



Research report

Genetic and childhood trauma interaction effect on age of onset in bipolar disorder: An exploratory analysis



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ABSTRACT

Introduction: This study investigated whether early life trauma mediates genetic effects on the age at onset (AAO) of bipolar disorder.

Method: Data from the BiGS Consortium case samples ($N=1119$) were used. Childhood traumatic events were documented using the Childhood Life Events Scale (CLES). Interaction between occurrence of childhood trauma and common genetic variants throughout the genome was tested to identify single nucleotide polymorphic gene variants (SNPs) whose effects on bipolar AAO differ between individuals clearly exposed ($CLES \geq 2$) and not exposed ($CLES=0$) to childhood trauma.

Results: The modal response to the CLES was 0 ($N=480$), but an additional 276 subjects had $CLES=1$, and 363 subjects reported 2 or more traumatic lifetime events. The distribution of age at onset showed a broad peak between ages 12 and 18, with the majority of subjects having onset during that period, and a significant decrease in age of onset with the number of traumatic events. No single SNP showed a statistically significant interaction with the presence of traumatic events to impact bipolar age at onset. However, SNPs in or near genes coding for calcium channel activity-related proteins (Gene Ontology: 0005262) were found to be more likely than other SNPs to show evidence of interaction using the INRICH method ($p < 0.001$).

Limitations: Retrospective ascertainment of trauma and AAO.

Conclusion: Interaction effects of early life trauma with genotype may have a significant effect on the development and manifestation of bipolar disorder. These effects may be mediated in part by genes involved in calcium signaling.

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1. Introduction

The interaction between genetic and environmental factors is recognized to be important in the development and manifestation of complex illnesses such as major psychiatric disorders. Bipolar Disorder (BPD) is a major mental illness, characterized by periods of depression, mania and normal mood, and is known to be strongly heritable. It typically first manifests itself in late adolescent and early adulthood.

Early age of onset (AAO) of BPD has been used to identify a subgroup of patients suffering from the disorder who may have a

more severe form of illness, and possibly a stronger genetic liability (Belmonte Mahon et al., 2011; Lin et al., 2006a). There is some evidence for specific genetic variants related to early-onset BPD (Priebe et al., 2012). We hypothesized that further understanding of AAO variability in BPD would be gained by taking specific environmental effects into account along with genetic factors.

While a number of environmental factors could conceivably be important, early life experiences and trauma in particular are known to affect vulnerability to psychiatric illness; this has been noted in particular for mood disorders (Caspi et al., 2003; Gillespie et al., 2005). Though most investigation and reports regarding early-life trauma have involved development of depression, early trauma and stress have also been shown to affect the age of onset, prognosis and course of bipolar disorder (Post and Leverich, 2006). Twin studies have shown a heritability of 0.8–0.9 for BPD, implying that the presence or absence of the disorder is substantially

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determined by genetic factors (Kieseppä et al., 2004; Nurnberger, 2012). Age of onset appears to be less clearly heritable, though some evidence for familiarity has emerged (Lin et al., 2006b; Schulze et al., 2006). A number of studies have shown that early-life trauma, such as sexual or physical abuse, is associated with an earlier age of onset of bipolar illness as well as a more complicated and treatment-resistant course (Brown et al., 2005; Garino et al., 2005; Gilman et al., 2015; Leverich et al., 2002; Leverich and Post, 2006; Romero et al., 2009). Importantly, presence or absence of childhood trauma and family history of BPD have been reported to demonstrate interaction in their influence on the age of onset and course of bipolar disorder; the effect of trauma upon age of onset was observed to be substantially larger when family history is present (Post and Leverich, 2006).

Genome wide association studies (GWAS) investigating the association between common single nucleotide polymorphisms (SNPs) and BPD have currently identified 14 genomewide significant susceptibility loci (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011). Common SNPs in aggregate appear to explain 25–40% of liability to BP (Lee et al., 2011), and current studies suggest that rare variants and gene–gene interactions explain substantial fractions of the remaining genetic contribution to BPD risk (Belmonte Mahon et al., 2011; Gershon et al., 2010; Judy et al., 2013). We hypothesized that the inclusion of environmental factors, such as early life trauma, in GWAS analyses would allow us to account for some additional unexplained variability in age of onset not modeled in other study designs.

2. Materials and methods

The GWAS SNPs and phenotypic data analyzed ($N=1119$ subjects; Table 1) were available from the NIMH Bipolar Disorder Genetic Association Information Network (GAIN-BP) and the Translational Genomics Institute (TGEN) bipolar case samples. The ascertainment and assessment procedures of the NIMH-BP sample are described elsewhere (Dick et al., 2003; Kassem et al., 2006). All subjects were assessed with the Diagnostic Interview for Genetic Studies (DIGS) and this was combined with family informant data and medical records to assign diagnoses based on DSM-III-R or DSM-IV criteria. Unrelated cases were genotyped in two separate efforts described in detail elsewhere, the Genetic Association Information Network Bipolar Sample (GAIN-BP, Smith et al., 2009) and the Bipolar Genome Study (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011). Genotyping in both efforts was performed using the Affymetrix 6.0 array, providing genotype data on approximately 700,000 SNPs.

Table 1
Subjects demographics and trauma history.

	CLES=0	CLES=1	CLES ≥ 2	Total
Males				
AAO ≤ 18	98	38	61	197
AAO > 18	109	46	55	210
Total	207	84	116	407
Females				
AAO ≤ 18	147	99	161	407
AAO > 18	126	93	86	305
Total	273	192	247	712
Combined				
AAO ≤ 18	245	137	222	604
AAO > 18	235	139	141	515
Total	480	276	363	1119

Note: GWAS SNP genotypes in all subjects with AAO ≥ 12 were tested for interaction effect upon AAO with CLES as a continuous measure ($n=1119$) and classified as CLES=0 versus CLES ≥ 2 (combined $n=843$). GWAS: Genome-wide association study; AAO: Age at onset; CLES: Childhood Life Events Scale.

2.1. Age of onset

Detailed information regarding age of onset of bipolar disorder (AAO) was available for 1119 of the genotyped cases, and AAO was determined best estimate using DIGS interview and medical records. The criterion was the age of occurrence of the first mood episode that met diagnostic criteria for either depression or mania.

2.2. Early-life trauma

Early-life trauma was documented using the Childhood Life Events Scale (CLES) (Lawson and Gershon, unpublished, Supplementary Table 3) an 11-point scale that asks the subject about various traumatic events that may have happened between ages 3 and 12. Scoring is the number of accumulated traumas during childhood (range 0–8 events, Table 1). The distributions of AAO of BPD and the number of traumatic events per individual in the GAIN and TGEN samples are shown in Fig. 1. As we were investigating the effects of trauma on age of onset, only subjects with bipolar onset at age 12 or older were included.

2.3. Statistical analysis

Early life trauma was considered as a binary measure—no trauma (CLES score=0) vs. two or more reported traumatic events (CLES score ≥ 2), omitting subjects with a single traumatic event to more clearly separate the two subgroups differing in degree of trauma exposure. A linear model was fitted to test the interaction of SNP genotype and early-life trauma upon age of onset, with main effects for the SNP and trauma variables included simultaneously. This corresponds to a comparison of the strength and direction of the SNP-AAO relationship between the trauma subgroups. To aid in interpretation of the genotype by trauma interaction results for a particular SNP, the main effect of SNP genotype on age of onset, covarying for trauma but omitting the interaction term, was also tested. The most significant SNP-trauma interactions in the binary analysis were also tested with the CLES score modeled as a continuous variable. This analysis was best powered to detect SNPs with an additive genetic effect upon bipolar AAO in subjects in the trauma group, but no effect (or an opposite effect) in the other group.

2.4. Pathway analysis

Enrichment of our top interaction GWAS findings within particular molecular pathways, as defined by Gene Ontology (GO) terms, was examined using the INRICH software (<http://atgu.mgh.harvard.edu/inrich>). This was performed for GO terms identified previously for other GWAS studies of psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics, 2013). Linkage disequilibrium (LD)-based clumping in PLINK was conducted to identify independent or nearly independent association regions ($LD\ r^2 < 0.25$) containing the top GWAS findings ($p < 10^{-4}$). A permutation approach implemented in INRICH was then used to approximate the nominal probability of the gene(s) in these regions intersecting with the gene set associated with each GO term by chance.

3. Results

Onset of bipolar disorder for the majority of the 1119 genotyped subjects with AAO and CLES data available occurred between ages 12 and 18 (Fig. 1A). All subjects were from the United States. The distribution of the CLES score in this sample is shown in Fig. 1B. The percentages for AAO less than 12 yrs, 12–18 yrs and greater than 18 yrs were 19%, 43% and 38% respectively. A significant decrease

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