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Research report

Investigating the genetic variation underlying episodicity in major depressive disorder: Suggestive evidence for a bipolar contribution

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ABSTRACT

Background: Highly recurrent major depressive disorder (MDD) has reportedly increased risk of shifting to bipolar disorder; high recurrence frequency has, therefore, featured as evidence of 'soft bipolarity'. We aimed to investigate the genetic underpinnings of total depressive episode count in recurrent MDD.
Methods: Our primary sample included 1966 MDD cases with negative family history of bipolar disorder from the RADIANT studies. Total episode count was adjusted for gender, age, MDD duration, study and center before being tested for association with genotype in two separate genome-wide analyses (GWAS), in the full set and in a subset of 1364 cases with positive family history of MDD (FH+). We also calculated polygenic scores from the Psychiatric Genomics Consortium MDD and bipolar disorder studies.
Results: Episodicity (especially intermediate episode counts) was an independent index of MDD familial aggregation, replicating previous reports. The GWAS produced no genome-wide significant findings. The strongest signals were detected in the full set at MAGI1 ($p=5.1\times10^{-7}$), previously associated with bipolar disorder, and in the FH+ subset at STIM1 ($p=3.9\times10^{-6}$ after imputation), a calcium channel signaling gene. However, these findings failed to replicate in an independent Munich cohort. In the full set polygenic profile analyses, MDD polygenes predicted episodicity better than bipolar polygenes; however, in the FH+ subset, both polygenic scores performed similarly.

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Limitations: Episode count was self-reported and, therefore, subject to recall bias.
Conclusions: Our findings lend preliminary support to the hypothesis that highly recurrent MDD with FH+ is part of a 'soft bipolar spectrum' but await replication in larger cohorts.

1. Introduction

Major depressive disorder (MDD) is a common disease with a lifetime prevalence of 16% (Kessler et al., 2003). It is associated with considerable morbidity, excess mortality and compromise of functioning and quality of life. The etiopathogenesis of MDD remains unclear despite extensive research in the field. MDD tends to run in families; the sibling relative risk $\lambda_{sibling}$ is estimated to be ~3 while heritability has been calculated on average at 0.37 (95% CI 0.31–0.42) (Sullivan et al., 2000). Eight genome-wide association studies (GWAS) of MDD have been published (Kohli et al., 2011; Lewis et al., 2010; Muglia et al., 2010; Rietschel et al., 2010; Shi et al., 2011; Shyn et al., 2011; Sullivan et al., 2009; Wray et al., 2012), with one locus of possible genome-wide significance (Kohli et al., 2011). A recently published mega-analysis of GWAS studies in MDD by the Psychiatric Genomics Consortium (PGC) failed to identify any genome-wide significant findings (PGC, 2013). Phenotypic and genetic heterogeneity have been suggested as two main reasons why the genetic architecture of MDD is still elusive.

One approach to improve power to detect genetic risk loci would therefore be to reduce phenotypic variation, using samples enriched in clinical subphenotypes of MDD that are associated with increased heritability. Recurrence and early onset have most often featured as clinical indices of higher familial aggregation and heritability (Kendler et al., 1999, 2005, 2007, 1994; McGuffin et al., 1996) while more limited evidence exists for other subphenotypes, such as severity, impairment, number of depressive symptoms endorsed, duration of the longest episode, clinical subtype (atypical, endogenous, psychotic) and comorbidities (Sullivan et al., 2000). For a given sample size, the power to identify genetic variants in GWAS should, therefore, increase when focusing on patients with a family history of depression, who have recurrent, early-onset, clinically ascertained MDD (McGuffin et al., 1996) which is reliably assessed through repeated measurements (Foley et al., 1998; Kendler et al., 1993).

Recurrence (episode count of two or higher) is, in fact, a binary/dichotomous approach to the episodicity subphenotype of MDD. Episodicity is most frequently examined as a binary rather than a quantitative/continuous phenotype in family/genetic studies of MDD. Recurrence is probably the most consistent index of familial aggregation of MDD (Sullivan et al., 2000). The pattern of association of quantitative episodicity (hereafter referred to as just 'episodicity') with familiality or heritability of MDD has been explored in a few population-based twin registries or birth cohorts (Kendler et al., 1999, 2007, 1994; Milne et al., 2009) and clinically ascertained samples (Hollon et al., 2006; Nierenberg et al., 2007). Findings have often been inconsistent. Interestingly, the risk for MDD of the co-twin of a twin with MDD was found to have a non-linear inverted-U shaped association with the number of lifetime episodes reported by the index twin, maximized at 7–9 lifetime episodes (Kendler et al., 1999). Similarly, the proportion of STAR*D patients with a positive family history of MDD was highest with intermediate (4–9) numbers of lifetime episodes (Hollon et al., 2006).

Episode frequency is a highly familial trait in bipolar disorder (Fisfalen et al., 2005). Highly recurrent MDD cases have reportedly increased risk of shifting to bipolar disorder (Angst et al., 2005). MDD cases with bipolar family history seem to present with more episodes (as well as an earlier age at onset and an atypical pattern) (Akiskal, 2003; Ghaemi et al., 2002; Souery et al., 2012). Moreover, the offspring of probands with bipolar disorder have increased risk of recurrent MDD (but not of single episodes) compared to offspring of healthy controls (Vandeleur et al., 2012). These observations have spurred the hypothesis that high recurrence frequency is evidence of a 'soft bipolar' component in MDD and highly recurrent MDD (often with early onset and a positive family history of bipolar disorder) has been included in 'bipolar spectrum disorder' (Akiskal, 2003; Ghaemi et al., 2002; Mitchell et al., 2008; Phelps et al., 2008).

The aims of this study were: first, investigate the relationship between episodicity and family history of MDD in a sample of cases with recurrent MDD and negative family history of bipolar disorder; second, perform a GWAS of MDD episodicity (the first of its kind) to identify genetic variants associated with the number of depressive episodes; and, third, to explore contributions of MDD and bipolar disorder polygenes to MDD episodicity through analyses of polygenic scores calculated from the PGC MDD and bipolar disorder studies. For the last two objectives of the study, we also investigated whether family history of MDD had a moderator effect.

2. Subjects and methods

2.1. Samples

A total of 1966 MDD cases from the RADIANT studies DeCC (N=994), DeNt (N=833) and GSK Case-Control study (N=139) with complete data sets on age, age at onset and episode count were analyzed as a discovery sample. The DeCC (Depression Case Control) study includes cases of recurrent depression fulfilling DSM-IV and/or ICD-10 criteria of at least moderate severity ascertained from three UK clinical sites (London, Cardiff and Birmingham) (Cohen-Woods et al., 2009). The DeNt (Depression Network) affected sibling pair linkage study (Farmer et al., 2004; McGuffin et al., 2005) comprises cases of recurrent depression of at least moderate severity, ascertained from three UK sites (London, Cardiff and Birmingham), four other European sites (Aarhus, Bonn, Dublin and Lausanne) and a site in St. Louis, USA. Only one proband from each family was genotyped and included in the analysis. The GSK Case-Control study included cases of recurrent depression collected in Bonn and Lausanne in collaboration with GSK, using exactly the same protocol as the DeNt study. In all three studies, only adults of European ancestry were recruited. Subjects were excluded if there was a history or family history (in first or second-degree relatives) of schizophrenia, schizoaffective disorder or bipolar disorder, if they had experienced mood incongruent psychotic symptoms, or if mood symptoms were solely related to alcohol or substance misuse or only secondary to medical illness or medication.

The replication sample consisted of cases of recurrent depression of at least moderate severity recruited for a case-control study in the Munich area in collaboration with GSK (Muglia et al., 2010; Tozzi et al., 2008). Assessment instruments and inclusion/exclusion criteria were identical to those used in the DeCC and DeNT studies, except that subjects with a family history of bipolar disorder were not excluded. After removing the latter, a total of 372 cases with complete data sets on age, age at onset and episode count were included in the analysis.

All cases in both samples were interviewed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990), focusing on their worst and second-worst episodes of