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The genetics of early-onset bipolar disorder: A systematic review

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ABSTRACT

Background: Early-onset bipolar disorder has been associated with a significantly worse prognosis than late-onset BD and has been hypothesized to be a genetically homogenous subset of BD. A sizeable number of studies have investigated early-onset BD through linkage-analyses, candidate-gene association studies, genome-wide association studies (GWAS), and analyses of copy number variants (CNVs), but this literature has not yet been reviewed.

Methods: A systematic review was conducted using the PubMed database on articles published online before January 15, 2015 and after 1990. Separate searches were made for linkage studies, candidate gene-association studies, GWAS, and studies on CNVs.

Results: Seventy-three studies were included in our review. There is a lack of robust positive findings on the genetics of early-onset BD in any major molecular genetics method.

Limitations: Early-onset populations were quite small in some studies. Variance in study methods hindered efforts to interpret results or conduct meta-analysis.

Conclusions: The field is still at an early phase for research on early-onset BD. The largely null findings mirror the results of most genetics research on BD. Although most studies were underpowered, the null findings could mean that early-onset BD may not be as genetically homogenous as has been hypothesized or even that early-onset BD does not differ genetically from adult-onset BD. Nevertheless, clinically the probabilistic developmental risk trajectories associated with early-onset that may not be primarily genetically determined continued to warrant scrutiny. Future research should dramatically expand sample sizes, use atheoretical research methods like GWAS, and standardize methods.

Contents

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1. Introduction

Bipolar disorder (BD) is a severe recurrent illness characterized by episodes of mania and depression (Goodwin and Jamison, 2007). Although it was once believe to primarily affect adults, evidence gathered since the 1980s has shown that it frequently begins in adolescence (Akiskal et al., 1985; Geller and Luby, 1997). This research also began to investigate the symptomatology of early-onset psychiatric disorders in comparison to adult-onset disorders (Akiskal et al., 1985). In the past 15 years, a number of studies have used admixture analysis to argue that bipolar disorder can be defined by two (Javaid et al., 2011; Kennedy et al., 2005; Kroon et al., 2013) or three distinct age-of-onset groups (Coryell et al., 2013; Lin et al., 2006; Severino et al., 2009; Tozzi et al., 2011). The early-onset group has typically been found to have an upper-bound of 18–22 years (Grigoroiu-Serbanescu et al., 2014). Early-onset BD has often been associated with a worse prognosis than late-onset BD, including more psychotic features, drug and alcohol abuse disorders, comorbidity with panic and obsessive–compulsive disorders, rapid cycling, lower lithium-response, and more suicide attempts (Cate Carter et al., 2003; Geoffroy et al., 2013; Grigoroiu-Serbanescu et al., 2014; Javaid et al., 2011; Lin et al., 2006; Perlis et al., 2004), although the specific clinical features associated with an early-onset have not always been consistent (e.g. Coryell et al., 2013; Ernst and Goldberg, 2004).

These findings have been taken as evidence that early-onset BD may have a qualitatively different genetic etiology than late-onset BD. Indeed, there is evidence that the age-of-onset is significantly correlated between siblings of a bipolar proband (Leboyer et al., 1998; Lin et al., 2006; O'Mahony et al., 2002), with heritability estimates for age-of-onset between 0.41 and 0.52 (Faraone et al., 2004; Visscher et al., 2001). Early-onset BD also appears to increase the morbidity risk of BD and other psychotic and affective disorders in relatives to a greater extent than late-onset BD, suggesting that early-onset BD may be a more heritable and severe form of the illness (Grigoroiu-Serbanescu et al., 2001, 2014; Schürhoff et al., 2000; Somanath et al., 2002; Taylor and Abrams, 1981). At least one large study, however, did not find significant familiality of age-of-onset for bipolar disorder (Schulze et al., 2006).

It is worth noting that these studies have often downplayed the role that environmental and developmental factors could play in shaping the clinical features of early-onset BD and the frequency of the disorder in relatives. For instance, one reason individuals who develop BD in adolescence will be more prone to long-term drug abuse than those who develop the disorder in middle age is the availability of narcotics, social pressures, and risk-taking behaviors that characterize adolescence. There do not have to be major genetic differences between early- and late-onset BD for this pattern to occur. A developmental psychopathology perspective could help explain how biological and environmental factors increase or decrease risk of bipolar disorder across the lifespan (Alloy et al., 2006; Klimes-Dougan et al., in press).

Over the past 15 years, a sizeable number of studies have investigated the genetics of early-onset BD, but there has not yet been an effort to review such studies (there have been two review of the genetics of *childhood*-onset BD; see Faraone et al., 2003; Mick and Faraone, 2009). The growing importance of Research Domain Criteria (RDoC) and "subphenotypes" in psychiatrics genetics research (Saunders et al., 2008) makes a review of this literature timely and all the more pertinent, given that early-onset BD has been one of the more studied subtypes of bipolar disorder. Moreover, as genetics research becomes an important source of therapeutic targets for psychopharmacology research, it is crucial to understand the relationship between early- and late-onset BD. Here, we systematically review the findings of these studies from four major methods of genetics research: linkage-analyses, candidate gene-association studies, genome-wide association studies (GWAS), and research on copy number variants (CNVs). We conclude by discussing the current status of the field and conclude by looking at future directions of genetics research on early-onset BD.

2. Methods

We conducted a systematic literature review of articles published (online) before January 15, 2015 and after 1990. Keyword searches were made using the PubMed database. For gene-linkage studies, we used the keywords "linkage AND bipolar disorder AND onset" which returned six papers that met our inclusion criteria. For candidate gene-association studies and genome-wide association studies we used the search terms "polymorphism AND bipolar disorder AND onset." Due to the large number of studies on a variety of polymorphisms, we limited our discussion to candidate genes that have been investigated by at least two papers. Fifty-nine studies were ultimately included. For GWAS, we also used the terms "genome wide association AND bipolar disorder AND onset" and included two studies. For copy number variants (CNVS), we searched the terms "copy number AND bipolar disorder AND onset" and included six studies.

For inclusion, a study must have specifically looked for associations with age-of-onset or "early-onset" BD, and could not have looked at age-of-onset in a mixed mood disorder or mixed-psychosis population. Although we required that DSM criteria for BD be met (either DSM-III or DSM-IV), we did not place any restrictions on the types of BD included such as bipolar I disorder (BDI) or bipolar II disorder (BDII). Historically a range of criteria have been applied children and adolescent BD diagnosis (as reviewed by Klimes-Dougan et al., in press), but the genetic studies reviewed here typically applied a "narrow" DSM definition of BD.

Most genetics research has defined early-onset bipolar disorder as occurring before the age of 18–25 and meeting narrow DSM criteria. We were not strict about the specific cut-off age that a study used to define "early-onset" (e.g. onset before 18 years, 22 years, 25 years, etc.), so long as the study clearly defined its methods. We excluded studies that primarily reported on children or pre-adolescents because the research to date with children rarely uses narrow DSM criteria and the relationship between childhood-onset BD and adult BD is still disputed (see Leibenluft and Rich, 2008). Moreover, two valuable reviews on the genetics of childhood BD have already been compiled (Faraone et al., 2003; Mick and Faraone, 2009).

Three types of studies were included in this review, as each sheds light on a unique aspect of the genetic architecture of early-onset BD: how those with early-onset BD differ from controls, how they differ from individuals with a late-onset, and how genetic