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Further confirmation of the association between anxiety and *CTNND2*: replication in humans

M. G. Nivard[†,‡,*], H. Mbarek[†,§], J. J. Hottenga[†,‡], J. H. Smit[‡,¶], R. Jansen[‡,¶], B. W. Penninx[‡,¶], C. M. Middeldorp[†,‡,] and D. I. Boomsma[†,‡]**

[†]Department of Biological Psychology, VU University Amsterdam, Amsterdam, the Netherlands, [‡]Neuroscience Campus Amsterdam, VU University Amsterdam, Amsterdam, the Netherlands, [§]Emgo+ Institute for Health and Care Research, Amsterdam, the Netherlands, [¶]Department of Psychiatry, and [**]Department of Child and Adolescent Psychiatry, GGZ inGeest, VU University Medical Center, Amsterdam, the Netherlands

**Corresponding author: M. G. Nivard, Department of Biological Psychology, Van der Boechorststraat 1, 1081 BT Amsterdam, the Netherlands. E-mail: m.g.nivard@vu.nl*

The rat genome sequencing and mapping consortium found evidence for an association between the catenin-δ2 gene (*CTNND2*) and anxious behaviour. We replicated these results in humans by carrying out a genetic association test in patients with panic disorder, social phobia, generalized anxiety disorder and/or agoraphobia ($N = 1714$) and controls ($N = 4125$). We further explored the association between *CTNND2* and other psychiatric disorders based on publicly available genome-wide association results. A gene-based test showed that single nucleotide polymorphisms (SNPs) in *CTNND2* have a significantly increased signal ($P < 1e^{-5}$) and decreased *P*-values. Single nucleotide polymorphism rs1012176 showed the strongest association with any anxiety disorder (odds ratio: 0.8128, SE = 0.063, $P = 0.00099$), but this effect was not significant after correction for multiple testing. In available genome-wide association results from the Psychiatric Genomics Consortium we found that SNPs in *CTNND2* collectively showed an increased signal for schizophrenia ($P < 1e^{-5}$) and major depressive disorder ($P < 1e^{-5}$), but not for bipolar disorder. These signals remained significant after correction for potential confounders. The association between *CTNND2* and anxiety was not strong enough to be picked up in the current generation of human genome-wide analyses, indicating the usefulness of and need for animal genetic studies to identify candidate genes for further study in human samples.

Keywords: Anxiety disorder, bipolar disorder, catenin δ2, genetic association, humans, major depression, rats, schizophrenia

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The rat genome sequencing and mapping consortium recently published an extensive sequence based analysis of 160 complex phenotypes, including disease models for anxiety, diabetes, hypertension, aortic elastic lamina ruptures, multiple sclerosis and osteoporosis and measures of risk factors for common diseases such as lipid and cholesterol levels in outbred rats (Rat Genome Sequencing Consortium 2013). The Rat Genome Consortium paper reported 28 quantitative trait locus (QTL) at which only a single gene contained candidate variants. At one QTL, a new gene for an anxiety-related phenotype was implicated. The catenin-δ2 gene (*CTNND2*, encoding catenin-δ2) was associated with anxiety-related traits in rats. This QTL explained 5% of the variance (see their online supplementary Table 3). *CTNND2* has also been found to be related to reduced hippocampal volume and synaptic dysfunction but not to anxiety-related traits in knockout mice (Israely *et al.* 2004). *CTNND2* is highly expressed in the human and foetal brain, and has been implicated in neuronal functioning, adhesion and migration (Lu *et al.* 1999). The gene has not yet been studied as a candidate for anxiety disorders in humans.

We explored the effects of *CTNND2* on anxiety disorders in 1714 patients with an anxiety disorder and 4125 screened controls who take part in the Netherlands Study of Depression and Anxiety (NESDA) (Penninx *et al.* 2008) and the Netherlands Twin Register (NTR) (Lubke *et al.* 2012; Willemsen *et al.* 2010, 2013). Firstly, we tested in a gene-based test whether all SNPs collectively obtained significantly lower *P*-values than expected, indicating an association between the gene and the phenotype. Next, individual SNPs within *CTNND2* were regressed on anxiety status using logistic regression.

Secondly, the association between *CTNND2* and major depressive disorder (MDD) (Ripke *et al.* 2012), schizophrenia (Schizophrenia Psychiatric GWAS consortium 2011) and bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011) was explored in published results based on the genome-wide association mega-analyses of these disorders by the Psychiatric Genetics Consortium (PGC). All three PGC genome-wide association (GWA) studies use a dichotomous case/control phenotype and logistic regression to determine the association of SNPs with each disorder. The PGC results were inspected for inflation in *P*-values for all SNPs in the *CTNND2* gene to test for an association between the gene and the phenotype and we again looked at the best individual SNP corrected for multiple testing.

Methods

Subjects

Anxiety disorder cases were derived from the NESDA and from the NTR. There were 1747 patients who met diagnostic criteria for a DSM-IV defined anxiety disorder (panic disorder, agoraphobia, social

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phobia and/or generalized anxiety disorder) as assessed with the Composite Interview Diagnostic Instrument (CIDI) (Ter Smitten *et al.* 1998). Controls came from the NESDA and NTR studies. In NESDA, the absence of any lifetime depressive and anxiety disorder was assessed by the CIDI (lifetime version 2.1). In NTR, controls were selected in a similar way as described in Boomsma *et al.* (2008). The selection was based on low scores on depression, anxiety or neuroticism scales in longitudinal surveys. These surveys contained the neuroticism and somatic anxiety scales of the Amsterdamse Biografische Vragenlijst (Wilde 1970), the Beck Depression Inventory (Beck *et al.* 1974), the anxious depression scale of the Adult Self Report (Achenbach & Rescorla 2003) and the State Trait Anxiety Inventory – Trait version (Van der Ploeg *et al.* 1979). In total, 4125 controls met the selection criteria.

Genotyping and imputation

Whole blood and/or buccal DNA samples were collected for various projects done by the NTR and NESDA studies (see Boomsma *et al.* 2008; Scheet *et al.* 2012; Sullivan *et al.* 2009; Willemsen *et al.* 2010). DNA extraction and purification of these samples have been performed at various stages in time, following several manufacturer specific protocols in order to obtain the best quality and concentration prior to SNP platform genotyping. Genotyping subsequently has been performed on multiple chip platforms, for several partly overlapping subsets of the total sample collection. Chronologically the following platforms have been used Affymetrix Perlegen 5.0 ($N = 3840$), Illumina 370 ($N = 290$), Illumina 660 ($N = 1501$), Illumina Omni Express 1M ($N = 445$) and Affymetrix 6.0 ($N = 10\,412$, 5 subsets). After array specific data analysis, genotype calls were made with the platform specific software (Genotyper, Beadstudio, and Birdseed).

Quality control was performed within and between chip platforms. For each platform, the individual SNP markers were lifted over to build 37 (HG19) of the Human reference genome, using the LiftOver tool (Kuhn *et al.* 2009). Single nucleotide polymorphisms that were not mapped at all, SNPs that had ambiguous locations, and SNPs that did not have matching – or strand opposite alleles were removed. Subsequently, the data were strand aligned with the 1000 Genomes phase 1 Integrated release version 3 ALL panel of March 2012 (1000 Genomes Project Consortium *et al.* 2012). Single nucleotide polymorphisms from each platform were removed if they still had mismatching alleles with this imputation reference set, if the allele frequencies differed more than 0.20 with the reference set, if the MAF was $<1\%$, if the HWE *P*-value was <0.00001 or if the call rate was $<95\%$. All samples were excluded from the data if their expected sex did not match their genotyped sex, if the genotype missing rate was above 10% or if the Plink *F* inbreeding value was either >0.10 or <-0.10. After these steps the data of the individual chips were merged into a single dataset using the Plink 1.07 software (Purcell *et al.* 2007).

Within the merged set, identity by descent (IBD) was calculated between all possible pairs of individuals and compared to the expected family structure of the NTR and NESDA studies. Samples were removed if the data did not match the expected IBD sharing, or if potentially consistent with biographic data, corrections were made to the family structure. DNA samples that were typed on multiple platforms were tested if the overlapping SNPs had a concordance rate above 99.0%. If this was not true, all data of these samples were removed. On the merged data, HWE and MAF SNP filters were re-applied as well as the reference allele frequency difference <0.20 checks. As a final prior step to imputation SNPs with C/G and A/T allele combinations were removed if the MAF was between 0.35 and 0.50 to avoid wrong strand alignment.

Imputation was performed using the two stage approach. Pre-imputation phasing and imputation of genotype platform specific SNPs was carried out using the mach software (Li *et al.* 2010). Subsequently, imputation of the reference set was carried out with Minimach. To avoid issues with monozygotic (MZ) twin pairs, prior to imputation a single person of a MZ twin with the highest SNP call rate of a pair was selected. Post imputation, the resulting imputed genotypes were duplicated back to the co-twin in the data. On the basis of phenotype, a single MZ twin was then selected for analysis in this study. From the imputed genotype data, for the cases and controls of this particular study all SNPS between the *CTNND2* gene borders as reported on genecards.org (Safran *et al.* 2010) were included for analysis. In total 1349 SNPs in the *CTNND2* gene met the post imputation QC standards (MAF > 0.05, INFO > 0.8, INFO < 1.1 & HWE $< 1e^{-3}$). Of these 1349 SNPs 475 were directly genotyped, and 874 are imputed.

Lookup in Psychiatric Genomics Consortium (PGC)

We retrieved results from the mega GWA analyses by PGC on MDD, bipolar disorder and schizophrenia. These data are available at https://pgc.unc.edu/Sharing.php#SharingOpp and more conveniently and completely at http://www.broadinstitute.org/mpg/ricopili/. Using the PGC summary statistics, the association between *CTNND2* and these psychiatric phenotypes was explored further. We applied the same QC standards to the SNPs reported by PGC as to the SNPs tested in the NTR/NESDA sample (MAF > 0.05, INFO > 0.8 and <1.1). We then retrieved the PGC *P*-values for SNPs in the *CTNND2* gene plus a 200 kb area around the gene.

Statistical analyses

For various significance tests, a correction for the number of individual signals in *CTNND2* was needed. To determine the number of independent signals, a principal component analysis (PCA) was carried out on the pair-wise correlation matrix between all SNPs in the gene. The number of independent signals was determined to be the number of components needed to explain 95% of variance in the SNPs in *CTNND2*. Pair-wise LD was retrieved using the SNAP online tool (SNP Annotation and Proxy Search) (Johnson *et al.* 2008). This tool can be used for SNPs to identify and to annotate nearby SNPs in linkage disequilibrium based on HapMap or 1000 genomes.

The anxiety disorder phenotype was regressed on the SNPs in *CTNND2* using logistic regression. Regression analyses were controlled for sex, study of origin within NTR/NESDA, genotyping platform and three principle components to control for population stratification (Abdellaoui *et al.* 2013). A sandwich estimator was used to control for the presence of related individuals in the sample (Purcell *et al.* 2007).

To determine if significant signals exist within the entire gene, we tested whether the *P*-values of SNPs in the *CTNND2* gene as found in the anxiety disorder results or reported by the PGC, were significantly lower than expected. The effect size for this test is λ (lambda), the inflation of *P*-values over the expected distribution of *P*-values. The significance of λ was tested against different null hypotheses using three different approaches (see Table 1).

We bootstrapped 10 000 distributions of *P*-values under these three null distributions. This yielded a mean λ and the variance of λ that reflects the distribution under the null distribution for each of these 10 000 bootstrapped sets of *P*-values. Next, the significance of λ observed in any anxiety disorder, MDD, Bipolar Disorder and Schizophrenia was tested against the expected λ obtained in each null distribution. To be certain the reported λ reflects actual effects, we step by step excluded other common causes of an inflated λ. First, we adapted the null hypothesis to reflect the fact that some inflation of λ is expected to be caused by population stratification and sample size. To counteract the effects of population stratification and sample size, the bootstrapped λ were drawn from samples that showed inflation by population stratification or sample size at the level of the genome-wide λ for each trade (method 2 in Table 1).The variance of the bootstrapped λ distribution is influenced by LD between the SNPs in *CTNND2*. Higher LD between the SNPs would result in fewer independent signals, thus λ based on sets of *P*-values representing a smaller number of signals results in an increase in the variance of these λ. To take into account the LD observed between SNPs we created a null distribution in which the λ was based on the number of independent signals in *CTNND2* (method 3 Table 1).

We also determined the significance of the best SNP in the gene for anxiety disorders as well as for schizophrenia, MDD and bipolar disorder based on the PGC results. To be clear about the significance of our results, we report *P*-values per best SNP which are uncorrected for multiple testing, and corrected for the number of independent signals in *CTNND2*.

Table 1: Models used to test the significance of λ

Method	*P*-values sampled from:	Null hypothesis
1: Uniform	Uniform distribution between 0 and 1	Observed λ is equal to the statistical expectation of λ (λ = 1)
2: Uniform controlled for population structure	Uniform distribition betweeen 0 and 1. λ then multiplied by the genome-wide λ	Observed λ is equal to the statistical expectation of λ in the case of no effect in the presence of population stratification (λ = genome wide λ)
3 Uniform independent signals and controlled for population structure	Sample from a uniform distribution the size of the number of independent signals in *CTNND2*. λ then multiplied by the genome-wide λ	Observed λ is equal to the expected λ for a set of *P*-values based on the number of independent signals in *CTNND2*, thereby taking into account LD, and pop stratification as in method 2 (λ for 1366 SNPs = λ 261 for signals)

Results

Test for the number of independent signals in CTNND2

From the 1349 SNPs in *CTNND2* that met QC standards, 1256 were also found in the SNAP pair-wise LD tool. The pair-wise LD between these SNPs was entered into a PCA in R. The eigenvalues derived from this PCA suggested that 261 components are needed to explain 95% of variance and 446 components are needed to explain 99% of variance in the 1256 SNPs found in SNAP. The Kaiser criterion suggested 180 independent signals.

Pair-wise correlations between all 1349 SNPs in the *CTNND2* gene were also calculated in the NTR/NESDA sample using a minimal cutoff of $r = 0.10$ ($r^2 = 0.01$). Principal component analysis was performed on the resulting pair-wise correlation matrix. The Kaiser criterion indicated 124 independent components existed, the PCA suggested 254 components are needed to explain 95% of variance and 563 components are needed to explain 99% of variance. These results are similar to the ones obtained using SNAP suggesting the LD structures are similar, at least in dimensionality.

The three criteria described did vary fairly widely in their conclusion on the number of independent signals, though they were in the same order of magnitude (i.e. hundreds of signals) and very similar in the 1000 genomes reference panel and the NTR/NESDA set. For all further significance testing we adjusted for 261 independent signals as found in SNAP, since adjusting for the Kaiser criterion would be too liberal and adjusting for 446 signals might be too strict.

Anxiety disorders in NTR/NESDA

All SNPs in the gene jointly showed significantly lower *P*-values than under the expected null distribution ($\lambda = 1.34$, $P < 0.0001$) using method 1 in Table 1. Testing the λ using method 2 in Table 1, taking into account population stratification and sample size, we again found that the λ significantly exceeded the null ($P < 0.0001$). Testing the λ using method 3 in Table 1, taking into account the effects of LD, population stratification and sample size, the λ remained significant ($P < 0.035$). This inflation of *P*-values indicates that the gene shows a significantly stronger association to anxiety disorders than expected under the null hypotheses considered (Table 1) indicating this gene has a significant association with anxiety disorders.

Single nucleotide polymorphism rs1012176 in *CTNND2* showed the strongest association with anxiety disorders (odds ratio: 0.8128, SE = 0.063, $P = 0.00099$) (Fig. 1). This individual SNP is not significant if corrected for the number of independent signals ($P = 0.22$). Table 2 provides the RS-numbers and locations for the 10 SNPs showing strongest association with anxiety disorders. Some of these 10 best SNPs are in complete or high, but not total LD with two SNPs in the coding region of *CTNND2* (see Table 2 for D' and *R*-squared). Two SNPs in the coding region, rs17802557 and rs1566622 are in LD with different SNPS from Table 2 and are both synonymous mutations in the coding region of *CTNND2*. Complete LD indicates the SNPs associated with anxiety disorder and SNP in the coding region of *CTNND2* are completely dependent, the lack of total LD can be caused by allele frequency differences and indicates that one SNP cannot be used to impute the other.

PGC lookup

Major depressive disorder (Ripke et al. *2012)*

In total, 632 SNPs were present in the PGC MDD results that were in *CTNND2*, or in a 200 kb window around, and met QC standards (MAF > 0.05, INFO > 0.8 and < 1.1). These SNPS showed inflation ($\lambda = 1.39$, $P < 1e^{-5}$) (Fig. 2, black). The λ was significant if tested using method 1 in Table 1 ($P < 0.0002$) and remained significant when correcting for potential effects of population structure and sample sizes ($P < 0.0013$) (method 2 in Table 1) and after further correction for the effects of LD ($P < 0.026$) (method 3 in Table 1). These results indicate the *P*-values observed in *CTNND2* show a stronger association to MDD than expected, even when we took into account the effects of population stratification, sample size and LD within the gene.

The best SNP (rs10059890) in the published results of the mega-analysis of the PGC for MDD (Ripke *et al.* 2012) had a nominally significant *P*-value of 0.00025 (Fig. 1). Corrected for the number of independent tests this result was no longer

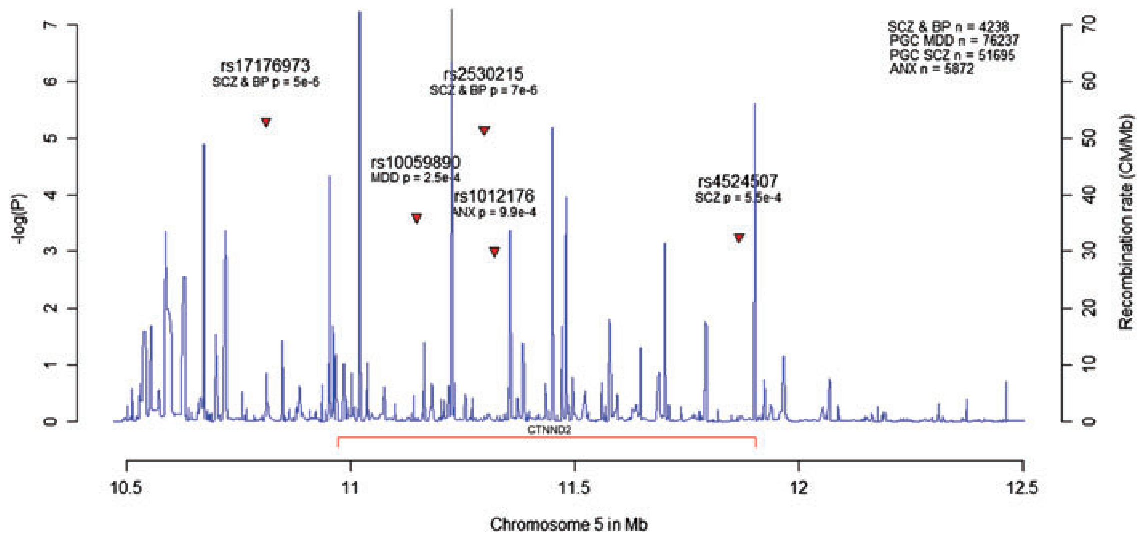

Figure 1: Regional plot for the *CTNND2* gene, with recombination rates plotted in blue. The best association results in the *CTNND2* gene are plotted in red for the GWA for anxiety in NESDA/NTR (ANX), and for three published GWA meta analyses for major depressive disorder (MDD) (Ripke *et al.* 2012), schizophrenia (SCZ) (Schizophrenia Psychiatric GWAS consortium 2011) and schizophrenia and bipolar disorder (SZC&BP) combined (Wang *et al.* 2010).

significant ($P = 0.06$). Table 2 provides the RS-numbers and locations for the 10 SNPs showing strongest association with MDD. The top SNP and several other SNPs present in Table 2 (See Table 2 for D′ and R-squared) are in complete, but not total, LD with SNP rs2285975, a synonymous mutation in the coding region of CTNND2

Schizophrenia (Schizophrenia Psychiatric GWAS consortium 2011)

A total of 614 SNPs in and around *CTNND2* were present in the PGC schizophrenia results and met QC standards (MAF > 0.05, INFO > 0.8 and < 1.1). These 614 SNPs showed large inflation ($\lambda = 2.54$; Fig. 2). This inflation was significantly higher than 1 as tested using method 1 in Table 1 ($P < 0.0001$). If we correct this test for the effects of population stratification and sample size, the observed inflation remained significant (method 2 in Table 1, $P < 0.0001$). It also remained significant after further correction for the LD in *CTNND2* (method 3 in Table 1) ($P < 0.0001$). These results indicate the P-values observed in *CTNND2* show a larger effect than expected, even when this expectation is corrected for population stratification, sample size and LD within the gene.

Uncorrected results for the single best SNP (rs4524507) showed an association ($P = 0.00056$; Fig. 1) with the *CTNND2* gene. Corrected for the number of independent signals the SNP effect is no longer significant ($P = 0.13$). Table 2 provides the RS-numbers and locations for the 10 SNPs showing strongest association with Schizophrenia.

Bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011)

In total 1123 SNPs were present in the PGC results that are in and around *CTNND2* and met QC standards (MAF > 0.05, INFO > 0.8 and < 1.1). None of the individual SNPs were significant if corrected for multiple testing. These SNPs did not show an inflation over the expected null (Fig. 2). These results indicate that variants in *CTNND2* have no association to bipolar disorder. Table 2 provides the RS-numbers and locations for the 10 SNPs showing strongest association with bipolar disorder.

Discussion

On the basis of the genetic association results presented here, the association between the *CTNND2* gene and anxiety found by the rat sequencing and mapping consortium is also present in humans. We confirmed the association in a sample of patients with an anxiety disorder and controls from the Netherlands. The PGC GWA results suggest an even broader role of *CTNND2* in psychiatric disorders, namely for schizophrenia and MDD. Our lookup in PGC results found no evidence for a role of *CTNND2* in bipolar disorder.

The top SNPs for MDD and anxiety have strong LD with different SNPs in the coding regions of CTNND2. The top SNPs for each of the four disorders are found in different areas of the CTNND2 gene. However, our strongest results are the inflated λ's for all SNPs in the gene. Those results currently do not point to a specific SNP within *CTNND2* but show a general association between the gene and psychiatric disorders. Further functional studies, for example based on sequence data and fine mapping are needed to see how *CTNND2* functionally relates to psychiatric phenotypes. Beyond the different types of evidence derived from association studies, there are additional studies indicating that the *CTNND2* gene functionally might be a plausible candidate. The gene is a sensor of synaptic activity and

Table 2: Top 10 SNPs per disorder and their association to SNPs in coding regions of CTNND2

Anxiety	RS-number	position	*P*	Relation to functional SNPs
	rs1012176	11320538	0.0009997	
	rs17216753	11484112	0.0017500	SNP in complete (D′ = 1) but not total LD ($R^2 = 0.015$) with coding SNP rs17802557
	rs17805573	11488568	0.0018800	SNP in complete (D′ = 1) but not total LD ($R^2 = 0.015$) with coding SNP rs17802557
	rs11747109	11493331	0.0018980	SNP in complete (D′ = 1) but not total LD ($R^2 = 0.015$) with coding SNP rs17802557
	rs79213734	11495176	0.0019010	SNP in complete (D′ = 1) but not total LD ($R^2 = 0.015$) with coding SNP rs17802557
	rs10513094	11482045	0.0020930	SNP in complete (D′ = 1) but not total LD ($R^2 = 0.015$) with coding SNP rs17802557
	rs11948339	11378306	0.0036560	
	rs2012187	11322037	0.0048130	Moderate D′ (0.681) and low R^2 (0.038) with coding SNP rs1566622
	rs32128	11343384	0.0051640	Moderate D′ (0.668) and low R^2 (0.096) with coding SNP rs1566622
	rs32129	11343200	0.0051740	Moderate D′ (0.668) and low R^2 (0.096)with coding SNP rs1566622
MDD				
	rs10059890	11199698	0.0002496	SNP in complete LD (D′ = 1) but not total LD ($r^2 = 0.087$) with coding SNP rs2285975
	rs1859382	11200672	0.0002700	SNP in complete LD (D′ = 1) but not total LD ($r^2 = 0.087$) with coding SNP rs2285975
	rs6859601	11200414	0.0002744	SNP in complete LD (D′ = 1) but not total LD ($r^2 = 0.087$) with coding SNP rs2285975
	rs886527	11200814	0.0003109	SNP in complete LD (D′ = 1) but not total LD ($r^2 = 0.087$) with coding SNP rs2285975
	rs6885587	11200114	0.0004313	
	rs6880938	11200302	0.0005098	
	rs10041627	11200082	0.0005604	
	rs10073056	11199253	0.0005922	
	rs730610	11192051	0.0007690	
	rs2057795	11207597	0.0008323	
Schizophrenia				
	rs4524507	11919716	0.0005537	
	rs4702836	11918658	0.0005870	
	rs4379193	11920393	0.0006311	
	rs4571470	11913452	0.0006315	
	rs11741312	11911555	0.0006453	
	rs12652699	11917077	0.0006957	
	rs4330462	11913217	0.0007980	
	rs6873547	11917482	0.0008481	
	rs4257769	11913395	0.0010907	
	rs4701924	11923554	0.0012963	
Bipolar disorder				
	rs10044218	11466046	0.0130900	
	rs7722906	11461708	0.0173200	
	rs7728281	11469941	0.0274300	
	rs16901579	11455272	0.0342900	
	rs4702761	10955733	0.0367000	
	rs7722560	11461527	0.0371500	
	rs1860245	10956537	0.0371600	
	rs2895578	10956553	0.0371600	
	rs6884596	11456540	0.0372200	
	rs1995364	10956781	0.0376200	

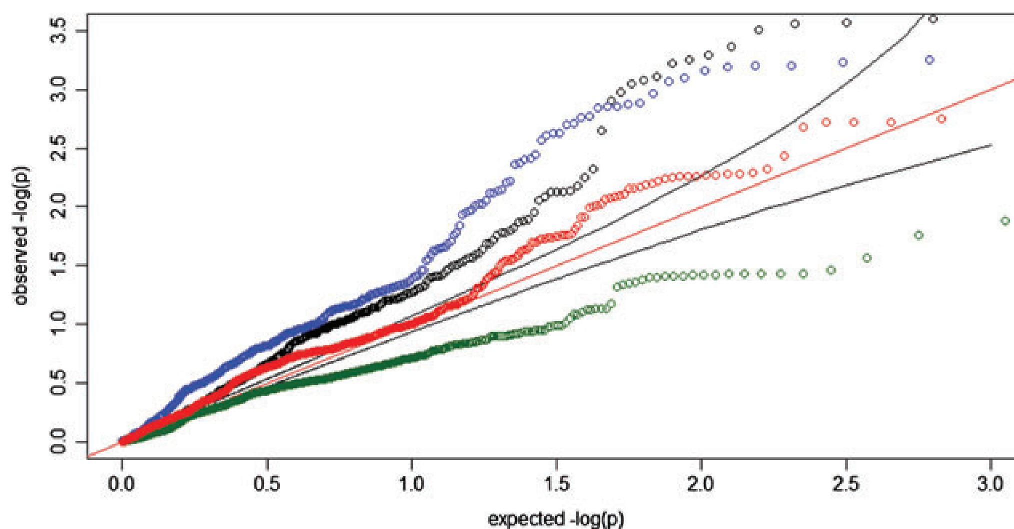

Figure 2: qq-plot for the *CTNND2* region in the PGC bipolar (dark green), anxiety (red), schizophrenia (blue) and MDD results (black). Expected qq values (red line) and their 95% confidence interval (black lines) are plotted for reference.

implements activity-related morphological changes at the synapse and cell adherence in adult brains (Kosik *et al.* 2005). In developing brains catenin-δ gene expression is related to both cortical and cerebral development (Duparc *et al.* 2006).

In addition to the results described here, there is more evidence for a role of *CTNND2* in psychiatry. Other researchers (Wang *et al.* 2010) have also submitted associations between SNPs in and near *CTNND2*, and bipolar disorder and schizophrenia (rs2530215, $P < 7e^{-6}$ and rs17176973, $P < 5e^{-6}$) (Fig. 1) to the catalogue of published GWAS studies (Hindorff *et al.* 2009). The samples in this study were later included in the PGC mega-analyses. From the website, it cannot be derived whether this association was driven by schizophrenia cases and not by bipolar disorder cases, as would be in line with the absence of an effect in the mega-analysis of bipolar disorder in PGC. Moreover, a rare CNV associated with schizophrenia has been found to disrupt *CTNND2* (Vrijenhoek *et al.* 2008) and *CTNND2* hemizygozity is implicated in mental retardation and behavioural symptoms in cri du chat syndrome (Cornish & Pigram 1996; Medina *et al.* 2000).

The rat genome mapping and sequencing consortium reported little overlap between mouse and rat genomes at the gene or pathway level. This was attributed to the relatively limited amount of sequence variation segregating within the two heterogeneous stock mice populations. As a consequence, the inability to detect shared loci may result from sampling. This problem would be smaller when comparing rats and human populations as the amount of sequence variation within the human population would probably be larger.

We would like to highlight that the involvement of *CTNND2* without the primary result presented by the rat genome sequencing and mapping consortium would not have stood out in a GWA analysis for any of these psychiatric disorders. This work can been seen as a successful synthesis between animal genetics studies and human genetics studies. Combining the results from the animal model with the replication for anxiety in humans and the previous findings in the literature provide us with ample reasons to further investigate the role of *CTNND2* in psychiatry.

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