR2	24191219 - 24223859	T	0.094	0.978	-0.11	-0.20 – -0.03	.011	540
rs6454676	CNR1	88860482 - 88885426	A	0.108	0.977	0.09	0.005 – 0.17	.038	539
	b.) **Change in symptom severity from post-treatment to follow-up**								
Sentinel SNP	**Gene**	**Clump BP**	**Minor allele**	**MAF**	**Info**	**β**	**95% CI**	***p***	**n**
rs806365	CNR1	88843390 - 88845949	T	0.392	Genotyped (microarray)	0.17	0.07 – 0.27	**.0011**	399
rs7769940	CNR1	88947649 - 88973751	T	0.216	Genotyped (microarray)	0.19	0.07 – 0.32	.003	399
rs2501431	CNR2	24108683 - 24206032	G	0.448	Genotyped (LGC)	0.14	0.04 –0.23	.004	495

Note: All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote

Effects that survived multiple testing corrections are highlighted in bold.

Regression weights (***β***) significantly less than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a greater reduction in symptom severity across the active treatment or follow-up period. Values significantly greater than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a poorer reduction in symptom severity.

[a] n reflects total number of cases included in regression analysis for the sentinel SNP.

Supplementary Information

Methods and Materials

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

Sydney, Australia (n = 641)

Participants aged 6-18 were recruited from the Centre for Emotional Health, Macquarie University, Sydney. All participants completed the Cool Kids program [Rapee et al 2006a], 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 randomised trials who received group, individual or phone-based CBT sessions [Rapee et al 2006b]; participants from a guided self-help trial with phone support for children in rural Australia [Lyneham et al 2006]; a group from a trial with additional parental anxiety management [Hudson et al 2013]; and those recruited from an ongoing randomised trial of progressive allocation to treatment (stepped care).

Reading and Oxford, UK (n = 302 & 15)

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 [Creswell et al 2015] Children whose mother also had a current anxiety disorder completed an 8 session manual-based CBT treatment based on the Cool Kids program. The mothers of these children also received extra sessions focussing 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 [Thirlwall et al 2013]. This consisted of 2-4 in-person sessions and 2-4 telephone sessions. A subset of this group with a primary anxiety disorder diagnosis of Social Phobia also received targeted Cognitive Bias Modification Training (CBM-I, [Orchard et al In Submission]; Vassilopoulos et al [2009].

Additionally, participants with highly anxious parents (screened using DASS or by meeting ADIS criteria) were randomised to groups in a trial including additional sessions for the parents, which focused on strategies for tolerating children's negative emotions [Hiller et al In Submission]. In Oxford, treatment was based on the same basic program, and delivered by primary health workers as part of a feasibility trial [Creswell et al 2010].

BRAVE. The final treatment group completed a therapist-supported online CBT program for adolescents (BRAVE, Spence et al [2011]), consisting of 10 sessions, half with 5 additional parent sessions and half without parent sessions.

Aarhus, Denmark (n = 123)

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 [Rapee et al 2006c]). 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 (n = 39)

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 (4^{th} edition [Barrett 2004; Barrett et al 2006]) in a randomised control trial comparing active treatment with a waitlist condition [Wergeland et al 2014].

Bochum, Germany (n = 52)

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 [Kendall

1994], or a family-based version of CBT specifically designed to target separation anxiety disorder (TAFF [Schneider et al 2013a; Schneider et al 2013b]). 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.

Groningen, the Netherlands (n = 36)

Participants aged 8 to 17 were recruited from the Department of Child and Adolescent Psychiatry, University of Groningen. All participants were treated within a randomised control trial of Coping Cat (Dutch version [Nauta et al 1998] including 12 individual child sessions and 2 parent sessions.

Florida, USA (n = 38)

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 manualised CBT. Additionally, two conditions included parental involvement focussing on different parent skills (Relationship Skills Training or Reinforcement Skills Training).

Basel, Switzerland (n = 47)

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 randomised control trial comparing a family-based version of CBT specifically designed to target separation anxiety disorder (TAFF[Schneider et al 2013a; Schneider et al 2013b]) with Coping Cat [Kendall 1994]. All participants received 16 sessions over 12 weeks.

Cambridge, UK (n = 12)

Participants aged 8–17 were recruited from the Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK. Participants were taking part in the Acute Stress Programme for Children and Teenagers (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,[Smith et al 2007] which consisted of up to 10 sessions over a 10-week period. Only participants that received treatment were included.

Amsterdam, the Netherlands (n = 4)

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."[Bögels 2008] Treatment was coded as low parental involvement. Diagnoses were provided separately for parent and child report, with the primary diagnosis selected from these data by the trial manager.

Supplementary Results

Change in symptom severity from baseline to post-treatment and post-treatment to follow-up: analyses restricted to White European ancestry subset (N = 916)

When the analyses were restricted to a subset that identified as having four White European grandparents (n = 916), none of the SNPs genotyped in the entire sample were significantly associated with treatment response across the active treatment period(all *p* values > .05). However rs2501431 ($p = 0.07$) was situated in an independent clump that was nominally associated with a more favourable treatment response (sentinel SNP rs35385477, see Table S2 for clump based test statistics). For the post-treatment to follow-up time period, three independent clumps were nominally associated with a poorer response (sentinel SNPs: rs806365; rs2501431; rs2070953), while one independent clump predicted a more favourable response (sentinel SNP: rs2023239, see Table S1). The top SNPs identified in the White European subset corresponded to the 1st, 2nd, 3rd and 4th clumps identified in the entire dataset.

Table SI: Sample characteristics by site for the subset of the sample with a fear-based anxiety disorder diagnosis

Characteristic	Sydney	Reading	Aarhus	Bergen	Bochum	Basel	Groningen	Oxford	Florida	Amsterdam	Total
N	**265**	**202**	**83**	**29**	**47**	**47**	**29**	**13**	**30**	**4**	**749**
Gender Female n (%)	129 (48.7)	109 (54.0)	46 (55.4)	19 (65.5)	27 (57.4)	26 (55.3)	16 (55.2)	7 (60.0)	16 (53.8)	0 (0)	395 (52.7)
Age: mean (SD)	9.30 (1.86)	9.59 (1.71)	10.99 (2.40)	11.38 (1.99)	10.91 (2.56)	8.49 (2.07)	11.69 (3.08)	8.77 (1.48)	9.40 (2.19)	12.00 (1.83)	9.80 (2.19)
Severity primary diagnosis: mean (SD)	6.36 (0.88)	5.65 (0.83)	6.67 (1.24)	6.52 (1.30)	6.77 (1.15)	5.98 (0.77)	6.28 (0.96)	5.54 (0.97)	6.97 (1.16)	5.75 (1.71)	6.21 (1.05)
Primary diagnosis: n (%)											
SoAD	136 (51.3)	62 (30.7)	18 (21.7)	17 (58.6)	15 (31.9)	0 (0)	14 (48.3)	6 (46.2)	10 (33.3)	1 (25.0)	279 (37.2)
SP	51 (19.2)	49 (24.3)	19 (22.9)	0 (0)	17 (36.2)	0 (0)	6 (20.7)	1 (7.7)	5 (16.7)	1 (25.0)	149 (19.9)
SAD	74 (27.9)	77 (38.1)	37 (44.6)	12 (41.4)	13 (27.7)	47 (100)	6 (20.7)	6 (46.2)	10 (33.3)	2 (50.0)	284 (37.9)
Other AD[a]	4 (1.5)	14 (6.9)	9 (10.8)	0 (0)	2 (4.3)	0 (0)	3 (10.3)	0 (0)	5 (16.7)	0 (0)	37 (4.9)
CBT treatment: n (%)											
Individual based	9 (3.4)	86 (42.6)	2 (2.4)	17 (58.6)	47 (100)	47 (100)	29 (100)	0 (0)	30 (100)	1 (25.0)	268 (35.8)
Group-based	224 (84.5)	0 (0)	81 (97.6)	12 (41.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (75.0)	320 (42.7)
Guided self-help	32 (12.1)	116 (57.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	13 (100)	0 (0)	0 (0)	161 (21.5)

Other anxiety disorders include Panic Disorder and Selective Mutism.

Table SII: Independent clumps nominally associated ($p < .05$) with treatment response between a.) baseline and post-treatment and b.) post-treatment and follow-up in the White European ancestry subset

Sentinel SNP	**Gene**	**Clump BP**	**Minor allele**	**MAF**	**Info**	**β**	**95% CI**	***p***
a.) **Change in symptom severity from baseline to post-treatment**								
rs35385477	CNR2	24108683-24206032	G	0.454	0.989	-0.05	-0.10 - -0.01	.030[a]
b.) **Change in symptom severity from post-treatment to follow-up**								
rs806365	CNR1	88843390-88845949	T	0.395	Genotyped (microarray)	0.13	0.04 – 0.22	.004
rs2501431	CNR2	24108683-24206032	G	0.435	Genotyped (LGC)	0.11	0.03 –0.19	.009
rs2070953	CNR2	24191219-24223859	C	0.103	0.995	0.18	0.04 – 0.32	.010
rs2023239	CNR1	88861208-88885326	C	0.183	0.966	-0.12	-0.23 – -0.00	.047

Note: All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote

Regression weights (**β**) significantly less than 0 indicate that the minor allele of that SNP was associated with a greater reduction in symptom severity across the active treatment or follow-up period. Values significantly greater than 0 indicate that the minor allele of that SNP was associated with a poorer reduction in symptom severity.

[a] This clump contains the directly genotyped SNP rs2501431. Test statistics for this SNP are β = -0.04, 95% CI: -0.08 – 0.004, $p = .073$.

Table SIII: Statistics for all clumps (identified by sentinel SNP) with treatment response between baseline and post-treatment for the full sample

Sentinel SNP (Gene)	**Clump BP**	**MAF/ Minor allele**	**β**	**95% CI**	***p***	**n[a]**	**Additional SNPs included in clump (SNPs with *p* values < .05 highlighted in bold, total number of additional SNPs in clump given in brackets e.g. (74))**
rs12133557 (CNR2)	24191219 - 24223859	0.098 T	-0.07	-0.14– -0.01	0.020	925	**rs74937660**, rs74223776, rs3003325,rs3003328, rs3003329, rs3003621, rs3003332, rs2070956, rs2070955, rs2070954, rs2070953, rs3003320, rs3003622, rs3003321, rs6664030, rs2503003, **exm31621**, rs12754324, rs12727867, rs28404091, rs7541711, rs7541713, rs7541819, rs7532916, rs7541841, rs12741866, rs12759455, rs12733278, rs12759917, rs4625225, rs60390132, rs7519729, rs111834151, rs12742876, rs61778195, rs5026902, rs4648919, rs143281762, rs2501398, rs6424127, rs6424128, rs6424129, rs6424130, rs7512349, rs2502967, rs2501399, rs2501400, rs2502968, rs2501401, rs2502969, rs2502970, rs2501402, rs6424131, rs7415219, rs7550908, rs7550371, rs7537224, rs12730734, rs201557597, rs2501403, rs3003326, rs28735813, rs35829803, rs9424397, rs9424398, rs12724034, kgp1774784, rs2502971, rs2502972, rs9424400, rs9424338, rs2501404, rs3003327, rs3003623, rs2502973, rs2502974 (76)
rs6454676 (CNR1)	88860482- 88885426	0.104 A	0.07	0.002 – 0.13	0.042	926	rs2023239, **rs1535255**, rs6928499, rs6928813, rs6912668, rs9450901, rs9450902, rs9444586, rs9450903, rs9450904, rs10485170, rs74471317, rs9450906, rs9444587, rs9450907, rs11966501, rs11968764, rs11963892, rs78335089, rs9444588, rs6454678 (21)
rs45540335 (FAAH)	46766751 - 46865387	0.121 A	-0.05	-0.11- 0.00	0.066	927	rs3753362, rs79783387, exm56515, rs77526109, rs76976909, rs76771627, exm56596, rs41294484, rs59082884, rs4110477, rs3891758, rs45480993, rs324416 (13)
rs12197767 (CNR1)	88907388 - 88941764	0.245 T	0.03	-0.01- 0.07	0.173	924	rs9450916, rs16880378, rs2038447, rs12212677, rs7766691, rs7752742, rs9362470, rs1555340, rs9294398, rs1358791, rs1324958, rs1324957, rs9344763, rs9344764, rs9353531, rs9362472, rs9344765, rs9351142, rs9351143, rs9344767 (20)
rs58370001 (CNR1)	88919215 - 88940323	0.067 C	-0.05	-0.13 – 0.02-	0.177	924	rs7754491, rs7769918, rs56396859, rs9450925, rs59449423, rs55882449, rs60315037, rs113006189, rs1216678, rs16880396, rs145705030, rs7756920, rs7757556, rs62431489, rs6927294, rs62431491, rs964647, rs59903039, rs6906154 (19)
exm56547 (FAAH)	46806959 - 46882753	0.329 G	0.03	-0.01- 0.07	0.186	939	rs11579255, rs34160166, rs2145409, rs11802866, rs12404971, rs12040179, rs10252, rs12075550, rs141064494, rs10890390, rs10890391, rs11211270, rs11804189, rs56733721, rs3863641, rs12073998, rs11211271, rs4660925, rs35056299, rs913168, rs11589812, rs4141964, rs3766246, rs2295633, rs11576941, rs61784641, rs55646923 (27)
rs4649123	24108683 -	0.432	-0.02	-0.06 –	0.237	929	rs10917425, rs12031592, rs2256179, rs974698, rs1018396, rs2502986, rs6679378, rs2502987, rs2982390, rs2473377, rs2179395, rs2502979, rs2502980, rs34883557, rs6697805, rs6424115,

(CNR2)	24206032	A		0.02			rs60013677, rs34477640, rs7519554, rs35385477, rs6424116, rs71575777, rs10917430, exm31570, rs12748109, rs11803575, rs12755062, rs12141409, rs34570472, rs10799804, rs3123554, rs4483353, rs2503002, rs2503001, rs2503000, rs2502999, rs2502998, rs2502997, rs2501417, rs6680132, rs6672157, rs2501423, rs2502996, rs2502995, rs2501425, rs6663474, rs3003334, rs35955796, rs3003335, rs6665733, rs1130321, rs1130320, rs1106, rs1105, rs2229585, rs2229584, rs2229583, rs2229581, rs2229580, rs2502993, rs4649124, rs3003336, rs2501431, rs2502992, exm31668, rs2502991, rs6667839, rs6672499, rs2501433, rs6658703, rs2501434, rs6673210, rs3123555, rs3123556, rs6424119, rs6424120, rs4341315, rs2501367, rs2502990, rs2502989, rs2502988, rs2501369 (82)
rs1886117 (FAAH)	46954587 - 46974497	0.315 T	0.02	-0.02-0.06	0.264	929	rs1998545, rs7531088 (2)
rs6676038 (FAAH)	46761389 - 46798466	0.017 A	-0.08	-0.23-0.06	0.276	933	rs7548226, rs144930516, rs142618742, rs7542864, rs7545120, rs200232349, rs17102133, rs114531159, rs140815810, rs199585121, rs112746922, rs112387082, rs147637102 (13)
rs55845894 (CNR1)	88947649 - 88971424	0.146 C	0.03	-0.03 – 0.08	0.294	920	rs11966650, rs7769940, rs28816226, rs6910128, rs2325103, rs7753442, rs35750466, rs6922315, rs5878063, rs3929734, rs34367043, rs59413611, rs6918613, rs7765818, rs61310563, rs76763854, rs7762344, rs59838907, rs1408701, rs7453339, rs6454683, rs6454685 (22)
rs806379 (CNR1)	88858648 - 88867925	0.449 T	0.02	-0.02-0.05	0.295	1022	rs806376, rs12205430 (2)
rs806374 (CNR1)	88850150 - 88857320	0.346 C	-0.02	-0.06 – 0.02	0.331	939	rs806368 (1)
rs2180619 (CNR1)	88877952	0.400 G	0.01	-0.02-0.05	0.429	1162	NONE
rs1408702 (CNR1)	88973751	0.442 G	0.01	-0.02-0.05	0.45	939	NONE
rs6683116 (FAAH)	46975773 - 46975877	0.189 T	0.02	-0.03-0.07	0.455	939	rs6698196 (1)

exm2268681 (FAAH)	46938837 – 46978946	0.375 C	0.01	-0.02 – 0.05	0.457	939	rs2031247, rs199790074, rs12132747, rs4660353, rs2209172, rs56393814 (6)
rs10890388 (FAAH)	46761496 - 46888039	0.240 T	-0.02	-0.06- 0.03	0.459	921	rs6678149, rs2145408, rs6429600, exm56619, rs324420, rs324418, rs12029329, rs201392030, rs4660928, rs6670926, rs4660346 (11)
rs6908693 (CNR1)	88817588 - 88817934	0.127 A	-0.02	-0.08 – 0.04	0.478	931	rs6908755, rs6913146 (2)
rs9344758 (CNR1)	88894422 - 88903557	0.462 T	-0.03	-0.11- 0.05	0.492	938	rs1535257, rs7747006, rs7751075, rs16880345, rs2038448, rs9294397, rs2875545, rs57809420, rs12209554, rs9353529, rs6920617, rs35670824, rs719537, rs1321361, rs9351140, rs9362468, rs9450914, rs9450915, rs2325098, rs2325099, rs12213790, rs2325100 (22)
rs324410 (FAAH)	46834173 - 46888905	0.056 T	-0.01	-0.05- 0.02	0.492	925	rs324425, rs324424, rs324423, rs324421 (4)
rs9450877 (CNR1)	88796053 - 88797885	0.334 A	-0.01	-0.05 – 0.03	0.505	938	rs9450876, rs1324075 (2)
rs806365 (CNR1)	88843390 - 88845949	0.405 T	-0.01	-0.05- 0.03	0.509	939	rs10485171 (1)
rs806371 (CNR1)	88856363	0.110 G	0.01	-0.04 – 0.07	0.684	974	NONE
rs4707441 (CNR1)	88899850 - 88904498	0.152 G	0.01	-0.04- 0.06	0.695	939	rs9450913, rs4707442 (2)
rs2281774 (FAAH)	46905802 - 46928349	0.214 T	0.01	-0.04- 0.06	0.711	920	rs11211276, rs12407178, rs12409747, rs7538292, rs3795315, rs72637962, rs12126376, rs11211278, rs11293072, rs2281775, rs4660347, rs942258, rs10890397, rs4660933, rs2031248, rs4660348, rs11211282 (17)
rs56953705 (FAAH)	46937668 - 46960043	0.016 T	-0.02	-0.17- 0.12	0.749	923	rs74810435, rs76181455, rs60712134, rs112699995, rs74342198 (5)

rs55939860 (FAAH)	46806242 - 46886953	0.278 G	-0.01	-0.05-0.03	0.775	923	rs67545510, rs112712935, rs41293273, rs41293275, rs17361749, rs41293277, rs10489769, rs72885163, rs68083747, rs66972124, rs17357621, rs56909107, rs41293285, rs17357628, rs17357635, rs68191463, rs41293287, rs56126529, rs7525309, rs7548675, rs7515284, rs41294456, rs66516678, rs41294458, rs79697925, rs17361763, rs6684274, rs11304172, rs6696777, rs6659228, rs10661193, rs6697123, rs67487250, rs113610895, rs112280595, rs112491752, rs112089006, rs72677585, rs17357676, rs17361791, rs41294460, rs72885198, rs79490411, rs7556425, rs61358317, rs72886903, rs68112720, rs17361805, rs72677587, rs17361812, rs66575205, rs72886907, rs111226885, rs111699884, rs72886911, rs56344958, rs56121132, rs5013329, rs5013330, rs17357683, rs6667861, rs1057533, rs1057534, rs1057535, rs1135459, rs1135460, rs1475390, rs5773907, rs1475389, rs1475388, rs57267378, rs58162700, rs1812705, rs966907, rs112324418, rs72677588, rs72677589, rs66828173, rs72677590, rs72677591, rs72677592, rs41294476, rs41294478, rs17413701, rs7515598, rs7529674, rs12385696, rs12385697, rs12385693, rs12385695, rs28699008, rs56179746, rs146398931, rs6679080, rs6690075, rs6666601, rs6682266, rs6679898, rs10158236, rs10157084, rs112980938, rs56363851, rs66990604, rs201127808, rs10158572, rs10158130, rs10157464, rs56030283, rs55971480, rs66911505, rs6659448, rs6677394, rs6674726, rs112911951, rs113033705, rs72677593, rs72677594, rs7520482, rs7520497, rs7532149, rs28578741, rs202085913, rs55999016, rs56063031, rs67276232, rs6669025, rs200601367, rs55887761, rs9661240, rs1053624, rs1053627, rs1053628, rs6429599, rs17361819, rs67142569, rs17361833, rs41534051, rs17357711, rs6683192, rs12062, rs111725921, rs66847432, rs67547686, rs113076306, rs17357759, rs17361873, rs72677596, rs72677599, rs72677600, rs17361887, rs55670684, rs56049453, rs67200518, rs72677602, rs67941619, rs66483119, rs55668511, rs55693298, rs68012736, rs143856001, rs144535648, rs147142636, rs66473412, rs6659681, rs6659788, rs55921163, rs55926300, rs111868160, rs13374893, rs13374968, rs6694628, rs6658556, rs6695043, rs72679807, rs56284503, rs17361915, rs113623605, rs144250006, rs113534835, rs56358525, rs6681857, rs56349187, rs79610407, rs72890715, rs4372193, rs111723629, rs3991877, rs57240150, rs113887859, rs201070992, rs61519400, rs56306849, rs1984491, rs1984490, rs45449893, rs45517837, rs932816, rs72890727, rs6674305, rs56130131, rs11288511, rs6703374, rs6703669, rs45524035, rs17361936, rs17361950, rs6662982 (207)
rs3766248 (FAAH)	46773488	0.021 A	0.01	-0.11 – 0.14	0.831	935	NONE
rs1049353 (CNR1)	88853635	0.274 A	0.00	-0.04-0.04	0.959	1175	NONE

rs10890398 (FAAH)	46925594	0.180 C	0.00	-0.05-0.05	0.981	939	NONE

Note: All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote

Regression weights (***β***) significantly less than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a greater reduction in symptom severity across the active treatment or follow-up period. Values significantly greater than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a poorer reduction in symptom severity.

[a] n reflects total number of cases included in regression analysis for the sentinel SNP.

Table SIV: Statistics for all clumps (identified by sentinel SNP) with treatment response between baseline and post-treatment in the subset of the sample with fear-based anxiety disorder diagnoses

Sentinel SNP (Gene)	**Clump BP**	**MAF/ Minor allele**	**β**	**95% CI**	***p***	**n[a]**	**Additional SNPs included in clump (SNPs with *p* values < .05 highlighted in bold, total number of additional SNPs in clump given in brackets e.g. (74))**
rs12133557 (CNR2)	24191219 - 24223859	0.094 T	-0.11	-0.20 – -0.03	.011	540	**rs74937660**, **rs74223776**, **rs3003325**, **rs3003328**, **rs3003329**, **rs3003621**, **rs3003332**, **rs2070956**, **rs2070955**, **rs2070954**, **rs2070953**, **rs3003320**, **rs3003622**, **rs3003321**, **rs6664030**, **rs2503003**, **exm31621**, rs12754324, rs12727867, rs28404091, rs7541711, rs7541713, rs7541819, rs7532916, rs7541841, rs12741866, rs12759455, rs12733278, rs12759917, rs4625225, rs60390132, rs7519729, rs111834151, rs12742876, rs61778195, rs5026902, rs4648919, rs143281762, rs2501398, rs6424127, rs6424128, rs6424129, rs6424130, rs7512349, rs2502967, rs2501399, rs2501400, rs2502968, rs2501401, rs2502969, rs2502970, rs2501402, rs6424131, rs7415219, rs7550908, rs7550371, rs7537224, rs12730734, rs201557597, rs2501403, rs3003326, rs28735813, rs35829803, rs9424397, rs9424398, rs12724034, kgp1774784, rs2502971, rs2502972, rs9424400, rs9424338, rs2501404, rs3003327, rs3003623, rs2502973, rs2502974 (76)
rs6454676 (CNR1)	88860482 - 88885426	0.108 A	0.09	0.005 – 0.17	.038	539	rs2023239, rs1535255, rs6928499, rs6928813, rs6912668, rs9450901, rs9450902, rs9444586, rs9450903, rs9450904, rs10485170, rs74471317, rs9450906, rs9444587, rs9450907, rs11966501, rs11968764, rs11963892, rs78335089, rs9444588, rs6454678 (21)
rs6927294 (CNR1)	88919215 - 88940323	0.068 T	-0.1	-0.20- 0.00	.053	547	rs7754491, rs7769918, rs56396859, rs58370001, rs9450925, rs59449423, rs55882449, rs60315037, rs113006189, rs1216678, rs16880396, rs145705030, rs7756920, rs7757556, rs62431489, rs62431491, rs964647, rs59903039, rs6906154 (19)
rs806379 (CNR1)	88858648 - 88867925	0.435 T	0.03	-0.02- 0.08	.182	588	rs806376, rs12205430 (2)
rs11966650 (CNR1)	88947649 - 88971424	0.134 G	0.05	-0.03- 0.13	.218	538	rs7769940, rs28816226, rs6910128, rs2325103, rs7753442, rs35750466, rs6922315, rs5878063, rs3929734, rs34367043, rs59413611, rs55845894, rs6918613, rs7765818, rs61310563, rs76763854, rs7762344, rs59838907, rs1408701, rs7453339, rs6454683, rs6454685 (22)
rs45540335 (FAAH)	46766751 - 46865387	0.131 A	-0.05	-0.12 - 0.03	.219	542	rs3753362, rs79783387, exm56515, rs77526109, rs76976909, rs76771627, exm56596, rs41294484, rs59082884, rs4110477, rs3891758, rs45480993, rs324416 (13)
rs16880345	88894422 -	0.201	-0.04	-0.10 -	.221	544	rs1535257, rs7747006, rs7751075, rs9344758, rs2875545, rs12209554, rs9353529, rs6920617,

(CNR1)	88902091	G		0.02			rs35670824, rs719537, rs1321361, rs9351140, rs9362468, rs9450914, rs9450915, rs2325099 (16)
rs56733721 (FAAH)	46806242 - 46888039	0.413 G	-0.03	-0.08- 0.02	.222	543	rs67545510, rs112712935, rs41293273, rs41293275, rs17361749, rs41293277, rs10489769, rs11579255, rs72885163, rs68083747, rs66972124, rs17357621, rs56909107, rs41293285, rs17357628, rs17357635, rs68191463, rs41293287, rs56126529, rs7525309, rs7548675, rs7515284, rs41294456, rs66516678, rs41294458, rs79697925, exm56547, rs17361763, rs6684274, rs11304172, rs6696777, rs6659228, rs10661193, rs6697123, rs67487250, rs113610895, rs112280595, rs112491752, rs112089006, rs72677585, rs17357676, rs17361791, rs41294460, rs72885198, rs79490411, rs7556425, rs61358317, rs72886903, rs68112720, rs17361805, rs72677587, rs17361812, rs66575205, rs72886907, rs111226885, rs111699884, rs72886911, rs56344958, rs56121132, rs5013329, rs5013330, rs17357683, rs6667861, rs1057533, rs1057534, rs1057535, rs1135459, rs1135460, rs1475390, rs5773907, rs1475389, rs1475388, rs57267378, rs58162700, rs1812705, rs966907, rs112324418, rs72677588, rs72677589, rs66828173, rs72677590, rs72677591, rs72677592, rs41294476, rs41294478, rs17413701, rs7515598, rs7529674, rs12385696, rs12385697, rs12385693, rs12385695, rs28699008, rs56179746, rs146398931, rs6679080, rs6690075, rs6666601, rs6682266, rs34160166, rs6679898, rs10158236, rs10157084, rs112980938, rs56363851, rs66990604, rs201127808, rs10158572, rs10158130, rs10157464, rs2145409, rs56030283, rs55971480, rs66911505, rs6659448, rs6677394, rs6674726, rs11802866, rs112911951, rs113033705, rs12404971, rs72677593, rs72677594, rs7520482, rs7520497, rs7532149, rs28578741, rs202085913, rs55999016, rs56063031, rs67276232, rs12040179, rs6669025, rs200601367, rs55887761, rs9661240, rs1053624, rs1053627, rs1053628, rs6429599, rs17361819, rs67142569, rs17361833, rs41534051, rs17357711, rs6683192, rs10252, rs12062, rs111725921, rs66847432, rs67547686, rs113076306, rs17357759, rs17361873, rs72677596, rs12075550, rs72677599, rs72677600, rs17361887, rs55670684, rs56049453, rs67200518, rs141064494, rs72677602, rs10890391, rs67941619, rs66483119, rs55668511, rs55693298, rs11211270, rs68012736, rs143856001, rs11804189, rs144535648, rs147142636, rs66473412, rs6659681, rs6659788, rs55921163, rs55926300, rs111868160, rs3863641, rs12073998, rs13374893, rs13374968, rs6694628, rs6658556, rs6695043, rs72679807, rs56284503, rs17361915, rs113623605, rs11211271, rs144250006, rs113534835, rs56358525, rs6681857, rs56349187, rs79610407, rs4660925, rs72890715, rs4372193, rs111723629, rs3991877, rs35056299, rs57240150, rs113887859, rs201070992, rs61519400, rs56306849, rs913168, rs1984491, rs1984490, rs11589812, rs45449893, rs45517837, rs932816, rs72890727, rs6674305, rs56130131, rs11288511, rs6703374, rs6703669, rs45524035, rs17361936, rs17361950, rs11576941, rs6662982, rs4660928, rs55939860, rs6670926, rs4660346 (232)
rs2502987 (CNR2)	24108683 - 24206032	0.439 A	-0.03	-0.08 - 0.02	.262	537	rs10917425, rs12031592, rs2256179, rs974698, rs1018396, rs2502986, rs6679378, rs2982390, rs2473377, rs2179395, rs2502979, rs2502980, rs34883557, rs6697805, rs6424115, rs60013677, rs34477640, rs7519554, rs35385477, rs6424116, rs71575777, rs10917430, exm31570, rs12748109,

							rs11803575, rs12755062, rs12141409, rs34570472, rs10799804, rs3123554, rs4483353, rs2503002, rs2503001, rs4649123, rs2503000, rs2502999, rs2502998, rs2502997, rs2501417, rs6680132, rs6672157, rs2501423, rs2502996, rs2502995, rs2501425, rs6663474, rs3003334, rs35955796, rs3003335, rs6665733, rs1130321, rs1130320, rs1106, rs1105, rs2229585, rs2229584, rs2229583, rs2229581, rs2229580, rs2502993, rs4649124, rs3003336, rs2501431, rs2502992, exm31668, rs2502991, rs6667839, rs6672499, rs2501433, rs6658703, rs2501434, rs6673210, rs3123555, rs3123556, rs6424119, rs6424120, rs4341315, rs2501367, rs2502990, rs2502989, rs2502988, rs2501369 (82)
rs806368 (CNR1)	88850150 - 88857320	0.223 G	0.03	-0.02- 0.08	.276	695	rs806371, rs806374 (2)
rs9450876 (CNR1)	88796053 - 88797885	0.350 A	-0.03	-0.08 - 0.02	.285	545	rs9450877, rs1324075 (2)
rs112699995 (FAAH)	46937668 - 46960043	0.020 T	0.1	-0.08- 0.28	.297	540	rs74810435, rs76181455, rs56953705, rs60712134, rs74342198 (5)
rs6683116 (FAAH)	46975773 - 46975877	0.190 T	0.03	-0.03- 0.10	.300	547	rs6698196 (1)
rs7548226 (FAAH)	46761389 - 46798466	0.013 A	0.11	-0.11 - 0.34	.334	544	rs6676038, rs144930516, rs142618742, rs7542864, rs7545120, rs200232349, rs17102133, rs114531159, rs140815810, rs199585121, rs112746922, rs112387082, rs147637102 (13)
rs9450913 (CNR1)	88899850 - 88904498	0.145 T	0.03	-0.04- 0.11	.342	538	rs4707441, rs4707442 (2)
rs11211282 (FAAH)	46905802 - 46928349	0.426 A	0.02	-0.03 - 0.07	.37	547	rs11211276, rs12407178, rs12409747, rs7538292, rs3795315, rs72637962, rs12126376, rs11211278, rs11293072, rs2281775, rs2281774, rs4660347, rs942258, rs10890397, rs4660933, rs2031248, rs10890398, rs4660348 (18)
exm2268681 (FAAH)	46938837 – 46978946	0.389 C	0.02	-0.03 - 0.08	.373	547	rs2031247, rs199790074, rs12132747, rs4660353, rs2209172, rs56393814 (6)
exm56619	46761496 -	0.212	0.03	-0.04 -	.400	547	rs10890388, rs10890390, rs6678149, rs2145408, rs6429600, rs4141964, rs3766246, rs324420, rs324418, rs2295633, rs12029329, rs201392030, rs61784641, rs55646923 (14)

(FAAH)	46882753	A		0.09			
rs2180619 (CNR1)	88877952	0.414 G	0.02	-0.03-0.06	.470	675	NONE
rs10485171 (CNR1)	88843390 - 88845949	0.458 G	-0.01	-0.06-0.04	.601	547	rs806365, rs1049353 (2)
rs12212677 (CNR1)	88907388 - 88941764	0.463 G	-0.01	-0.06-0.04	.633	539	rs9450916, rs16880378, rs2038447, rs7766691, rs7752742, rs9362470, rs9294398, rs1358791, rs1324958, rs1324957, rs9344763, rs9344764, rs9353531, rs9362472, rs9344765, rs9351142, rs12197767, rs9351143, rs9344767 (19)
rs1886117 (FAAH)	46954587 - 46974497	0.306 T	0.01	-0.04-0.07	.646	545	rs1998545, rs7531088 (2)
rs324410 (FAAH)	46834173 - 46888905	0.061 T	-0.02	-0.13-0.09	.68	539	rs324425, rs324424, rs324423, rs324421 (4)
rs1408702 (CNR1)	88973751	0.452 G	-0.01	-0.06-0.04	.726	547	NONE
rs3766248 (FAAH)	46773488	0.018 A	-0.03	-0.21 - 0.15	.751	544	NONE
rs2038448 (CNR1)	88898440 - 88902564	0.376 C	0.01	-0.04 - 0.06	.785	538	rs57809420, rs2325098, rs12213790 (3)
rs6908755 (CNR1)	88817588 - 88817934	0.130 T	0.01	-0.07-0.09	.808	547	rs6908693, rs6913146 (2)
rs9294397 (CNR1)	88898611 - 88903557	0.274 C	-0.01	-0.06 - 0.05	.829	547	rs2325100 (1)
rs1555340	88922785	0.244	0.00	-0.05 -	.926	547	NONE

(CNR1)		C		0.06			

Note: All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote

Regression weights (***β***) significantly less than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a greater reduction in symptom severity across the active treatment or follow-up period. Values significantly greater than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a poorer reduction in symptom severity.

[a] n reflects total number of cases included in regression analysis for the sentinel SNP.

Table SV: Statistics for all clumps (identified by sentinel SNP) with treatment response between post-treatment and follow-up for the full sample

Sentinel SNP (Gene)	**Clump BP**	**MAF/ Minor allele**	**β**	**95% CI**	***p***	**n[a]**	**Additional SNPs included in clump (SNPs with *p* values < .05 highlighted in bold, total number of additional SNPs in clump given in brackets e.g. (74))**
rs806365 (CNR1)	88843390 - 88845949	0.408 T	0.11	0.04 – 0.18	.004	702	rs10485171 (1)
rs2501431 (CNR2)	24108683 - 24206032	0.423 G	0.09	0.03 – 0.16	.007	874	rs10917425, rs12031592, rs2256179, rs974698, rs1018396, rs2502986, rs6679378, rs2502987, rs2982390, rs2473377, rs2179395, rs2502979, rs2502980, rs34883557, rs6697805, rs6424115, rs60013677, rs34477640, rs7519554, rs35385477, rs6424116, rs71575777, rs10917430, exm31570, rs12748109, rs11803575, rs12755062, rs12141409, rs34570472, rs10799804, rs3123554, rs4483353, **rs2503002**, rs2503001, rs4649123, rs2503000, rs2502999, rs2502998, rs2502997, rs2501417, rs6680132, rs6672157, rs2501423, rs2502996, rs2502995, rs2501425, rs6663474, rs3003334, **rs35955796**, rs3003335, rs6665733, rs1130321, rs1130320, rs1106, rs1105, rs2229585, rs2229584, rs2229583, rs2229581, rs2229580, rs2502993, rs4649124, rs3003336, rs2502992, exm31668, rs2502991, rs6667839, rs6672499, rs2501433, rs6658703, rs2501434, rs6673210, **rs3123555**, **rs3123556**, rs6424119, rs6424120, rs4341315, rs2501367, rs2502990, **rs2502989**, rs2502988, **rs2501369** (82)
rs2070956 (CNR2)	24191219 - 24223859	0.101 C	0.14	0.02 – 0.26	.021	698	rs12133557, **rs74937660**, **rs74223776**, **rs3003325**, **rs3003328**, **rs3003329**, rs3003621, rs3003332, **rs2070955**, **rs2070954, rs2070953**, **rs3003320**, **rs3003622**, **rs3003321**, **rs6664030, rs2503003**, **exm31621**, rs12754324, rs12727867, rs28404091, rs7541711, rs7541713, rs7541819, rs7532916, rs7541841, rs12741866, rs12759455, rs12733278, rs12759917, rs4625225, rs60390132, rs7519729, rs111834151, rs12742876, rs61778195, rs5026902, rs4648919, rs143281762, rs2501398, rs6424127, rs6424128, rs6424129, rs6424130, rs7512349, rs2502967, rs2501399, rs2501400, rs2502968, rs2501401, rs2502969, rs2502970, rs2501402, rs6424131, rs7415219, rs7550908, rs7550371, rs7537224, rs12730734, rs201557597, rs2501403, rs3003326, rs28735813, rs35829803, rs9424397, rs9424398, rs12724034, kgp1774784, rs2502971, rs2502972, rs9424400, rs9424338, rs2501404, rs3003327, rs3003623, rs2502973, rs2502974 (76)
rs6928813 (CNR1)	88860482 - 88885426	0.180 G	-0.11	-0.20 – -0.01	.033	702	**rs2023239**, rs1535255, rs806379, rs6928499, rs6454676, rs6912668, rs9450901, rs9450902, rs9444586, rs9450903, rs9450904, rs10485170, rs74471317, rs9450906, rs9444587, rs9450907, rs11966501, rs11968764, rs11963892, rs78335089, rs9444588, rs6454678 (22)

rs7769940 (CNR1)	88947649 - 88973751	0.209 T	0.10	0.01 – 0.19	.034	702	rs11966650, rs28816226, rs6910128, rs2325103, rs7753442, rs35750466, rs6922315, rs5878063, rs3929734, rs34367043, rs59413611, rs55845894, rs6918613, rs7765818, rs61310563, rs76763854, rs7762344, rs59838907, rs1408701, rs7453339, rs6454683, rs6454685, rs1408702 (23)
rs2209172 (FAAH)	46938837 - 46978946	0.206 T	0.09	0.00 – 0.18	.044	702	rs2031247, rs199790074, exm2268681, rs12132747, **rs4660353**, **rs56393814** (6)
rs74342198 (FAAH)	46937668 - 46960043	0.019 A	0.26	-0.01 - 0.53	0.06	689	rs74810435, rs76181455, rs56953705, rs60712134, rs112699995 (5)
rs2325100 (CNR1)	88898611 - 88903557	0.271 G	-0.08	-0.16- 0.01	0.073	693	rs9294397, rs9344758, rs12209554, rs9353529, rs6920617, rs35670824, rs719537, rs9351140, rs9362468, rs2325099 (10)
rs806371 (CNR1)	88850150 - 88857320	0.107 G	-0.09	-0.20 - 0.01	0.087	742	rs806368 (1)
rs6678149 (FAAH)	46761496 - 46888039	0.280 A	-0.07	-0.15 - 0.01	0.089	694	rs10890388, rs10890390, rs4660925, rs2145408, rs6429600, rs4141964, rs3766246, exm56619, rs324420, rs324418, rs2295633, rs12029329, rs201392030, rs61784641, rs55646923, rs4660928, rs6670926, rs4660346 (18)
rs140815810 (FAAH)	46761389 - 46798466	0.010 I[b]	0.29	-0.08 - 0.66	0.125	693	rs6676038, rs7548226, rs144930516, rs142618742, rs7542864, rs7545120, rs200232349, rs17102133, rs114531159, rs199585121, rs112746922, rs112387082, rs147637102 (13)
rs1049353 (CNR1)	88853635	0.284 A	-0.05	-0.12 - 0.02	0.181	900	NONE
rs1358791 (CNR1)	88907388 - 88941764	0.244 T	-0.05	-0.14- 0.03	0.226	696	rs9450916, rs16880378, rs2038447, rs12212677, rs7766691, rs9362470, rs1555340, rs9294398, rs1324958, rs1324957, rs9344763, rs9344764, rs9353531, rs9362472, rs9344765, rs9351142, rs12197767, rs9351143, rs9344767 (19)
rs6906154 (CNR1)	88919215 - 88940323	0.053 T	0.10	-0.07- 0.27	0.244	690	rs7754491, rs7769918, rs56396859, rs58370001, rs9450925, rs59449423, rs55882449, rs60315037, rs113006189, rs1216678, rs16880396, rs145705030, rs7756920, rs7757556, rs62431489, rs6927294, rs62431491, rs964647, rs59903039 (19)
rs12213790 (CNR1)	88898440 - 88902564	0.395 A	0.04	-0.03 - 0.12	0.259	702	rs2038448, rs57809420, rs2325098 (3)

rs4110477 (FAAH)	46766751 - 46865387	0.119 A	0.06	-0.05 - 0.18	0.287	694	rs3753362, rs79783387, exm56515, rs77526109, rs76976909, rs76771627, exm56596, rs41294484, rs59082884, rs3891758, rs45480993, rs45540335, rs324416 (13)
rs12075550 (FAAH)	46806242 - 46886953	0.400 C	0.04	-0.04 - 0.11	0.312	696	rs67545510, rs112712935, rs41293273, rs41293275, rs17361749, rs41293277, rs10489769, rs11579255, rs72885163, rs68083747, rs66972124, rs17357621, rs56909107, rs41293285, rs17357628, rs17357635, rs68191463, rs41293287, rs56126529, rs7525309, rs7548675, rs7515284, rs41294456, rs66516678, rs41294458, rs79697925, exm56547, rs17361763, rs6684274, rs11304172, rs6696777, rs6659228, rs10661193, rs6697123, rs67487250, rs113610895, rs112280595, rs112491752, rs112089006, rs72677585, rs17357676, rs17361791, rs41294460, rs72885198, rs79490411, rs7556425, rs61358317, rs72886903, rs68112720, rs17361805, rs72677587, rs17361812, rs66575205, rs72886907, rs111226885, rs111699884, rs72886911, rs56344958, rs56121132, rs5013329, rs5013330, rs17357683, rs6667861, rs1057533, rs1057534, rs1057535, rs1135459, rs1135460, rs1475390, rs5773907, rs1475389, rs1475388, rs57267378, rs58162700, rs1812705, rs966907, rs112324418, rs72677588, rs72677589, rs66828173, rs72677590, rs72677591, rs72677592, rs41294476, rs41294478, rs17413701, rs7515598, rs7529674, rs12385696, rs12385697, rs12385693, rs12385695, rs28699008, rs56179746, rs146398931, rs6679080, rs6690075, rs6666601, rs6682266, rs34160166, rs6679898, rs10158236, rs10157084, rs112980938, rs56363851, rs66990604, rs201127808, rs10158572, rs10158130, rs10157464, rs2145409, rs56030283, rs55971480, rs66911505, rs6659448, rs6677394, rs6674726, rs11802866, rs112911951, rs113033705, rs12404971, rs72677593, rs72677594, rs7520482, rs7520497, rs7532149, rs28578741, rs202085913, rs55999016, rs56063031, rs67276232, rs12040179, rs6669025, rs200601367, rs55887761, rs9661240, rs1053624, rs1053627, rs1053628, rs6429599, rs17361819, rs67142569, rs17361833, rs41534051, rs17357711, rs6683192, rs10252, rs12062, rs111725921, rs66847432, rs67547686, rs113076306, rs17357759, rs17361873, rs72677596, rs72677599, rs72677600, rs17361887, rs55670684, rs56049453, rs67200518, rs141064494, rs72677602, rs10890391, rs67941619, rs66483119, rs55668511, rs55693298, rs11211270, rs68012736, rs143856001, rs11804189, rs144535648, rs147142636, rs56733721, rs66473412, rs6659681, rs6659788, rs55921163, rs55926300, rs111868160, rs3863641, rs12073998, rs13374893, rs13374968, rs6694628, rs6658556, rs6695043, rs72679807, rs56284503, rs17361915, rs113623605, rs11211271, rs144250006, rs113534835, rs56358525, rs6681857, rs56349187, rs79610407, rs72890715, rs4372193, rs111723629, rs3991877, rs35056299, rs57240150, rs113887859, rs201070992, rs61519400, rs56306849, rs913168, rs1984491, rs1984490, rs11589812, rs45449893, rs45517837, rs932816, rs72890727, rs6674305, rs56130131, rs11288511, rs6703374, rs6703669, rs45524035, rs17361936, rs17361950, rs11576941, rs6662982, rs55939860 (228)
rs2875545	88894422 -	0.195	0.05	-0.04-	0.322	702	rs1535257, rs7747006, rs7751075, rs16880345, rs1321361, rs9450914, rs9450915 (7)

(CNR1)	88901540	G		0.14			
rs806376 (CNR1)	88858648 - 88867925	0.495 C	-0.04	-0.11 - 0.04	0.326	702	rs12205430 (1)
rs6698196 (FAAH)	46975773 - 46975877	0.184 C	0.04	-0.06- 0.13	0.468	695	rs6683116 (1)
rs324425 (FAAH)	46834173 - 46888905	0.058 T	-0.05	-0.21- 0.10	0.494	696	rs324410, rs324424, rs324423, rs324421 (4)
rs9450876 (CNR1)	88796053 - 88797885	0.344 A	-0.02	-0.10 - 0.06	0.565	700	rs9450877, rs1324075 (2)
rs3766248 (FAAH)	46773488	0.020 A	-0.07	-0.33 - 0.19	0.592	698	NONE
rs7752742 (CNR1)	88914904	0.462 C	0.02	-0.05 - 0.09	0.629	702	NONE
rs806374 (CNR1)	88857320	0.341 C	-0.02	-0.09 - 0.06	0.698	702	NONE
rs11211282 (FAAH)	46905802 - 46928349	0.427 A	-0.01	-0.09 - 0.06	0.729	702	rs11211276, rs12407178, rs12409747, rs7538292, rs3795315, rs72637962, rs12126376, rs11211278, rs11293072, rs2281775, rs2281774, rs4660347, rs942258, rs10890397, rs4660933, rs2031248, rs10890398, rs4660348 (18)
rs4707441 (CNR1)	88899850 - 88904498	0.144 G	-0.02	-0.12- 0.09	0.73	702	rs9450913, rs4707442 (2)
rs7531088 (FAAH)	46954587 - 46974497	0.177 C	0.01	-0.09- 0.11	0.803	691	rs1998545, rs1886117 (2)
rs6913146	88817588 -	0.123	0.00	-0.11-	0.954	697	rs6908693, rs6908755 (2)

(CNR1)	88817934	T		0.12			
rs2180619 (CNR1)	88877952	0.401 G	0.00	-0.07-0.06	0.978	875	NONE

Note: All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote

Regression weights (***β***) significantly less than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a greater reduction in symptom severity across the active treatment or follow-up period. Values significantly greater than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a poorer reduction in symptom severity.

[a] n reflects total number of cases included in regression analysis for the sentinel SNP.

[b] Insertion is TATTCACATG

Table SVI: Statistics for all clumps (identified by sentinel SNP) with treatment response between post-treatment and follow-up in the subset of the sample with fear-based anxiety disorder diagnoses

Sentinel SNP (Gene)	**Clump BP**	**MAF/ Minor allele**	**β**	**95% CI**	***p***	**n[a]**	**Additional SNPs included in clump (SNPs with *p* values < .05 highlighted in bold, total number of additional SNPs in clump given in brackets e.g. (74))**
rs806365 (CNR1)	88843390 - 88845949	0.392 T	0.17	0.07 – 0.27	**.001**	399	rs10485171 (1)
rs7769940 (CNR1)	88947649 - 88973751	0.216 T	0.19	0.07 – 0.32	.003	399	**rs11966650**, **rs28816226**, **rs6910128**, **rs2325103**, **rs7753442**, **rs35750466**, **rs6922315**, **rs5878063**, **rs3929734**, **rs34367043**, **rs59413611**, **rs55845894**, **rs6918613**, **rs7765818**, **rs61310563**, **rs76763854**, **rs7762344**, **rs59838907**, **rs1408701**, **rs7453339**, **rs6454683**, **rs6454685**, rs1408702 (23)
rs2501431 (CNR2)	24108683 – 24206032	0.448 G	0.14	0.04 – 0.23	.004	495	rs10917425, rs12031592, rs2256179, rs974698, rs1018396, rs2502986, rs6679378, rs2502987, **rs2982390**, **rs2473377**, rs2179395, **rs2502979**, **rs2502980**, **rs34883557**, **rs6697805**, **rs6424115**, **rs60013677**, **rs34477640**, **rs7519554**, rs35385477, rs6424116, rs71575777, rs10917430, exm31570, rs12748109, rs11803575, rs12755062, rs12141409, rs34570472, rs10799804, **rs3123554**, **rs4483353**, rs**2503002**, **rs2503001**, **rs4649123**, **rs2503000**, **rs2502999**, **rs2502998**, **rs2502997**, **rs2501417**, **rs6680132**, **rs6672157**, **rs2501423**, **rs2502996**, **rs2502995**, **rs2501425**, **rs6663474**, **rs3003334**, **rs35955796**, **rs3003335, rs6665733**, **rs1130321**, **rs1130320**, **rs1106**, **rs1105**, **rs2229585**, **rs2229584**, **rs2229583**, **rs2229581**, **rs2229580**, **rs2502993**, **rs4649124**, **rs3003336**, **rs2502992**, **exm31668**, **rs2502991**, **rs6667839**, **rs6672499**, **rs2501433**, **rs6658703**, rs**2501434**, **rs6673210**, **rs3123555**, **rs3123556**, **rs6424119**, **rs6424120**, **rs4341315**, **rs2501367**, **rs2502990**, **rs2502989**, **rs2502988**, **rs2501369** (82)
rs1049353 (CNR1)	88853635	0.282 A	-0.09	-0.19 - 0.01	0.067	512	NONE
exm2268681 (FAAH)	46938837 – 46978946	0.391 C	0.1	-0.01 - 0.20	0.070	399	rs2031247, rs199790074, rs12132747, rs4660353, rs2209172, rs56393814 (6)
rs74342198	46937668 -	0.020	0.31	-0.04 -	0.084	393	rs74810435, rs76181455, rs56953705, rs60712134, rs112699995 (5)

(FAAH)	46960043	A		0.67			
rs2070954 (CNR2)	24191219 - 24223859	0.101 G	0.14	-0.03-0.30	0.103	398	rs12133557, rs74937660, rs74223776, rs3003325, rs3003328, rs3003329, rs3003621, rs3003332, rs2070956, rs2070955, rs2070953, rs3003320, rs3003622, rs3003321, rs6664030, rs2503003, exm31621, rs12754324, rs12727867, rs28404091, rs7541711, rs7541713, rs7541819, rs7532916, rs7541841, rs12741866, rs12759455, rs12733278, rs12759917, rs4625225, rs60390132, rs7519729, rs111834151, rs12742876, rs61778195, rs5026902, rs4648919, rs143281762, rs2501398, rs6424127, rs6424128, rs6424129, rs6424130, rs7512349, rs2502967, rs2501399, rs2501400, rs2502968, rs2501401, rs2502969, rs2502970, rs2501402, rs6424131, rs7415219, rs7550908, rs7550371, rs7537224, rs12730734, rs201557597, rs2501403, rs3003326, rs28735813, rs35829803, rs9424397, rs9424398, rs12724034, kgp1774784, rs2502971, rs2502972, rs9424400, rs9424338, rs2501404, rs3003327, rs3003623, rs2502973, rs2502974 (76)
rs2325100 (CNR1)	88898611 - 88903557	0.280 G	-0.1	-0.22-0.02	0.110	393	rs9294397, rs9344758, rs12209554, rs9353529, rs6920617, rs35670824, rs719537, rs9351140, rs9362468, rs2325099 (10)
rs806368 (CNR1)	88850150 - 88857320	0.217 G	-0.08	-0.18-0.02	0.128	520	rs806371, rs806374 (2)
rs4110477 (FAAH)	46766751 - 46865387	0.129 A	0.11	-0.04 - 0.27	0.143	395	rs3753362, rs79783387, exm56515, rs77526109, rs76976909, rs76771627, exm56596, rs41294484, rs59082884, rs3891758, rs45480993, rs45540335, rs324416 (13)
exm56547 (FAAH)	46806959 - 46882753	0.298 G	0.08	-0.03-0.18	0.164	399	rs11579255, rs34160166, rs2145409, rs11802866, rs12404971, rs12040179, rs10252, rs12075550, rs141064494, rs10890390, rs10890391, rs11211270, rs11804189, rs56733721, rs3863641, rs12073998, rs11211271, rs4660925, rs35056299, rs913168, rs11589812, rs4141964, rs3766246, rs2295633, rs11576941, rs61784641, rs55646923 (27)
rs6678149 (FAAH)	46761496 - 46888039	0.282 A	-0.08	-0.20 - 0.04	0.173	393	rs10890388, rs2145408, rs6429600, exm56619, rs324420, rs324418, rs12029329, rs201392030, rs4660928, rs6670926, rs4660346 (11)
rs10890398 (FAAH)	46925594 - 46928349	0.173 C	0.09	-0.04 - 0.23	0.181	399	rs4660348, rs11211282 (2)
rs1358791 (CNR1)	88907388 - 88941764	0.244 T	-0.07	-0.19-0.04	0.211	393	rs9450916, rs16880378, rs2038447, rs12212677, rs7766691, rs9362470, rs1555340, rs9294398, rs1324958, rs1324957, rs9344763, rs9344764, rs9353531, rs9362472, rs9344765, rs9351142, rs12197767, rs9351143, rs9344767 (19)

rs61358317 (FAAH)	46806242 - 46886953	0.280 T	-0.07	-0.19-0.04	0.216	396	rs67545510, rs112712935, rs41293273, rs41293275, rs17361749, rs41293277, rs10489769, rs72885163, rs68083747, rs66972124, rs17357621, rs56909107, rs41293285, rs17357628, rs17357635, rs68191463, rs41293287, rs56126529, rs7525309, rs7548675, rs7515284, rs41294456, rs66516678, rs41294458, rs79697925, rs17361763, rs6684274, rs11304172, rs6696777, rs6659228, rs10661193, rs6697123, rs67487250, rs113610895, rs112280595, rs112491752, rs112089006, rs72677585, rs17357676, rs17361791, rs41294460, rs72885198, rs79490411, rs7556425, rs72886903, rs68112720, rs17361805, rs72677587, rs17361812, rs66575205, rs72886907, rs111226885, rs111699884, rs72886911, rs56344958, rs56121132, rs5013329, rs5013330, rs17357683, rs6667861, rs1057533, rs1057534, rs1057535, rs1135459, rs1135460, rs1475390, rs5773907, rs1475389, rs1475388, rs57267378, rs58162700, rs1812705, rs966907, rs112324418, rs72677588, rs72677589, rs66828173, rs72677590, rs72677591, rs72677592, rs41294476, rs41294478, rs17413701, rs7515598, rs7529674, rs12385696, rs12385697, rs12385693, rs12385695, rs28699008, rs56179746, rs146398931, rs6679080, rs6690075, rs6666601, rs6682266, rs6679898, rs10158236, rs10157084, rs112980938, rs56363851, rs66990604, rs201127808, rs10158572, rs10158130, rs10157464, rs56030283, rs55971480, rs66911505, rs6659448, rs6677394, rs6674726, rs112911951, rs113033705, rs72677593, rs72677594, rs7520482, rs7520497, rs7532149, rs28578741, rs202085913, rs55999016, rs56063031, rs67276232, rs6669025, rs200601367, rs55887761, rs9661240, rs1053624, rs1053627, rs1053628, rs6429599, rs17361819, rs67142569, rs17361833, rs41534051, rs17357711, rs6683192, rs12062, rs111725921, rs66847432, rs67547686, rs113076306, rs17357759, rs17361873, rs72677596, rs72677599, rs72677600, rs17361887, rs55670684, rs56049453, rs67200518, rs72677602, rs67941619, rs66483119, rs55668511, rs55693298, rs68012736, rs143856001, rs144535648, rs147142636, rs66473412, rs6659681, rs6659788, rs55921163, rs55926300, rs111868160, rs13374893, rs13374968, rs6694628, rs6658556, rs6695043, rs72679807, rs56284503, rs17361915, rs113623605, rs144250006, rs113534835, rs56358525, rs6681857, rs56349187, rs79610407, rs72890715, rs4372193, rs111723629, rs3991877, rs57240150, rs113887859, rs201070992, rs61519400, rs56306849, rs1984491, rs1984490, rs45449893, rs45517837, rs932816, rs72890727, rs6674305, rs56130131, rs11288511, rs6703374, rs6703669, rs45524035, rs17361936, rs17361950, rs6662982, rs55939860 (207)
rs1886117 (FAAH)	46954587 - 46974497	0.313 T	0.06	-0.05-0.17	0.290	398	rs1998545, rs7531088 (2)
rs16880345 (CNR1)	88894422 - 88901540	0.191 G	0.06	-0.06 - 0.19	0.333	396	rs1535257, rs7747006, rs7751075, rs2875545, rs1321361, rs9450914, rs9450915 (7)

rs9450913 (CNR1)	88899850 - 88904498	0.134 T	0.06	-0.08-0.21	0.393	392	rs4707441, rs4707442 (2)
rs12205430 (CNR1)	88858648 - 88867925	0.196 C	0.05	-0.07 - 0.18	0.394	399	rs806376, rs806379 (2)
rs1535255 (CNR1)	88860482 - 88885426	0.158 G	-0.05	-0.18 - 0.07	0.420	492	rs2023239, rs6928499, rs6928813, rs6454676, rs6912668, rs9450901, rs9450902, rs9444586, rs9450903, rs9450904, rs10485170, rs74471317, rs9450906, rs9444587, rs9450907, rs11966501, rs11968764, rs11963892, rs78335089, rs9444588, rs6454678 (21)
rs7752742 (CNR1)	88914904	0.454 C	0.04	-0.06 - 0.14	0.422	399	NONE
rs9450876 (CNR1)	88796053 - 88797885	0.364 A	-0.04	-0.15 - 0.07	0.481	398	rs9450877, rs1324075 (2)
rs200232349 (FAAH)	46761389 - 46798466	0.011 I[b]	-0.16	-0.63-0.32	0.520	394	rs6676038, rs7548226, rs144930516, rs142618742, rs7542864, rs7545120, rs17102133, rs114531159, rs140815810, rs199585121, rs112746922, rs112387082, rs147637102 (13)
rs324424 (FAAH)	46834173 - 46888905	0.059 A	-0.07	-0.28 - 0.15	0.553	396	rs324410, rs324425, rs324423, rs324421 (4)
rs6908755 (CNR1)	88817588 - 88817934	0.123 T	0.04	-0.11-0.20	0.577	399	rs6908693, rs6913146 (2)
rs58370001 (CNR1)	88919215 - 88940323	0.043 C	0.07	-0.18 - 0.32	0.589	392	rs7754491, rs7769918, rs56396859, rs9450925, rs59449423, rs55882449, rs60315037, rs113006189, rs1216678, rs16880396, rs145705030, rs7756920, rs7757556, rs62431489, rs6927294, rs62431491, rs964647, rs59903039, rs6906154 (19)
rs6698196 (FAAH)	46975773 - 46975877	0.184 C	0.03	-0.10 - 0.17	0.635	395	rs6683116 (1)
rs11211276 (FAAH)	46905802 - 46923102	0.232 T	0.02	-0.10-0.14	0.775	399	rs12407178, rs12409747, rs7538292, rs3795315, rs72637962, rs12126376, rs11211278, rs11293072, rs2281775, rs2281774, rs4660347, rs942258, rs10890397, rs4660933, rs2031248 (15)

rs12213790 (CNR1)	88898440 - 88902564	0.390 A	0.01	-0.09 - 0.11	0.825	399	rs2038448, rs57809420, rs2325098 (3)
rs3766248 (FAAH)	46773488	0.018 A	0.02	-0.34 - 0.39	0.900	396	NONE
rs2180619 (CNR1)	88877952	0.413 G	0.00	-0.09- 0.09	0.997	494	NONE

Note: All genotypes were coded to reflect an additive model where -1 = common homozygote, 0 = heterozygote and 1 = rare homozygote

Regression weights (***β***) significantly less than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a greater reduction in symptom severity across the active treatment or follow-up period. Values significantly greater than 0 indicate that an increasing number of copies of the minor allele of the SNP was associated with a poorer reduction in symptom severity.

[a] n reflects total number of cases included in regression analysis for the sentinel SNP.

[b] Insertion is CA

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