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Letter to the Editor

Further evidence is required to confirm association between *CACNA1C* gene variants and bipolar affective disorder

In their invited review on the genetics of bipolar affective disorder (BP), Keers *et al*. (2009) reported multiple association signals across the *CACNA1C* gene and suggested that because 'these association signals were located in three blocks of largely distinct regions of linkage disequilibrium (LD)' they 'may therefore be considered as three relatively independent associations between *CACNA1C* and BP'.

However, it should be noted that non-negligible LD often exists between non-contiguous single nucleotide polymorphisms (SNPs), separated by tens to sometimes hundreds of kilobases and within separate so-called 'LD blocks', and that in the specific case reported by Keers *et al*., the moderate associations ($7.38 \times 10^{-5} \leqslant p \leqslant 3.88 \times 10^{-4}$) between 15 SNPs and BP across *CACNA1C* can be completely explained by a single effect.

As shown in Fig. 1, substantial LD (r^2) (calculated using release 22 HapMapI+II CEU data; http://www.hapmap.org) exists between the 15 SNPs listed in table 1 of Keers *et al*. (2009), thus indicating that these SNPs are expected to provide similar evidence for association. Indeed, this can be easily demonstrated through simulating the results of Keers *et al*. by splitting the HapMap CEU samples into two groups to approximate the evidence for association ($p \cong 7 \times 10^{-5}$) of the most significant SNP (rs2238054) reported by Keers *et al*. and performing association analysis with and without conditioning on rs2238054.

Results from allelic association analyses utilizing logistic regression within the PLINK program (Purcell *et al*. 2007) (Table 1), clearly demonstrate that after conditioning on rs2238054, none of the 14 remaining SNPs listed in table 1 of Keers *et al*. show evidence for association.

As a consequence, while the reported association(s) between *CACNA1C* and BP remain an interesting, although non-genome-wide significant finding, there is currently no evidence for multiple independent effects and further studies are therefore required to confirm involvement of *CACNA1C* variants with BP susceptibility.

Declaration of Interest

None.

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The authors reply

We welcome Dr Nyholt's further analyses of our findings from the WTCCC data and any further discussion regarding this important candidate for bipolar disorder (BP). We agree that Dr Nyholt's analysis suggests that the association signals we detected between variants in the *CACNA1C* and BP may not be entirely independent. This should not, however, detract from the body of evidence now linking *CACNA1C* with BD or from the focus in our original article, that this candidate also represents a potential drug target (Keers *et al*. 2009).

In addition to the positive findings reported by Sklar *et al*. (2002, 2008), a large collaborative study combining data from three genome-wide association datasets identified a genome-wide significant association signal in *CACNA1C* (Ferreira *et al*. 2008). The top hit from this study has subsequently been associated with schizophrenia and major depression (Green *et al*. 2009) and, consistent with previous studies of both disorders and BP, shown to confer specific verbal fluency deficits in a population sample (Krug *et al*. 2009).

CACNA1C encodes the alpha subunit of the calcium channel $Ca_v1.2$. The association between calcium dysregulation and BP is well documented (Warsh *et al*. 2004), as is the overlap between BP and other 'channelopathies' such as migraine and epilepsy (Sheftell & Atlas, 2002). Moreover, drugs which affect

Table 1. *Simulated unconditional and conditional association results for the 15 CACNA1C SNPs listed in table 1 of Keers et al. (2009)*

				Unconditional results			Conditioned on rs2238054[a]		
CHR	SNP	Position (bp)	Allele	OR	Stat	*p*	OR	Stat	*p*
12	rs10848628	2182750	C	6.61	3.93	8.44×10^{-5}	N.A.	N.A.	N.A.
12	rs12422554	2182881	C	5.57	3.92	8.93×10^{-5}	N.A.	N.A.	N.A.
12	rs4765902	2183226	A	5.57	3.92	8.93×10^{-5}	N.A.	N.A.	N.A.
12	rs10848632	2186254	T	5.35	3.77	1.65×10^{-4}	4.31×10^{-9}	-7.90×10^{-4}	1.00
12	rs10848633	2186280	G	5.33	3.78	1.56×10^{-4}	4.38×10^{-9}	-7.90×10^{-4}	1.00
12	rs10848634	2186388	C	5.40	3.84	1.21×10^{-4}	N.A.	N.A.	N.A.
12	rs10848635	2186456	A	5.25	3.76	1.71×10^{-4}	N.A.	N.A.	N.A.
12	rs10848636	2186754	T	5.57	3.92	8.93×10^{-5}	N.A.	N.A.	N.A.
12	rs11062156	2187784	A	5.60	3.92	8.90×10^{-5}	N.A.	N.A.	N.A.
12	rs2238054[a]	2187905	C	5.57	3.92	8.93×10^{-5}	N.A.	N.A.	N.A.
12	rs1006737	2215556	A	4.15	3.57	3.55×10^{-4}	1.89	1.24	0.22
12	rs4765905	2219845	C	4.14	3.60	3.24×10^{-4}	1.90	1.24	0.21
12	rs10744560	2257360	T	4.27	3.67	2.41×10^{-4}	1.92	1.26	0.21
12	rs4765914	2290638	T	2.89	2.58	9.95×10^{-3}	1.00	-3.84×10^{-3}	1.00
12	rs10774037	2290787	G	2.92	2.66	7.89×10^{-3}	1.10	0.20	0.84

OR, Odds ratio; Stat, *t* statistic; N.A. indicates rs2238054 completely accounted for the association signal at this locus.
[a] SNP rs2238054 produced the most significant association signal in Keers *et al.* (2009).

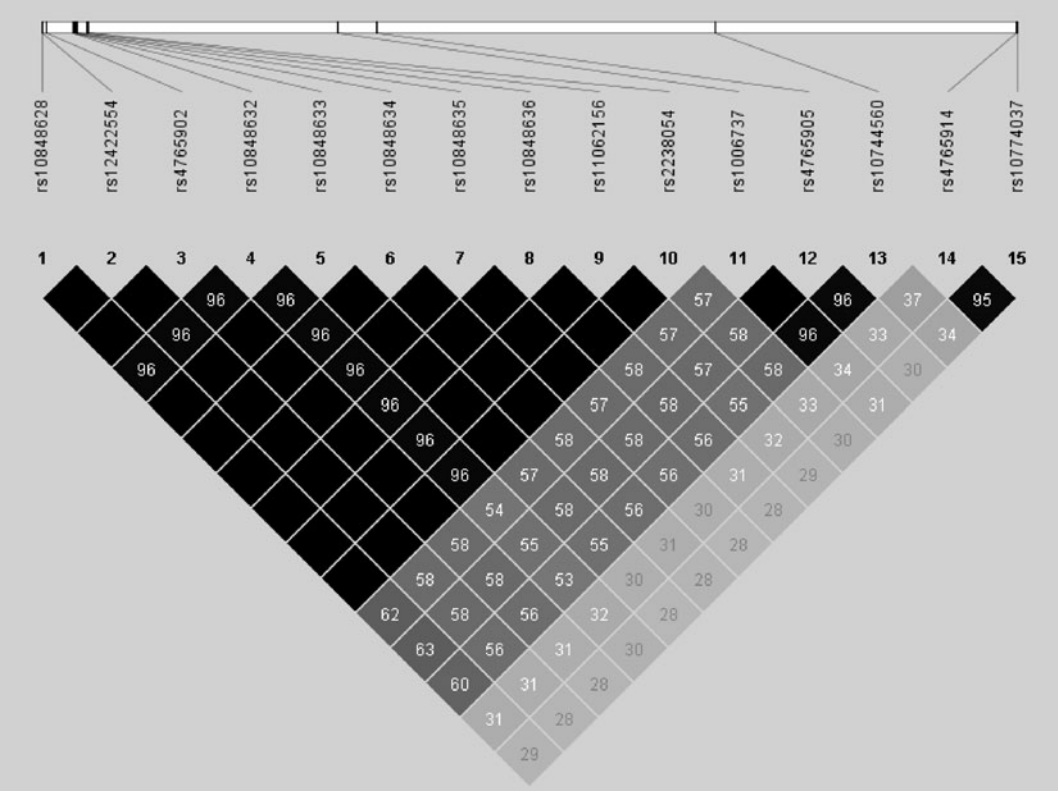

Fig. 1. Linkage disequilibrium (r^2) plot showing high correlation among the 15 SNPs listed in Table 1 of Keers *et al.* (2009); where white cells represent $r^2 = 0$, shades of grey represent $0 < r^2 < 1$, and black cells represent $r^2 = 1$.

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interneuronal calcium ion activity by targeting $Ca_v1.2$ have been shown to be effective in the treatment of BP (Levy & Janicak, 2000).

CACNA1C remains a biologically plausible drug target associated with BP. More in-depth genetic and pharmacogenetic studies of *CACNA1C* and BP may yet provide a greater understanding of the aetiology and treatment of the disorder.

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