



Research report

Genome wide association study identifies variants in *NBEA* associated with migraine in bipolar disorder

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ABSTRACT

Background: Migraine is a common comorbidity among individuals with bipolar disorder, but the underlying mechanisms for this co-occurrence are poorly understood. The aim of this study was to investigate the genetic background of bipolar patients with and without migraine.

Methods: We performed a genome-wide association analysis contrasting 460 bipolar migraineurs with 914 bipolar patients without migraine from the Bipolar Genome Study (BiGS).

Results: We identified one genome-wide significant association between migraine in bipolar disorder patients and rs1160720, an intronic single nucleotide polymorphism (SNP) in the *NBEA* gene ($P=2.97 \times 10^{-8}$, OR: 1.82, 95% CI: 1.47–2.25), although this was not replicated in a smaller sample of 289 migraine cases.

Limitations: Our study is based on self-reported migraine.

Conclusions: *NBEA* encodes neurobeachin, a scaffolding protein primarily expressed in the brain and involved in trafficking of vesicles containing neurotransmitter receptors. This locus has not previously been implicated in migraine per se. We found no evidence of association in data from the GWAS migraine meta-analysis consortium ($n=118,710$ participants) suggesting that the association might be specific to migraine co-morbid with bipolar disorder.

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1. Introduction

Migraine is a common neurological disorder, affecting approximately 12–15% of populations of European ancestry and costing close to \$ 20 billion in the United States and € 27 billion in Europe each year (Andlin Sobocki et al., 2005; Holland et al., 2012). Among neurological disorders, it accounts for the greatest number of years lived with disability (YLDs), ranking eighth among all human disorders (Vos et al., 2012). Migraine is 3–4 times more common in women, and its estimated heritability is between 40% and 65% (Anttila et al., 2008; Holland et al., 2012; Schürks et al., 2010). The diagnosis of common migraine includes recurrent attacks of disabling unilateral headaches along with nausea, vomiting, photo- and phonophobia, and about 20–30% have accompanying aura symptoms (Freilinger et al., 2012; Holland et al., 2012).

Mendelian forms of familial hemiplegic migraine (FHM) are rare. Most are caused by mutations in the *CACNA1A*, *ATP1A2* and *SCN1A* genes (Di Lorenzo et al., 2012). Non-familial migraine is perceived to be polygenic, with considerable diversity regarding

both the number as well as the severity and duration of attacks (Maher and Griffiths, 2011). Linkage and candidate gene studies of non-familial migraine have yielded few replicable results. Recently, genome wide association studies (GWAS) have provided new insights into the disorder, with several associated genes such as the ion channel gene *TRPM8* (Chasman et al., 2011; Di Lorenzo et al., 2012; Freilinger et al., 2012; Maher and Griffiths, 2011), as well as *FHL5*, *ASTN2* and *LRP1* (Anttila et al., 2013).

Bipolar disorder (BPD) has a prevalence of about 1% and a heritability close to 60% (Oedegaard et al., 2010). BPD has a high socioeconomic impact and is the sixth most common cause of YLDs within neurological disorders (Vos et al., 2012). Sufferers of BPD experience periods of elevated and lowered mood in a cyclic pattern, sometimes peaking in full-blown mania and psychosis or severe depression (Chen et al., 2013; Holland and Agius, 2011; Lee et al., 2012). A comprehensive meta-analysis of candidate gene studies in BPD by Seifuddin et al. (2012) did not confirm consistent association with any of the genes examined. GWAS analyses of BPD have pointed to *CACNA1C*, *ZNF804A*, *NCAN*, *ODZ* and *ANK3* as strong

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candidates, with replication across several studies (Green et al., 2012; Lee et al., 2012; Offord, 2012). In addition, numerous other genes have also been found to be significant in one of the studies of BPD, but, so far, failed to replicate (Green et al., 2012; Lee et al., 2012; Offord, 2012).

Both clinical and population based studies have shown that the prevalence of migraine in patients with BPD is 2–3 times higher than in the overall population (Dilsaver et al., 2009; Hirschfeld et al., 2003; McIntyre et al., 2006). It has also been noted that migraine attacks are more frequent in sufferers of BPD compared to those of unipolar depression (Fasmer, 2001). In addition, BPD patients with migraine have earlier onset of bipolar symptoms, more comorbid anxiety, greater use of medical services, more medications and disability payments, and a lower rating of subjective health compared to bipolar patients without migraine (Mahmood et al., 1999; McIntyre et al., 2006). Both migraine and BPD can evolve from irregular occurrences into a drug resistant, more constant disorder, namely transformed migraine and rapid cycling BPD (Low et al., 2003). In addition, anti-epileptic drugs, such as valproate, are used to treat both migraine and BPD (Oedegaard et al., 2010); and both disorders have been linked to genes encoding ion channels in the serotonergic and glutamatergic neurotransmitter systems, including voltage gated calcium channels (Anttila et al., 2010; Freilinger et al., 2012; Oedegaard et al., 2010). These strong links between migraine and bipolar disorder, suggest either common etiology or co-morbid migraine as a sub-phenotype of bipolar disorder.

In this study, we aimed to search for genetic variants associated with increased risk for migraine in individuals with BPD through genome wide association analyses.

2. Materials and methods

2.1. Subjects

Subjects for this study were derived from the Bipolar Genetics Study (BiGS) Consortium, collected as wave 5 of the National Institute of Mental Health (NIMH) Genetics Initiative for Bipolar Disorder. Wave 5 consists of bipolar I singletons and healthy controls genotyped in two phases by the Translational Genomics Institute (TGEN): TGEN1 and TGEN2. All bipolar patients were interviewed using the Diagnostic Interview for Genetic Studies (DIGS), which included questions regarding migraine. Questions about aura symptoms were not included in the DIGS. Controls for the BiGS, which were ascertained through a separate recruitment effort, did not answer these questions about migraine, and, thus, were excluded from association analyses (Sanders et al., 2010). The recruitment process and interviews are described in more detail by Greenwood and Kelsoe, 2013. Replication was attempted in the bipolar I sample that was genotyped as part of the Genetics Association Information Network (GAIN), and a part of the overall BiGS sample. All subjects were of European descent. Written informed consent was obtained for each subject following a detailed description of study participation in accordance with local Institutional Review Board protocols.

2.2. Genotyping and quality control

All subjects in both TGEN and GAIN were genotyped on the Affymetrix Genome-Wide Human SNP array 6.0 chip (Affymetrix Inc., Santa Clara, CA, USA), using the standard protocol. For details, see the two papers by Smith et al. 2009; 2011. Quality control (QC) thresholds were set to exclude individuals with > 5% failed genotypes and markers with less than 95% genotyping rate, minor allele frequency (MAF) below 1% and out of Hardy–Weinberg

Equilibrium (P -value < 0.0001). In addition, individuals displaying heterozygosity rate outside the range of three standard deviations of the mean were also excluded. Identity by state (IBS) was used to identify cryptic relatedness. An X chromosome inbreeding estimate was applied to confirm gender. Genetic homogeneity of the sample was assured by multidimensional scaling (MDS). We did not find any batch effects between TGEN1 and TGEN2 when comparing the first three MDS components using a t -test, this is also shown in the three dimensional MDS-plot (Supplementary Fig. 1). Thus TGEN1 and TGEN2 were pooled for quality control analyses; GAIN was screened separately, except for identification of cryptic relatedness, which was done across all datasets combined. All genotype analyses were performed in PLINK version 1.07 (Purcell et al., 2007).

2.3. Statistical analyses and imputation

Genome-wide association was tested using logistic regression with an additive genetic model implemented in PLINK, with and without gender as a covariate. Manhattan-plots, MDS-plots and QQ-plots were generated in R-software (<http://www.R-project.org>). A genome wide significance level of 5×10^{-8} was chosen in accordance with recommended general GWAS significance thresholds and specific thresholds for the Affymetrix 6.0 chip (Dudbridge and Gusnanto, 2008; Li et al., 2012). Power calculations were done using the Genetic Power Calculator (Purcell et al., 2003). Imputation and statistical analyses of the top locus on chromosome 13 were performed using Impute2, GTOOL and PLINK, based on HapMap build 36 data (Freeman and Marchini, 2007; Howie et al., 2009; International HapMap Consortium, 2003). We applied the recommended cut-off for the 'info' confidence measure (0.3) and the default cut-off settings for the genotype probability (0.9) in Impute2 and GTOOL, and used the same model of logistic regression in PLINK as for the main analysis to assess association between migraine and the imputed SNPs. As the results showed no genomic inflation ($\lambda=1.00$), we did not use any MDS-components in the regression analyses.

2.4. Replication in the GAIN sample

The GAIN sample, which is further described in our previous paper, contains information about both self-reported migraine and doctor-diagnosed migraine (Oedegaard et al., 2010). Doctor-diagnosed migraine phenotype was not available in the discovery TGEN sample; thus, self-reported migraine was used for replication. Logistic regression analysis of rs1160720 was performed in the same manner as in TGEN.

2.5. Evaluation of NBEA region in the international headache genetics consortium (IHGC) sample

In order to evaluate the possible role of NBEA in migraine, and whether its association is more pronounced in migraine comorbid with BPD or migraine in itself, we selected all genotyped and imputed SNPs with $P < 10^{-4}$ in the 5 Mb NBEA region and tested them in the GWAS meta-analysis of International Headache Genetics Consortium (IHGC) which included 23,285 migraine patients and 95,425 controls (Anttila et al., 2013). Association of rs1160720 only was examined in all migraine cases as well as subgroups of migraine with and without aura. Data on bipolar comorbidity was not available for this dataset.

3. Results

3.1. Initial discovery set: TGEN

In total, 1411 bipolar disorder patients were available for the analyses. After excluding 15 heterozygosity outliers and 22 subjects due to cryptic relatedness, association was tested in a total of 460 bipolar migraineurs (mig^+) and 914 bipolar patients without migraine (mig^-). All individuals reported European–American ethnicity and there were no outliers in MDS analyses. There was a lower percentage of males among mig^+ (23%) compared to mig^- (41%).

Overall, 723,224 SNPs remained for analyses after excluding 587 SNPs that failed HWE test and 182,789 with low genotyping rate or MAF below 1%. A QQ plot shows an excess of strong associations, without any genomic inflation (Fig. 1).

Fig. 2 shows the Manhattan plot of our results. All loci with P -value less than 1×10^{-4} are reported in Table 1. We found one genome-wide significant SNP, rs1160720 ($P=2.97 \times 10^{-8}$, OR=1.82, 95% confidence interval (CI)=1.47–2.25) in the

Neurobeachin (NBEA) gene on chromosome 13 (Fig. 3). The results remained similar, albeit slightly weaker, when gender was included as a covariate in the model (OR=1.76, 95% CI=1.42–2.18, $P=2.5 \times 10^{-7}$). Gender stratified analyses showed that the size and direction of effect were similar between males and females, with P -value of 2.77×10^{-6} (OR=1.81, 95% CI=1.41–2.33) in women compared to P -value of 0.03 (OR=1.61, 95% CI=1.05–2.48) in men.

3.2. Replication in a second bipolar sample: GAIN

After QC, the GAIN sample consisted of 289 mig^+ and 697 mig^- individuals with bipolar disorder. This resulted in approximately 80% power to nominally detect an OR > 1.3 from the primary study, given a minor allele frequency of 0.2. We found no evidence of an association between rs1160720 and self-reported migraine in this sample of bipolar patients (OR=0.93, 95% CI=0.72–1.20, $P=0.57$).

3.3. Imputation of top locus

Imputation of the region spanning from 32 to 37 Mbp for the chromosome 13 NBEA locus resulted in a total of 1618 imputed SNPs with 98.3% overall concordance cross validation. Fig. 3 illustrates the results from the candidate region on chromosome 13 after imputation. One imputed SNP showed a marginally stronger association than the genotyped discovery variant ($P=1.91 \times 10^{-8}$ and OR=1.85 (95% CI=1.49–2.29)). Both the imputed SNPs info measure (level of certainty of imputation) and average maximum posterior call were > 99%, indicating good quality of the imputation.

3.4. Evaluation of NBEA region in the IHGC sample

In the IHGC migraine GWAS meta-analysis, rs1160720 showed no association with migraine overall ($P=0.11$, OR=0.98, 95% CI=0.95–1.01), migraine without aura ($P=0.74$, OR=0.99, 95% CI=0.94–1.04), or migraine with aura ($P=0.02$, OR=0.93, 95% CI=0.88–0.99). None of the other examined top SNP yielded significant association with migraine in the IHGC sample (data not shown).

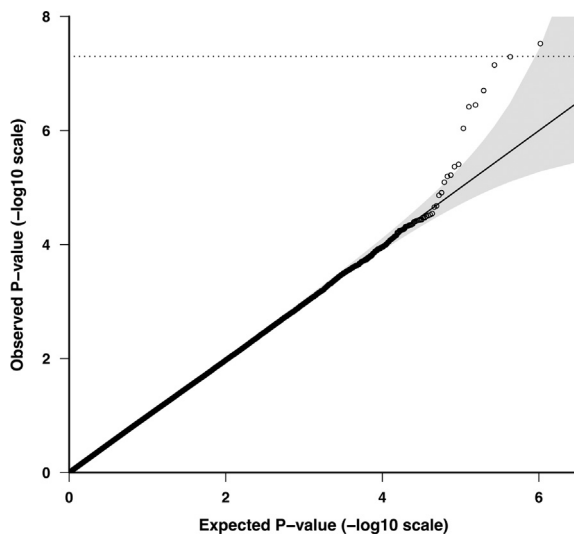


Fig. 1. Quantile–Quantile plot (QQ-plot) of observed and expected P -values, $-\log$ transformed. The genetic inflation factor (λ) was 1. The dashed horizontal line indicates a P -value of 5×10^{-8} . The grey shading indicates a 95% Confidence Interval.

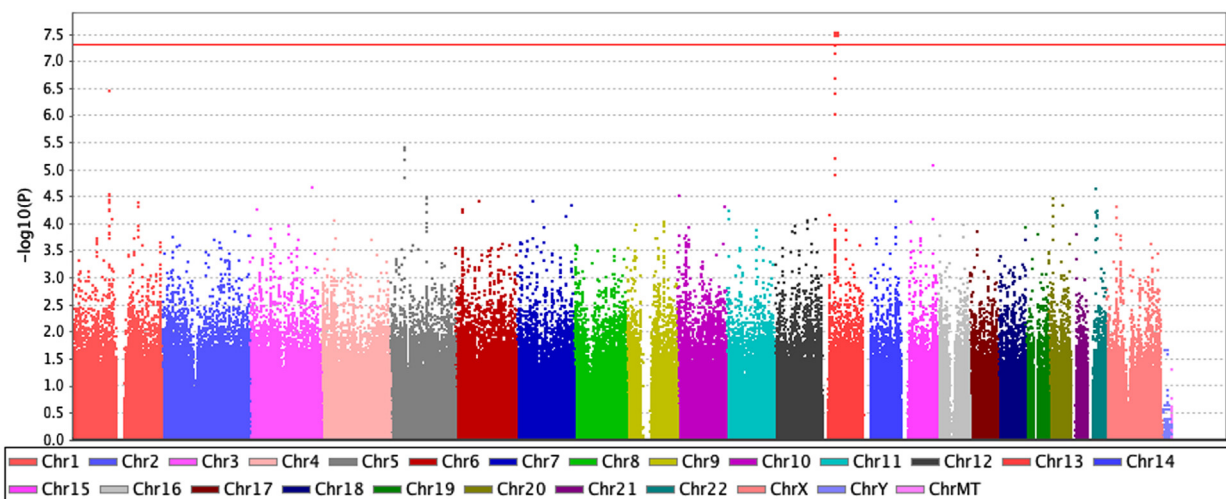


Fig. 2. Manhattan plot of results of logistical regression analyses. Chromosomes are pictured along the x-axis in alternating colors. $-\log_{10} P$ -values are plotted on y-axis. Red line indicates genome wide significance at 5×10^{-8} . A locus on chromosome 13 surpasses the threshold for genome wide significance.

Table 1
Top associated loci with P -value $< 1 \times 10^{-4}$.

Chr	SNP	Position	Gene	Gene function or previous gene association from the literature	Allele [*]	CEU freq	OR [†]	95% CI [‡]	P-value
1	rs10875290	100626343	CDC14A	Cell cycle control	T	0.35	1.53	1.30–1.80	3.55E-07
1	rs1571346	110478611	Intergenic		G	0.48	1.38	1.18–1.62	7.94E-05
1	rs6667692	182820193	C1orf21	No putative function	C	0.39	0.71	0.61–0.84	4.01E-05
3	rs3860579	21539353	ZNF385D	Among top hits in partial epilepsy GWAS (Kasperaviciute et al., 2010) and GWAS on negative symptoms in schizophrenia (Xu et al., 2013)	A	0.36	0.7	0.59–0.83	5.36E-05
3	rs10936719	173485820	FNDC3B	Various non-psychiatric traits like height.	G	0.52	0.7	0.59–0.83	2.09E-05
4	rs4832800	36033902	Intergenic		A	0.21	0.65	0.52–0.81	8.90E-05
5	rs350033	40240372	Intergenic		T	0.11	1.9	1.45–2.50	3.91E-06
5	rs17167531	99329060	Intergenic		C	0.33	0.69	0.58–0.82	3.17E-05
6	rs1474618	18763549	Intergenic		C	0.32	0.69	0.57–0.83	5.52E-05
6	rs4644033	67614614	Intergenic		T	0.37	1.42	1.20–1.68	3.73E-05
7	rs2854843	45897660	IGFBP1	Binds Insuline-like growth factor (IGF)	C	0.17	1.58	1.27–1.96	3.81E-05
7	rs6949094	136934899	DGKI	Diacyl glycerol kinase, iota type. Associated with dyslexia (Matsson et al., 2011), and schizophrenia (Moskvina et al., 2008)	C	0.05	2.05	1.44–2.92	7.19E-05
7	rs2058448	150077753	Intergenic		T	0.27	0.67	0.56–0.81	4.47E-05
9	rs1529191	101885729	ERP44	Regulation of serotonin transporter (Freyaldenhoven et al., 2012)	A	0.45	0.72	0.61–0.85	9.41E-05
10	rs10904109	3886686	Intergenic		G	0.00	2.51	1.62–3.86	2.99E-05
10	rs11016132	129908545	Intergenic		G	0.05	0.38	0.24–0.61	4.68E-05
11	rs2344350	6281254	Intergenic		T	0.16	0.59	0.46–0.77	5.64E-05
11	rs2682095	6393280	APBB1	APP binding protein, possibly regulating cell cycle and transcription.	G	0.24	1.4	1.18–1.66	8.37E-05
12	rs11106592	91417726	Intergenic		A	0.05	0.55	0.40–0.74	8.62E-05
12	rs6490045	114872013	Intergenic		A	0.10	1.73	1.32–2.27	8.09E-05
13	rs1887894	20505600	LATS2	Mitosis regulating protein.	A	0.26	1.43	1.19–1.70	6.98E-05
13	rs1160720	34784675	NBEA	Involved in neuronal post-Golgi trafficking, including neurotransmitter receptors.	G	0.16	1.82	1.47–2.25	2.97E-08
14	rs2282031	89800696	PSMC1	Proteasome subunit, with chaperone-like activity. Associated with formation of Lewy bodies Bedford et al., 2008.	C	0.32	0.69	0.59–0.83	3.77E-05
15	rs8026848	27361149	FAM189A1	No putative function	G	0.24	1.45	1.20–1.75	9.04E-05
15	rs7168815	85238303	AGBL1	Variants associated with Fuchs cornea dystrophy.	A	0.09	0.41	0.27–0.61	8.05E-05
20	rs41392045	13022330	SPTLC3	Subunit of SPT, catalyzing sphingolipid synthesis. Trend in bipolar disorder with aggressiveness/hostility (Alliey-Rodriguez et al., 2011).	C	0.04	2.07	1.46–2.91	3.38E-05
20	rs4635580	40383245	PTPRT	Possible role in signal transduction and cell adhesion in CNS.	T	0.06	0.34	0.21–0.57	4.50E-05
22	rs6004447	23869631	KIAA1671	Decreased expression in thyroid cancer	G	0.32	1.47	1.23–1.75	2.20E-05
23	rs5972211	30609088	GK	Phosphorylates glycerol , initiating its metabolism.	A	0.30	0.67	0.55–0.81	4.79E-05

* Tested allele in this study.

† OR=Odds ratio.

‡ 95% CI=95% Confidence Interval.

4. Discussion

Here, we present the results of a GWAS on migraine in bipolar disorder, culminating in a genome-wide significant association with the *NBEA* locus. The top SNP was rs1160720 (P -value 2.97×10^{-8} , OR=1.82, 95% CI=1.47–2.25), with several other SNPs in linkage disequilibrium (LD) showing a trend for association, including an imputed SNP with P -value of 1.91×10^{-8} .

Interestingly, our top hit, rs1160720, did not show any association with migraine (IHGC sample in this study) nor bipolar disorder itself ($P=0.19$ in PGC meta-analysis, <http://www.broadinstitute.org/mpg/ricopili/>). Thus, the only significant result noted in this study was that of *NBEA* and migraine among bipolar disorder patients. These observations may suggest possible etiological specificity of this gene to such a combined phenotype, confirming our initial hypothesis of co-morbid migraine in BPD being a distinct syndrome with slightly different genetic risk factors than common migraine itself or isolated bipolar disorder.

NBEA is located on chromosome 13q13, and encodes two isoforms. It harbors another gene, *MAB21L1*, in intron 41 of the long isoform, that contains a fragile site (FRA13A) (Tsang et al., 2009). The top SNP of our analyses is located in a LD-region surrounding intron 36 of the long isoform of *NBEA*. *NBEA* encodes neurobeachin (*NBEA*), a BEACH (BEige And Chediak-Higashi) scaffolding protein primarily expressed in the brain (Lauks et al.,

2012). Cellular studies show that *NBEA* is involved in trafficking of vesicles containing neurotransmitter receptors, specifically GABA and glutamate receptors (Lauks et al., 2012; Nair et al., 2013). In addition, it interacts with a glycine receptor in inhibitory neurons (del Pino et al., 2011). Changes in *NBEA* function due to partial or complete knockout of the gene cause functional and morphological alterations in neuronal spines and synapses (Medrihan et al., 2009; Niesmann et al., 2011). Nair et al. (2013) showed that *Nbea*^{−/−} neurons have lower level of glutamate- and GABA receptors on their surface, and that these receptors accumulate at the post-Golgi site where *Nbea* would normally be located. In addition, *NBEA* has been linked to autism and autism symptoms (Castermans et al., 2003; Nuytens et al., 2013; Smith et al., 2002).

Studies on *MAB21L1* gene indicate a possible role in neurodevelopmental disorders, probably due to expansion of CAG repeats, which could also influence *NBEA* (Meira-Lima et al., 2001). However, the close proximity makes it difficult to separate effects of the two genes (Cullinane et al., 2013; Tsang et al., 2009). Moreover, the identified associated region is also physically close to *DCLK1*, a gene which has been implemented in neurodevelopment, vesicle transport, verbal memory, schizophrenia and attention deficit/hyperactivity disorder (ADHD) (Håvik et al., 2012; Smith et al., 2002). However, there is a recombination hot spot between *NBEA* and *DCLK1*, and we found no LD between a previously reported significant SNP in *DCLK1* and our top hit ($r^2=0.001$ and $D'=0.035$).

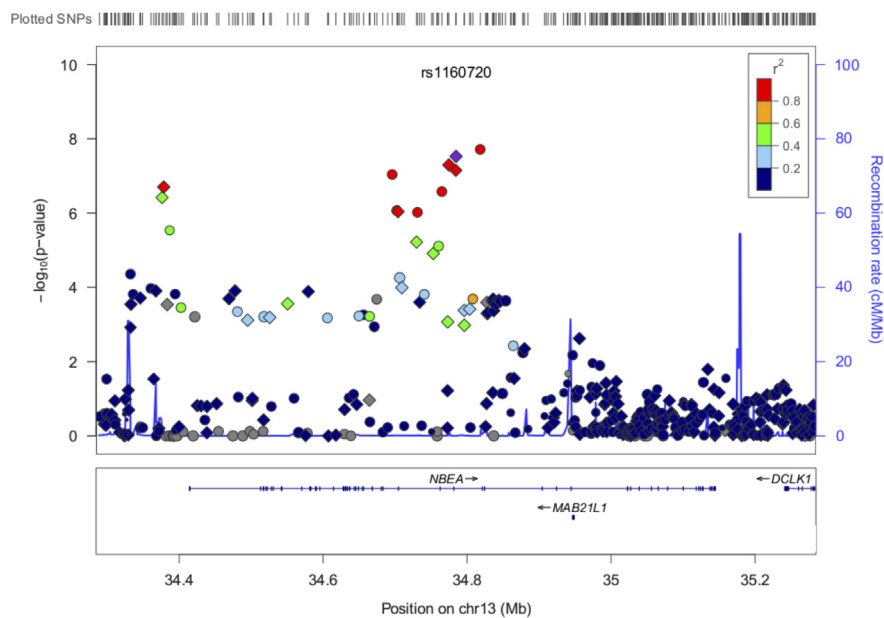


Fig. 3. LocusZoom plot of the candidate region on chromosome 13. Imputed SNPs are shown as circles, directly genotyped SNPs as diamonds. The color scheme indicates linkage disequilibrium (LD) structure across the region. The blue line indicates recombination rate. P -values are $-\log$ transformed. The top SNPs are in intronic regions of neurobeachin (*NBEA*). Rs1160720 is marked by a purple diamond (P -value 2.97×10^{-8} , OR: 1.82, 95% CI: 1.47–2.25).

Thus, it is unlikely that these associations represent the same signal.

Migraine aura is thought to be caused by cortical spreading depression, a wave of neuronal depolarization or hyperexcitability followed by a period of decreased neuronal activity (Cutrer and Smith, 2013; Stuart et al., 2012). The exact cause of cortical spreading depression is not known, but a disturbance of glutamate homeostasis in the brain is thought to be involved (Ligthart et al., 2011). Previous GWA studies in migraine have found an association with genes of the glutamatergic system, including *MTDH*, which in turn regulates *SLC1A2*, a major glutamate transporter in the brain (Anttila et al., 2010; Ligthart et al., 2011). The glutamate system is also associated with bipolar disorder through several studies, such as genetic association, abnormal mRNA expression and increased glutamate levels in magnetic resonance spectroscopy (Cherlyn et al., 2010; Gigante et al., 2012). Notably, Sklar et al. (2008) found an association between bipolar disorder and *MYO5B*, which encodes a vesicle transportation protein involved in the trafficking of glutamate receptors (Lisé et al., 2006). Based on the knowledge that glutamate is important in both disorders studied, it is striking that our top SNP is located in a gene with such direct involvement in the glutamatergic system. Thus, we may hypothesize that *NBEA*-caused disturbances of this system might lead to the development of a specific bipolar disorder sub-phenotype, represented by its co-occurrence with migraine.

5. Limitations

Our study should be viewed in the light of some limitations. First it is based on self-reported migraine, while the gold standard is a physician diagnosis. Nonetheless, Schürks et al. (2009) verified doctor-diagnosed migraine in more than 87% of women with self-reported migraine, indicating a high validity of such records. Still, we must assume a certain level of phenotypic heterogeneity in our sample, which affects both the power within our study and the chances of replication in samples with stricter diagnostic criteria, such as the IHGC. Second, we unfortunately did not have access to bipolar co-morbidity information in the IHGC migraine

Table 2
Overview of allele frequencies of rs1160720.

Sample	Minor allele frequency	Sample size
TGEN bp mig+	0.218	460
TGEN bp mig−	0.135	914
TGEN controls	0.163	479
GAIN bp mig+	0.167	283
GAIN bp mig−	0.178	686
GAIN controls	0.184	1014
IHGC mig+	0.168	23285
IHGC mig−	0.171	95425
HapMap CEU	0.155	113

meta-analysis sample, and thus, could not test for a putative interaction with bipolar diagnosis. The data however, clearly show that the *NBEA*-locus is not associated with common migraine. The similar allele frequency of rs1160720 across the samples without the combination of bipolar disorder and migraine (Table 2) support the notion that *NBEA* is not a major risk factor for either bipolar disorder or migraine, but that it is a risk factor for a specific bipolar disorder phenotype, where co-morbid migraine is one of the features. Such a hypothesis is in line with the epidemiological findings of a more severe phenotype among bipolar patients with migraine.

Third, although the results in the current study are at the whole genome significance level, we were not able to replicate our top hit in the smaller GAIN sample. This could indicate that the true effect size is considerably over-estimated in the TGEN sample (i.e. “winner’s curse”) and this would consequently lead to an over-estimation of our power to replicate rs1160720 in GAIN sample. Despite TGEN and GAIN being by far the largest published GWAS collections of bipolar patients with information on co-morbid migraine, they may be considered small compared to most GWA studies performed to date and the divergent findings show that much larger samples are needed. One could also be concerned about the validity of the genotyping, however the QC, including Hardy–Weinberg equilibrium tests in both cases and controls, and the strong LD-structure with support from several other SNPs in close vicinity does not support genotype error as a cause of false

association. Furthermore, there might be clinical differences between the samples, as they have been collected with slightly different recruitment strategies.

6. Conclusion

We report a genome-wide significant association between a SNP in *NBEA* and risk of migraine among individuals with BPD. In contrast, there was no association observed between this variant and common migraine nor BPD itself. Thus, a shared genetic component between these two disorders within a specific subgroup of patients may be hypothesized. The likely involvement of *NBEA* gene in both migraine and BPD highlights the role of the glutamatergic system as a putative pathway leading to the development of co-morbid migraine and BPD (Cherlyn et al., 2010; Ligthart et al., 2011).

Conflict of interest

None of the authors report any conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2014.10.004>.

References

- Alliey-Rodriguez, N., Zhang, D., Badner, J.A., Lahey, B.B., Zhang, X., Dinwiddie, S., Romanos, B., Pleny, N., Liu, C., Gershon, E.S., 2011. Genome-wide association study of personality traits in bipolar patients. *Psychiatr. Genet.* 21, 190–194.
- Andlin Sobocki, P., Jönsson, B., Wittchen, H.U., Olesen, J., 2005. Cost of disorders of the brain in Europe. *Eur. J. Neurol.* 12, 1–27.
- Anttila, V., Nyholt, D.R., Kallela, M., Artto, V., Vepsäläinen, S., Jakkula, E., Wennerström, A., Tikka-Kleemola, P., Kaunisto, M.A., Hämäläinen, E., Widén, E., Terwilliger, J., Merikangas, K., Montgomery, G.W., Martin, N.G., Daly, M., Kaprio, J., Pelttonen, L., Färkkilä, M., Wessman, M., Palotie, A., 2008. Consistently replicating locus linked to migraine on 10q22–q23. *Am. J. Hum. Genet.* 82, 1051–1063.
- Anttila, V., Stefansson, H., Kallela, M., Todt, U., Terwindt, G.M., Calafato, M.S., Nyholt, D.R., Dimas, A.S., Freilinger, T., Müller-Myhsok, B., Artto, V., Inouye, M., Alakurtti, K., Kaunisto, M.A., Hämäläinen, E., de Vries, B., Stam, A.H., Weller, C.M., Heinze, A., Heinze-Kuhn, K., Goebel, I., Borck, G., Göbel, H., Steinberg, S., Wolf, C., Björnsson, A., Gudmundsson, G., Kirchmann, M., Hauge, A., Werge, T., Schoenen, J., Eriksson, J.G., Hagen, K., Stovner, L., Wichmann, H.E., Meitinger, T., Alexander, M., Moebus, S., Schreiber, S., Aulchenko, Y.S., Breteler, M.M.B., Uitterlinden, A.G., Hofman, A., van Duijn, C.M., Tikka-Kleemola, P., Vepsäläinen, S., Lucae, S., Tozzi, F., Muglia, P., Barrett, J., Kaprio, J., Färkkilä, M., Pelttonen, L., Stefansson, K., Zwart, J.-A., Ferrari, M.D., Olesen, J., Daly, M., Wessman, M., van den Maagdenberg, A.M.J.M., Dichgans, M., Kubisch, C., Dermitzakis, E.T., Frants, R.R., Palotie, A., International Headache Genetics Consortium, 2010. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. *Nat. Genet.* 42, 869–873.
- Anttila, V., Winsvold, B.S., Gormley, P., Kurth, T., Bettella, F., McMahon, G., Kallela, M., Malik, R., de Vries, B., Terwindt, G., Medland, S.E., Todt, U., McArdle, W.L., Quaye, L., Koiranen, M., Ikram, M.A., Lehtimäki, T., Stam, A.H., Ligthart, L., Wedenoja, J., Dunham, I., Neale, B.M., Palta, P., Hamalainen, E., Schürks, M., Rose, L.M., Buring, J.E., Ridker, P.M., Steinberg, S., Stefansson, H., Jakobsson, F., Vawlor, D.A., Evans, D.M., Ring, S.M., Färkkilä, M., Artto, V., Kaunisto, M.A., Freilinger, T., Schoenen, J., Frants, R.R., Pelzer, N., Weller, C.M., Zielman, R., Heath, A.C., Madden, P.A.F., Montgomery, G.W., Martin, N.G., Borck, G., Göbel, H., Heinze, A., Heinze-Kuhn, K., Williams, F.M.K., Hartikainen, A.-L., Pouta, A., van den Ende, J., Uitterlinden, A.G., Hofman, A., Amin, N., Hottenga, J.-J., Vink, J. M., Heikkilä, K., Alexander, M., Muller-Myhsok, B., Schreiber, S., Meitinger, T., Wichmann, H.E., Aromaa, A., Eriksson, J.G., Traynor, B.J., Trabzuni, D., Rossin, E., Lage, K., Jacobs, S.B.R., Gibbs, J.R., Birney, E., Kaprio, J., Penninx, B.W., Boomsma, D.I., van Duijn, C., Raitakari, O., Jarvelin, M.-R., Zwart, J.-A., Cherkas, L., Strachan, D.P., Kubisch, C., Ferrari, M.D., van den Maagdenberg, A.M.J.M., Dichgans, M., Wessman, M., Smith, G.D., Stefansson, K., Daly, M.J., Nyholt, D.R., Chasman, D.I., Palotie, A., North American Brain Expression Consortium, UK Brain Expression Consortium, International Headache Genetics Consortium, 2013. Genome-wide meta-analysis identifies new susceptibility loci for migraine. *Nat. Genet.* 45, .
- Bedford, L., Hay, D., Devoy, A., Paine, S., Powe, D.G., Seth, R., Gray, T., Topham, I., Fone, K., Rezvani, N., Mee, M., Soane, T., Layfield, R., Sheppard, P.W., Ebendal, T., Usoskin, D., Lowe, J., Mayer, R.J., 2008. Depletion of 26S proteasomes in mouse brain neurons causes neurodegeneration and Lewy-like inclusions resembling human pale bodies. *J. Neurosci.* 28, 8189–8198.
- Castermans, D., Wilquet, V., Parthoens, E., Huysmans, C., Steyaert, J., Swinnen, L., Frys, J.-P., Van de Ven, W., Devriendt, K., 2003. The neurobeachin gene is disrupted by a translocation in a patient with idiopathic autism. *J. Med. Genet.* 40, 352–356.
- Chasman, D.I., Schürks, M., Anttila, V., de Vries, B., Schminke, U., Launer, L.J., Terwindt, G.M., van den Maagdenberg, A.M.J.M., Fendrich, K., Völzke, H., Ernst, F., Griffiths, L., Buring, J.E., Kallela, M., Freilinger, T., Kubisch, C., Ridker, P.M., Palotie, A., Ferrari, M.D., Hoffmann, W., Zee, R.Y.L., Kurth, T., 2011. Genome-wide association study reveals three susceptibility loci for common migraine in the general population. *Nat. Genet.* 43, 695–698.
- Chen, D.T., Jiang, X., Akula, N., Shugart, Y.Y., Wendland, J.R., Steele, C.J.M., Kassem, L., Park, J.-H., Chatterjee, N., Jamain, S., Cheng, A., Leboyer, M., Muglia, P., Schulze, T.G., Cichon, S., Nöthen, M.M., Rietschel, M., BiGS, McMahon, F.J., Kelsøe, J.R., Greenwood, T.A., Nievergelt, C.M., McKinney, R., Shilling, P.D., Schork, N.J., Smith, E.N., Bloss, C.S., Nurnberger, J.L., Edenberg, H.J., Foroud, T., Koller, D.L., Gershon, E.S., Liu, C., Badner, J.A., Scheftner, W.A., Lawson, W.B., Nwulia, E.A., Hipolito, M., Coryell, W., Rice, J., Byerley, W., McMahon, F.J., Chen, D.T., Berrettini, W.H., Potash, J.B., Zandi, P.P., Mahon, P.B., McInnis, M.G., Zöllner, S., Zhang, P., Craig, D.W., Szlinger, S., Barrett, T.B., Schulze, T.G., 2013. Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Mol. Psychiatry* 18, 195–205.
- Cherlyn, S.Y.T., Woon, P.S., Liu, J.J., Ong, W.Y., Tsai, G.C., Sim, K., 2010. Genetic association studies of glutamate, GABA and related genes in schizophrenia and bipolar disorder: a decade of advance. *Neurosci. Biobehav. Rev.* 34, 958–977.

- Cullinane, A.R., Schäffer, A.A., Huizing, M., 2013. The BEACH is hot: a LYST of emerging roles for BEACH-domain containing proteins in human disease. *Traffic* 14, 749–766.
- Cutrer, F.M., Smith, J.H., 2013. Human studies in the pathophysiology of migraine: genetics and functional neuroimaging. *Headache* 53, 401–412.
- del Pino, I., Paarmann, I., Karas, M., Kilimann, M.W., Betz, H., 2011. The trafficking proteins vacuolar protein sorting 35 and neurobeachin interact with the glycine receptor β -subunit. *Biochem. Biophys. Res. Commun.* 412, 435–440.
- Di Lorenzo, C., Grieco, G.S., Santorelli, F.M., 2012. Migraine headache: a review of the molecular genetics of a common disorder. *J. Headache Pain* 13, 571–580.
- Dilsaver, S.C., Benazzi, F., Oedegaard, K.J., Fasmer, O.B., Akiskal, H.S., 2009. Is a family history of bipolar disorder a risk factor for migraine among affectively ill patients? *Psychopathology* 42, 119–123.
- Dudbridge, F., Gusnanto, A., 2008. Estimation of significance thresholds for genomewide association scans. *Genet. Epidemiol.* 32, 227–234.
- Fasmer, O.B., 2001. The prevalence of migraine in patients with bipolar and unipolar affective disorders. *Cephalalgia* 21, 894–899.
- Freeman, C., Marchini, J. (Eds.), 2007. GTOOL. URL (<http://www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html>) (accessed 08.23.13).
- Freilinger, T., Anttila, V., de Vries, B., Malik, R., Kallela, M., Terwindt, G.M., Pozo-Rosich, P., Winsvold, B., Nyholt, D.R., van Oosterhout, W.P.J., Arto, V., Todt, U., Hämäläinen, E., Fernández-Morales, J., Louter, M.A., Kaunisto, M.A., Schoonen, J., Raitakari, O., Lehtimäki, T., Vila-Pueyo, M., Göbel, H., Wichmann, E., Sintas, C., Uitterlinden, A.G., Hofman, A., Rivadeneira, F., Heinze, A., Tronvik, E., van Duijn, C.M., Kaprio, J., Cormand, B., Wessman, M., Frants, R.R., Meitinger, T., Müller-Mysok, B., Zwart, J.-A., Färkkilä, M., Macaya, A., Ferrari, M.D., Kubisch, C., Palotie, A., Dichgans, M., van den Maagdenberg, A.M.J.M., International Headache Genetics Consortium, 2012. Genome-wide association analysis identifies susceptibility loci for migraine without aura. *Nat. Genet.* 44, 777–782.
- Freyaldenhoven, S., Li, Y., Kocabas, A.M., Ziu, E., Ucer, S., Ramanagoudr-Bhojappa, R., Miller, G.P., Kilic, F., 2012. The role of ERp44 in maturation of serotonin transporter protein. *J. Biol. Chem.* 287, 17801–17811.
- Gigante, A.D., Bond, D.J., Lafer, B., Lam, R.W., Young, L.T., Yatham, L.N., 2012. Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: a meta-analysis. *Bipolar Disord.* 14, 478–487.
- Green, E.K., Hamshere, M., Forty, L., Gordon-Smith, K., Fraser, C., Russell, E., Grozeva, D., Kirov, G., Holmans, P., Moran, J.L., Purcell, S., Sklar, P., Owen, M.J., Donovan, M.C.O.A., Jones, L., WTCCC, Jones, I.R., Craddock, N., 2012. Replication of bipolar disorder susceptibility alleles and identification of two novel genome-wide significant associations in a new bipolar disorder case–control sample. *Mol. Psychiatry* 1–6.
- Greenwood, T.A., Kelsoe, J.R., 2013. Genome-wide association study of irritable vs. elated mania suggests genetic differences between clinical subtypes of bipolar disorder. *PLoS One*.
- Hävik, B., Degenhardt, F.A., Johansson, S., Fernandes, C.P.D., Hinney, A., Scherag, A., Lybæk, H., Djurovic, S., Christoforou, A., Erslund, K.M., Giddaluru, S., O'donovan, M.C., Owen, M.J., Craddock, N., Mühleisen, T.W., Mattheisen, M., Schimmelmann, B.G., Renner, T., Warnke, A., Herpertz-Dahlmann, B., Sinzig, J., Albayrak, Ö., Rietschel, M., Nöthen, M.M., Bramham, C.R., Werge, T., Hebebrand, J., Haavik, J., Andreassen, O.A., Cichon, S., Steen, V.M., Le Hellard, S., 2012. DCLK1 variants are associated across schizophrenia and attention deficit/hyperactivity disorder. *PLoS One* 7, e35424.
- Hirschfeld, R.M.A., Calabrese, J.R., Weissman, M.M., Reed, M., Davies, M.A., Frye, M. A., Keck, P.E., Lewis, L., McElroy, S.L., McNulty, J.P., Wagner, K.D., 2003. Screening for bipolar disorder in the community. *J. Clin. Psychiatry*, 64, pp. 53–59.
- Holland, J., Agius, M., 2011. Neurobiology of bipolar disorder—lessons from migraine disorders. *Psychiatr. Danub.* 23 (Suppl. 1), S162–S165.
- Holland, P.R., Akerman, S., Andreou, A.P., Karsan, N., Wemmie, J.A., Goadsby, P.J., 2012. Acid-sensing ion channel 1: a novel therapeutic target for migraine with aura. *Ann. Neurol.* 72, 559–563.
- Howie, B.N., Donnelly, P., Marchini, J., 2009. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet.* 5, e1000529.
- International HapMap Consortium, 2003. The international HapMap project. *Nature* 426, 789–796.
- Kasperaviciute, D., Catarino, C.B., Heinzen, E.L., Depondt, C., Cavalleri, G.L., Caboclo, L.O., Tate, S.K., Jamnadas-Khoda, J., Chinthapalli, K., Clayton, L.M.S., Shianna, K. V., Radtke, R.A., Mikati, M.A., Gallentine, W.B., Husain, A.M., Alhusaini, S., Leppert, D., Middleton, L.T., Gibson, R.A., Johnson, M.R., Matthews, P.M., Hosford, D., Heuser, K., Amos, L., Ortega, M., Zumsteg, D., Wieser, H.G., Steinhoff, B.J., Kramer, G., Hansen, J., Dorn, T., Kantanen, A.M., Gjerstad, L., Peuralinna, T., Hernandez, D.G., Eriksson, K.J., Kalviainen, R.K., Doherty, C.P., Wood, N.W., Pandolfo, M., Duncan, J.S., Sander, J.W., Delanty, N., Goldstein, D.B., Sisodiya, S.M., 2010. Common genetic variation and susceptibility to partial epilepsies: a genome-wide association study. *Brain* 133, 2136–2147.
- Lauks, J., Klemmer, P., Farzana, F., Karupothula, R., Zalm, R., Cooke, N.E., Li, K.W., Smit, A.B., Toonen, R., Verhage, M., 2012. Synapse associated protein 102 (SAP102) binds the C-terminal part of the scaffolding protein neurobeachin. *PLoS One* 7, e39420.
- Lee, K.W., Woon, P.S., Teo, Y.Y., Sim, K., 2012. Genome wide association studies (GWAS) and copy number variation (CNV) studies of the major psychoses: what have we learnt? *Neurosci. Biobehav. Rev.* 36, 556–571.
- Li, M.-X., Yeung, J.M.Y., Cherny, S.S., Sham, P.C., 2012. Evaluating the effective numbers of independent tests and significant *p*-value thresholds in commercial genotyping arrays and public imputation reference datasets. *Hum. Genet.* 131, 747–756.
- Ligthart, L., de Vries, B., Smith, A.V., Ikram, M.A., Amin, N., Hottenga, J.-J., Koelewijn, S.C., Kattenberg, V.M., de Moor, M.H.M., Janssens, A.C.J.W., Aulchenko, Y.S., Oostra, B.A., de Geus, E.J.C., Smit, J.H., Zitman, F.G., Uitterlinden, A.G., Hofman, A., Willemsen, G., Nyholt, D.R., Montgomery, G.W., Terwindt, G.M., Gudnason, V., Penninx, B.W.J.H., Breteler, M., Ferrari, M.D., Launer, L.J., van Duijn, C.M., van den Maagdenberg, A.M.J.M., Boomsma, D.I., 2011. Meta-analysis of genome-wide association for migraine in six population-based European cohorts. *Eur. J. Hum. Genet.* 19, 901–907.
- Lisé, M.-F., Wong, T.P., Trinh, A., Hines, R.M., Liu, L., Kang, R., Hines, D.J., Lu, J., Goldenring, J.R., Wang, Y.T., El-Husseini, A., 2006. Involvement of myosin Vb in glutamate receptor trafficking. *J. Biol. Chem.* 281, 3669–3678.
- Low, N.C.P., Fort, D., G.G., Cervantes, P., 2003. Prevalence, clinical correlates, and treatment of migraine in bipolar disorder. *Headache* 43, 940–949.
- Maher, B.H., Griffiths, L.R., 2011. Identification of molecular genetic factors that influence migraine. *Mol. Genet. Genomics* 285, 433–446.
- Mahmood, T., Romans, S., Silverstone, T., 1999. Prevalence of migraine in bipolar disorder. *J. Affect. Disord.* 52, 239–241.
- McIntyre, R.S., Konarski, J.Z., Wilkins, K., Bouffard, B., Soczynska, J.K., Kennedy, S.H., 2006. The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian community health survey. *Headache* 46, 973–982.
- Matsson, H., Tammimies, K., Zucchelli, M., Anthoni, H., Onkamo, P., Nopola-Hemmi, J., Lyytinen, H., Leppanen, P.H., Neuhoff, N., Warnke, A., Schulte-Körne, G., Schumacher, J., Nöthen, M.M., Kere, J., Peyrard-Janvid, M., 2011. SNP variations in the 7q33 region containing DGKI are associated with dyslexia in the Finnish and German populations. *Behav. Genet.* 41, 134–140.
- Medrihan, L., Rohlmann, A., Fairless, R., Andrae, J., Döring, M., Missler, M., Zhang, W., Kilimann, M.W., 2009. Neurobeachin, a protein implicated in membrane protein traffic and autism, is required for the formation and functioning of central synapses. *J. Physiol.* 587, 5095–5106.
- Meira-Lima, I.V., Zhao, J., Sham, P., Pereira, A.C., Krieger, J.E., Vallada, H., 2001. Association and linkage studies between bipolar affective disorder and the polymorphic CAG/CTG repeat loci ERDA1, SEF2-1B, MAB21L and KCNN3. *Mol. Psychiatry* 6, 565–569.
- Moskvina, V., Craddock, N., Holmans, P., Nikolov, I., Pahwa, J.S., Green, E., Owen, M. J., O'donovan, M.C., 2008. Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. *Mol. Psychiatry* 14, 252–260.
- Nair, R., Lauks, J., Jung, S., Cooke, N.E., de Wit, H., Brose, N., Kilimann, M.W., Verhage, M., Rhee, J., 2013. Neurobeachin regulates neurotransmitter receptor trafficking to synapses. *J. Cell Biol.* 200, 61–80.
- Niesmann, K., Breuer, D., Brockhaus, J., Born, G., Wolff, I., Reissner, C., Kilimann, M. W., Rohlmann, A., Missler, M., 2011. Dendritic spine formation and synaptic function require neurobeachin. *Nat. Commun.* 2, 557.
- Nuytens, K., Gantois, I., Stijnen, P., Iscru, E., Laeremans, A., Serneels, L., Van Eylen, L., Liebhauer, S.A., Devriendt, K., Balschun, D., Arckens, L., Creemers, J.W.M., D'Hooge, R., 2013. Haploinsufficiency of the autism candidate gene Neurobeachin induces autism-like behaviors and affects cellular and molecular processes of synaptic plasticity in mice. *Neurobiol. Dis.* 51, 144–151.
- Oedegaard, K.J., Greenwood, T.A., Johansson, S., Jacobsen, K.K., Halmøy, A., Fasmer, O.B., Akiskal, H.S., Bipolar Genome Study (BiGS)/Haavik, J., Kelsoe, J.R., 2010. A genome-wide association study of bipolar disorder and comorbid migraine. *Genes Brain Behav.* 9, 673–680.
- Offord, J., 2012. Genetic approaches to a better understanding of bipolar disorder. *Pharmacol. Ther.* 133, 133–141.
- Purcell, S., Cherny, S.S., Sham, P.C., 2003. Genetic power calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* 19, 149–150.
- Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A.R., Bender, D., Maller, J., Sklar, P., De Bakker, P.I.W., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* 81, 559–575.
- Sanders, A.R., Levinson, D.F., Duan, J., Dennis, J.M., Li, R., Kendler, K.S., Rice, J.P., Shi, J., Mowry, B.J., Amin, F., Silverman, J.M., Buccola, N.G., Byerley, W.F., Black, D.W., Freedman, R., Cloninger, C.R., Gejman, P.V., 2010. The Internet-based MGS2 control sample: self report of mental illness. *Am. J. Psychiatry* 167, 854–865.
- Schürks, M., Buring, J.E., Kurth, T., 2009. Agreement of self-reported migraine with ICHD-II criteria in the Women's Health Study. *Cephalalgia* 29, 1086–1090.
- Schürks, M., Rist, P.M., Kurth, T., 2010. 5-HTTLPR polymorphism in the serotonin transporter gene and migraine: a systematic review and meta-analysis. *Cephalalgia* 30, 1296–1305.
- Seifuddin, F., Mahon, P.B., Judy, J., Pirooznia, M., Jancic, D., Taylor, J., Goes, F.S., Potash, J.B., Zandi, P.P., 2012. Meta-analysis of genetic association studies on bipolar disorder. *Am. J. Med. Genet.* 159B, 508–518.
- Sklar, P., Smoller, J.W., Fan, J., Ferreira, M.A.R., Perlis, R.H., Chambert, K., Nimgaonkar, V.L., McQueen, M.B., Faraone, S.V., Kirby, A., de Bakker, P.I.W., Ogdie, M.N., Thase, M.E., Sachs, G.S., Todd-Brown, K., Gabriel, S.B., Sougnez, C., Gates, C., Blumenstiel, B., Defelice, M., Ardlie, K.G., Franklin, J., Muir, W.J., McGhee, K.A., Macintyre, D.J., McLean, A., VanBeck, M., McQuillin, A., Bass, N.J., Robinson, M., Lawrence, J., Anjorin, A., Curtis, D., Scolnick, E.M., Daly, M.J., Blackwood, D.H., Gurling, H.M., Purcell, S.M., 2008. Whole-genome association study of bipolar disorder. *Mol. Psychiatry* 13 (558–569).
- Smith, E.N., Bloss, C.S., Badner, J.A., Barrett, T., Belmonte, P.L., Berrettini, W., Byerley, W., Coryell, W., Craig, D., Edenberg, H.J., Eskin, E., Foroud, T., Gershon, E., Greenwood, T.A., Hipolito, M., Koller, D.L., Lawson, W.B., Liu, C., Lohoff, F., McInnis, M.G., McMahon, F.J., Mirel, D.B., Murray, S.S., Nievergelt, C., Nurnberger, J., Nwulia, E.A., Paschall, J., Potash, J.B., Rice, J., Schulze, T.G., Scheftner, W.,

- Panganiban, K., Zaitlen, N., Zandi, P.P., Illner, S.Z.O., Schork, N.J., Kelsoe, J.R., 2009. Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol. Psychiatry* 14, 755–763.
- Smith, E.N., Koller, D.L., Panganiban, C., Szlinger, S., Zhang, P., Badner, J.A., Barrett, T.B., Berrettini, W.H., Bloss, C.S., Byerley, W., Coryell, W., Edenberg, H.J., Foroud, T., Gershon, E.S., Greenwood, T.A., Guo, Y., Hipolito, M., Keating, B.J., Lawson, W. B., Liu, C., Mahon, P.B., McInnis, M.G., McMahon, F.J., McKinney, R., Murray, S.S., Nievergelt, C.M., Nurnberger, J.I., Nwulia, E.A., Potash, J.B., Rice, J., Schulze, T.G., Scheftner, W.A., Shilling, P.D., Zandi, P.P., Zöllner, S., Craig, D.W., Schork, N.J., Kelsoe, J.R., 2011. Genome-wide association of bipolar disorder suggests an enrichment of replicable associations in regions near genes. *PLoS Genet.* 7, e1002134.
- Smith, M., Woodroffe, A., Smith, R., Holguin, S., Martinez, J., Filipek, P.A., Modahl, C., Moore, B., Bocian, M.E., Mays, L., Lulhere, T., Flodman, P., Spence, M.A., 2002. Molecular genetic delineation of a deletion of chromosome 13q12]13 in a patient with autism and auditory processing deficits. *Cytogenet. Genome Res.* 98, 233–239.
- Stuart, S., Cox, H.C., Lea, R.A., Griffiths, L.R., 2012. The role of the MTHFR gene in migraine. *Headache* 52, 515–520.
- Tsang, W.H., Shek, K.F., Lee, T.Y., Chow, K.L., 2009. An evolutionarily conserved nested gene pair—Mab21 and Lrba/Nbea in metazoan. *Genomics* 94, 177–187.
- Vos, T., Flaxman, A.D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J.A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S.Y., Ali, M.K., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Bahalim, A.N., Barker-Collo, S., Barrero, L.H., Bartels, D.H., Basáñez, M.-G., Baxter, A., Bell, M.L., Benjamin, E.J., Bennett, D., Bernabé, E., Bhalla, K., Bhandari, B., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Black, J.A., Blencowe, H., Blore, J.D., Blyth, F., Bolliger, I., Bonaventure, A., Boufous, S., Bourne, R., Boussinesq, M., Braithwaite, T., Brayne, C., Bridgett, L., Brooker, S., Brooks, P., Brugha, T.S., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Buckle, G., Budke, C.M., Burch, M., Burney, P., Burstein, R., Calabria, B., Campbell, B., Canter, C.E., Carabin, H., Carapetis, J., Carmona, L., Cella, C., Charlson, F., Chen, H., Cheng, A.T.-A., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K. E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Dahiya, M., Dahodwala, N., Damsere-Derry, J., Danaei, G., Davis, A., De Leo, D., Degenhardt, L., Dellavalle, R., Delossantos, A., Denenberg, J., Derrett, S., Jarlais, Des, D.C., Dharmanatne, S.D., Dherani, M., Diaz-Torne, C., Dolk, H., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Edmond, K., Elbaz, A., Ali, S.E., Erskine, H., Erwin, P.J., Espindola, P., Ewoigbokhan, S.E., Farzadfar, F., Feigin, V., Felson, D.T., Ferrari, A., Ferri, C.P., Fèvre, E.M., Finucane, M.M., Flaxman, S., Flood, L., Foreman, K., Forouzanfar, M.H., Fowkes, F.G.R., Franklin, R., Fransen, M., Freeman, M.K., Gabbe, B.J., Gabriel, S.E., Gakidou, E., Ganatra, H.A., Garcia, B., Gaspari, F., Gillum, R.F., Gmel, G., Gosselin, R., Grainger, R., Groeger, J., Guillemin, F., Gunnell, D., Gupta, R., Haagsma, J., Hagan, H., Halasa, Y.A., Hall, W., Haring, D., Haro, J.M., Harrison, J.E., Havmoeller, R., Hay, R.J., Higashi, H., Hill, C., Hoen, B., Hoffman, H., Hotez, P.J., Hoy, D., Huang, J.J., Ibeanusi, S.E., Jacobsen, K.H., James, S.L., Jarvis, D., Jassasaria, R., Jayaraman, S., Johns, N., Jonas, J.B., Karthikeyan, G., Kassebaum, N., Kawakami, N., Keren, A., Khoo, J.-P., King, C.H., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Laloo, R., Laslett, L.L., Lathlean, T., Leasher, J.L., Lee, Y.Y., Leigh, J., Lim, S.S., Limb, E., Lin, J.K., Lipnick, M., Lipshultz, S.E., Liu, W., Loane, M., Ohno, S.L., Lyons, R., Ma, J., Mabweijano, J., MacIntyre, M.F., Malekzadeh, R., Mallinger, L., Manivannan, S., Marcenes, W., March, L., Margolis, D.J., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B.M., McAnulty, J.H., McDermott, M.M., McGill, N., McGrath, J., Medina-Mora, M.E., Meltzer, M., Mensah, G.A., Merriman, T.R., Meyer, A.-C., Miglioli, V., Miller, M., Miller, T.R., Mitchell, P.B., Mocumbi, A.O., Moffitt, T.E., Mokdad, A.A., Monasta, L., Montico, M., Moradi-Lakeh, M., Moran, A., Morawska, L., Mori, R., Murdoch, M. E., Mwaniki, M.K., Naidoo, K., Nair, M.N., Naldi, L., Narayan, K.M.V., Nelson, P.K., Nelson, R.G., Nevitt, M.C., Newton, C.R., Nolte, S., Norman, P., Norman, R., O'Donnell, M., O'Hanlon, S., Olives, C., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Page, A., Pahari, B., Pandian, J.D., Rivero, A.P., Patten, S.B., Pearce, N., Padilla, R.P., Perez-Ruiz, F., Perico, N., Pesudovs, K., Phillips, D., Phillips, M.R., Pierce, K., Pion, S., Polanczyk, G.V., Polinder, S., Pope, C.A., Popova, S., Porrini, E., Pourmalek, F., Prince, M., Pullan, R.L., Ramaiah, K.D., Ranganathan, D., Razavi, H., Regan, M., Rehm, J.T., Rein, D.B., Remuzzi, G., Richardson, K., Rivara, F.P., Roberts, T., Robinson, C., De León, F.R., Ronfani, L., Room, R., Rosenfeld, L.C., Rushton, L., Sacco, R.L., Saha, S., Sampson, U., Sanchez-Riera, L., Sanman, E., Schwebel, D.C., Scott, J.G., Segui-Gomez, M., Shahraz, S., Shepard, D.S., Shin, H., Shrivakoti, R., Singh, D., Singh, G.M., Singh, J.A., Singleton, J., Sleet, D.A., Sliwa, K., Smith, E., Smith, J.L., Stapelberg, N.J.C., Steer, A., Steiner, T., Stolk, W.A., Stovner, L.J., Sudfeld, C., Syed, S., Tamburlini, G., Tavakkoli, M., Taylor, H.R., Taylor, J.A., Taylor, W.J., Thomas, B., Thomson, W.M., Thurston, G.D., Tleyjeh, I.M., Tonelli, M., Towbin, J.A., Truelsen, T., Tsilimbaris, M.K., Ubeda, C., Undurraga, E.A., van der Werf, M.J., van Os, J., Vavilala, M.S., Venketasubramanian, N., Wang, M., Wang, W., Watt, K., Weatherall, D.J., Weinstock, M.A., Weintraub, R., Weisskopf, M.G., Weissman, M.M., White, R.A., Whiteford, H., Wiersma, S.T., Wilkinson, J.D., Williams, H.C., Williams, S.R.M., Witt, E., Wolfe, F., Woolf, A.D., Wulf, S., Yeh, P.-H., Zaidi, A.K.M., Zheng, Z.-J., Zonies, D., Lopez, A.D., Murray, C.J.L., AlMazroa, M. A., Memish, Z.A., 2012. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 380, 2163–2196.
- Xu, C., Aragam, N., Li, X., Villa, E.C., Wang, L., Briones, D., Petty, L., Posada, Y., Arana, T.B., Cruz, G., Mao, C., Camarillo, C., Su, B.B., Escamilla, M.A., Wang, K., 2013. BCL9 and C9orf5 are associated with negative symptoms in Schizophrenia: meta-analysis of two genome-wide association studies. *PLoS One* 8, e51674.