Published in final edited form as:

J Affect Disord. 2015 September 15; 184: 1–12. doi:10.1016/j.jad.2015.05.017.

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

Kevin P. Kennedy, Kathryn R. Cullen, Colin G. DeYoung, and Bonnie Klimes-Dougan*

University of Minnesota, Minneapolis, MN, USA

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.

Keywords

Genetics; Early-onset; Bipolar disorder

*Corresponding author at: 75 East River Parkway, 412 Elliot Hall, Department of Psychology, University of Minnesota, Minneapolis, MN 55455, USA. Tel.: +1 612 626 4347; fax: +1 612 626 2079. klimes@umn.edu (B. Klimes-Dougan).

Conflict of Interest

Disclosures: The authors have no conflicts of interests to disclose. All authors have approved the final article.

Role of funding source

There was no funding source for this review.

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 believed 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 (Grigoriu-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; Grigoriu-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 (Grigoriu-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 familiarity 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 reviews 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 variants affect age-of-onset more generally. One type of study uses the presumed genetic homogeneity of

the early-onset subtype as a way to identify susceptibility genes for BD in small samples. This research stems from the notion that the heterogeneity of BD has hindered genetics studies, even studies using thousands of participants. This branch of research compares an early-onset group to controls, often without comparing them to a late-onset BD group (e.g. GWAS). The second type of study has focused on determining the genetic differences between early- and late-onset BD and compares these two groups directly, often without a comparison to a control. Statistical analysis is typically used to sort patients into two or three separate onset-age groups, based on admixture analysis for the specific sample or on an arbitrary cut-off. The third type of study makes no effort to classify patients as early- or late-onset. Instead, it simply attempts to find an association between age-of-onset and a genetic variant. This type of analysis is often applied as an addendum to studies where age-of-onset data were collected for each participant.

Because this is a relatively new field, we did not set a minimum sample size or require the use of specific types of statistical analysis. Admittedly, the sample sizes of some studies were quite small, but we felt that it was useful to report results even if this research might be considered preliminary or have methodological limitations. We generally made note of the specific methodology used by each study, given that these parameters could influence the genetic heterogeneity of the sample and therefore the results of gene-associations. The small number of studies and the wide variance in methodology were two reasons that we did not attempt to meta-analyze or bundle these studies.

3. Linkage studies

Linkage analysis is a low-resolution molecular genetics technique that is able to implicate chromosomal regions that harbor variants with large phenotypic effects. More than 40 linkage studies have been conducted on BD. They have implicated regions on nearly every chromosome and findings have rarely been consistently or convincingly reproduced (Barnett and Smoller, 2009; Juli et al., 2012). Many researchers have interpreted these results as evidence that BD is not caused by common variants with large effect sizes, but by a large number of common variants of small effect size and/or very rare variants with much larger effect sizes (Craddock and Sklar, 2013; Gratten et al., 2014).

A small number of linkage studies have been conducted on early-onset BD, either on the disorder directly or by re-analyzing data from previous linkage studies on BD. Faraone et al. (2004) applied multipoint variance-components linkage analysis to the NIMH BD Genetics Initiative linkage study, consisting of 539 individuals in 97 families. They found that regions 12p, 14q, and 15q had minor (non-significant) associations with age-of-onset. Faraone et al. (2006) employed an ordered-subset analysis for early-onset BD (<20 years) on the same sample, which did not replicate the three previously-implicated regions. Chromosome 9q34 was implicated among the early-onset population, though this association was no longer significant after correcting for multiple comparisons. Lin et al. (2005) found that early age-of-onset (< 21 years) was associated with chromosomes 18p11.2 (LOD=2.83) and 21q22.13 (LOD=3.29) in a scan of 150 multiplex pedigrees with 874 individuals. Neither of these regions was implicated in a later study (Zandi et al., 2007), although this study did find a slight trend of linkage on 18p, given that the LOD increased from 0.0 to 1.03 when age-of-

onset was included in the analysis. In this later study, Zandi et al. did not find any region significantly associated with an early-onset (< 21 years). No positive finding from any linkage study was significantly replicated in a second study.

Etain et al. (2006) performed a linkage scan on 87 sibling pairs in which a proband had an early-onset (< 21 years) of a mood disorder, with 29 sib-pairs having a proband with early-onset BD-I (the “narrow” phenotype). The study found three associations with the narrow early-onset group (3p14, 5q33, and 16q23) and six with the broad phenotype. These eight regions were evaluated in 51 new families in addition to the previous sample by Mathieu et al. (2010). When comparisons were made between early-onset and late-onset siblings, only the 2q14 region was significantly associated with the early-onset BD-I subtype. However, a candidate gene-association study by the same research group (Etain et al., 2010) found SNPs in the 20p12 region that were associated with the early-onset subtype, specifically synaptosomal-associated protein of 25 kDa (SNAP25).

Taken together, linkage studies on early-onset BD have returned conflicting results that have very rarely been replicated. However, as Mathieu et al. (2010) pointed out, these studies have employed noticeably different methodologies that may have contributed to the inconsistent findings, including types of statistical analyses, sample sizes, definitions of age-of-onset, inclusion of BD-II, and criteria for selecting affected families. These inconsistencies make it difficult to assess the results of current linkage studies. The fact that these regions have generally not been replicated by other candidate gene or GWAS may suggest that the vast majority of causal variants are still too small to show up in linkage analyses, even when using a more homogenous subtype. In this regard, linkage studies suggest that early-onset BD appears to have a similar genetic etiology as adult BD: many common polymorphisms with small effect and very rare variants with larger effects.

4. Candidate gene-association studies

Candidate gene-association studies detect associations among a small number of single nucleotide polymorphisms (SNPs) derived from *a priori* hypotheses about the neurobiological mechanisms of a disorder. Hundreds of candidate gene-association studies have been conducted on BD, with most focusing on genes related to serotonin, dopamine, glutamate, and brain-derived neurotrophic factor (BDNF) (Juli et al., 2012; Seifuddin et al., 2012). Like linkage analyses, these studies have primarily yielded inconsistent findings. A recent meta-analysis reviewed 487 candidate gene studies and found SNPs in only four genes with nominal significance before correcting for multiple comparisons: *BDNF*, *DRD4*, *DAOA*, and *TPHI* (Seifuddin et al., 2012). None was significant after this correction. Neither were these polymorphisms significantly implicated in any of the 15 major genome-wide association studies (GWAS) on BD (Shinozaki and Potash, 2014). These negative results are not entirely surprising, given the substantial evidence that the majority of causal genetic variants in BD are common with very small effect sizes (OR=1.05 to 1.20) (Craddock and Sklar, 2013; Gratten et al., 2014). Large sample sizes are needed to detect an association, and even then, the polymorphism will only weakly increase risk of the disorder.

A sizeable number of candidate gene-association studies have been conducted on the early-onset subtype. Here, we report research only on polymorphisms and genes that have been investigated by at least two studies that met the criteria described above. However, we also describe single studies when they focused on biological systems or pathways that have been the subject of many early-onset BD gene-association studies (e.g., dopaminergic genes, oxidative stress, etc.). Candidate genes that have been investigated by only one study that nonetheless met our inclusion-criteria include: dysbindin-1 (*DTNBP1*); neurotrophic tyrosine kinase receptor 2 and 3 (*NTRK2* and *NTRK3*); *G72/G30 (DAOA)*; FYN kinase; the methylenetetrahydrofolate reductase (*MTHFR*); the nicotinic acetylcholine receptor; the norepinephrine transporter; G protein-coupled receptor 50 (*GPR50*); apolipoprotein E; the L-type calcium ion channel subunit *CACNA1C*; and the nuclear receptor *NR2E1*. Although candidate gene-association studies on early-onset BD have the advantage of using a subtype that possibly has a more homogenous presentation than mixed age-of-onset population, these studies have typically employed small populations (<300 cases) and very few positive findings have been independently replicated. Therefore, these results should be interpreted cautiously.

4.1. Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor (BDNF) regulates neuronal survival, differentiation, maintenance, synaptic plasticity, and axon growth (Huang and Reichardt, 2001). There is compelling evidence that BDNF is involved in the pathophysiology of BD, including involvement in lithium response (Rybakowski et al., 2005) and being inversely correlated to the severity of manic and depressive symptoms (reviewed in Scola and Andreazza, 2015; Tang et al., 2008). Most candidate gene-association studies on *BDNF* have focused on the valine to methionine substitution at codon 66, which has been associated with rapid cycling (Müller et al., 2006), smaller grey matter, and lithium responsiveness (see Wu et al., 2014). Surprisingly, no polymorphisms in *BDNF* have been significantly associated with BD in the largest meta-analysis of candidate gene-association studies (Seifuddin et al., 2012) or in the largest GWAS on BD (Shinozaki and Potash, 2014).

Tang et al. (2008) searched for two polymorphisms in *BDNF*, Val66Met (r6265) and C270T, in an early-onset (<18 years, $n=67$) and late-onset population ($n=130$). They found a significant increase in the Val allele in the early-onset population compared to the late-onset group, but no association between *BDNF* and BD as a whole. Rybakowski et al. (2003) found that the Val/Val genotype was significantly associated with an earlier onset than the Val/Met genotype, but the sample size was quite small ($N=54$) with only one individual with the Met/Met genotype. Conversely, Skibinska et al. (2004) found an association between the Met/Met genotype and early-onset BD (< 18 years; $p=.03$) but not for the alleles, but this study was limited by a very small early-onset population ($n=28$) and only 3 early-onset cases with Met/Met. Miller et al. (2013) also found that the Met allele was associated with a 35% earlier onset among individuals with childhood sexual abuse, but this association was not significant after regression analysis. Two larger studies did not find any association between Val66Met and age-of-onset: Kunugi et al. (2004) ($N=519$ cases) and Neves-Pereira et al. (2002) ($N=283$ cases). At least one study has implicated *BDNF* in pre-pubertal and early-adolescent BD (Geller et al., 2004), though a later study ($N=170$ cases) failed to replicate

this association (Mick et al., 2009). Thus, the fact that the positive results have only come from very small studies suggests that these findings are false positives. Still, all of these studies have been fairly small. Larger samples are needed to convincingly confirm the involvement of *BDNF* in early-onset BD.

4.2. Dopamine receptor genes

The five dopamine receptors have been connected to cognitive impairments, memory and learning, reward and reinforcement, and stress response, and have been implicated in a range of psychiatric conditions, including alcoholism, schizophrenia, BD, ADHD, and depression (Brisch, 2014; Glatt et al., 2015; Noble, 2003). Dozens of studies have been conducted on the different dopamine receptor genes in adult BD, but no finding has remained significant in meta-analysis after Bonferroni correction (Kirov et al., 1999; Seifuddin et al., 2012). A small number of studies have evaluated the dopamine receptor genes in early-onset BD. Two studies have looked at the gene for the D1 receptor (*DRD1*), specifically the –48A/G polymorphism in *DRD1*, and age-of-onset in BD and schizophrenia. Among 380 BD cases, Dmitrzak-Weglarz et al. (2006) found that the G/G genotype was associated with a BD onset after 18 years and with BD-II, but not with schizophrenia or BD in general. Ni et al. (2002) not find an association between age of onset in BD and three *DRD1* polymorphisms (–48A/G, –800T/C, and –1403T/C) in 286 BD trios.

Other studies have focused on the gene for the D2 receptor. Squassina et al. (2011) identified an association between the *DRD2* TaqIA polymorphism and early-onset BD (< 21 years) in 300 BD cases. A study looking at 339 Polish BD cases found no association between BD and the *DRD2* –141C ins/del polymorphism, including in 29 early-onset BD cases (<18 years; Leszczyńska-Rodziewicz et al., 2005). Serretti et al. (1999a) found an association between *DRD2* and disorganized symptoms in a very small sample of early-onset BD (<25 years, $n=13$). Massat et al. (2002) found a significant association between *DRD2* and BD in 358 cases that was also significant between early-onset BD (< 25 years) and controls. Thus, if *DRD2* plays any role in the etiology of BD, it is likely a general risk factor, not one specific for early-onset. In this same study, the Ser9Gly polymorphism in *DRD3* was not associated with BD, MDD, or with early-onset BD.

With regards to the gene for the D4 receptor, Gonçalves et al. (2012) found an association for the *DRD4* variable number of tandem repeat (VNTR) 7-repeat allele and a 2.7 year earlier onset in BD ($p=.03$; $N=274$ BD subjects). This VNTR was also associated with a late onset in females with schizophrenia. The 7-repeat (7R) allele in exon 3 causes functional changes to the G-protein-coupled receptor, making it less responsive to dopamine (Gonçalves et al., 2012). By contrast, Serretti et al. (1999b) did not find any association between *DRD4* exon 1 and 3 variants and early-onset BD (<25 years) in 210 BD-I and BD-II subjects. *DRD5* has not been investigated by a (published) candidate gene-association study in an early-onset population. Finally, two studies have looked for an association between early-onset BD and polymorphisms for tyrosine hydroxylase (the rate-limiting enzyme in the biosynthesis of the catecholamines) but neither has found any significant association (Ho et al., 2000; Souery et al., 1999).

4.3. Catechol-O-methyltransferase (COMT)

Catechol-*O*-methyltransferase (COMT) is a methylation enzyme located on chromosome 22q11.2 involved in the catabolism of catecholamines (dopamine, epinephrine, and norepinephrine). The Val/Met polymorphism (rs4680) has been the primary subject of gene-association studies and has implicated in schizophrenia, anxiety disorder, and BD (Glatt et al., 2015). The Met allele results in 3-to-4 fold lower COMT activity, resulting in increased synaptic dopamine (reviewed in Brisch, 2014). Although *COMT* has not been implicated in the largest meta-analysis of gene-association studies, one meta-analysis found a significant association among Asians but not among Caucasians, showing that it may have a specific role only in certain ethnicities (Zhang et al., 2009).

Only a few studies have evaluated the role of *COMT* in the etiology of early-onset BD. In one study, Massat et al. (2011) found an association between the Val/Met polymorphism and early-onset BD (<18 years) in 147 cases. Associations with rs2075507 and rs4818 lost significance after correcting for multiple comparisons. Zhang et al. (2009) also found an association between the Val/Met SNP and early-onset BD (<20 years) that lost significance after the Bonferroni correction. Benedetti et al. (2011) did not find an association between the Val/Met polymorphism and age-of-onset in 163 BD-I individuals. Two candidate studies on *COMT* in pre-pubertal and early-adolescent BD also failed to find an association (Mick et al., 2009; Geller and Cook, 2000).

4.4. Serotonin transporter and receptor genes

Serotonin is one of the major neurotransmitters and has been implicated in a wide range of psychopathology, including BD and major depression (see Glatt et al., 2015; Mann, 1999). Although serotonin-related genes have been popular targets in candidate gene-association studies on BD, almost none have been validated by meta-analyses or GWAS (Seifuddin et al., 2012). A moderate number of studies have investigated the role of serotonin-related genes in early-onset BD with conflicting results.

The serotonin transporter returns serotonin from the synapse to the pre-synaptic neuron, effectively decreasing the amount of neurotransmitter in the synapse (see Glatt et al., 2015). Two polymorphisms in the serotonin transporter gene *SLC6A4* have been the major targets of investigation: the variable-number tandem repeat (5-HTT-VNTR) and the 5-HTTLPR polymorphism in the promoter (44-bp insertion/deletion), both of which affect transcription of the gene (see Glatt et al., 2015). A recent meta-analysis involving 3778 cases and 4997 controls attempted to account for the heterogeneity of studies on 5-HTTLPR and found that the Short allele slightly increased risk of BD in European populations (OR=1.10; Jiang et al., 2013).

In a small sample ($N=83$), Yen et al. (2003) did not find an association between BD age of onset and genotype or allele frequencies of the 5-HTT-VNTR. Among 216 patients with BD, Bellivier et al. (2002) found that the 5-HTT-VNTR polymorphism was significantly associated with age-of-onset, but that the 5-HTTLPR polymorphism was not. In 88 BD cases, Gutierrez et al. (1998) did not detect any association between the VNTR or 5-HTTLPR polymorphisms, with BD in general or with age-of-onset. Mendlewicz et al.

(2004) found no association for the 5-HTTLPR polymorphism with age-of-onset in BD or with BD in general ($N=572$ BD cases). By contrast, Pinto et al. (2011) did find a significant association between an earlier age of onset and the Short allele of the 5-HTTLPR polymorphism ($p=.02$) in 350 BD patients and 693 unaffected relatives. Manchia et al. (2010) and Mohammadi et al. (2015) also found an association for earlier-onset and the Short allele of the 5-HTTLPR polymorphism in 230 and 150 BD patients, respectively. Conversely, among 83 patients with BD, Serretti et al. (2004) found a trend towards the Long allele being associated with a lower age of onset ($p=.07$). Ospina-Duque et al. (2000) did not find a significant difference between the Short and Long alleles and age-of-onset in 85 BD cases, although the Short allele was overrepresented in early-onset cases (<21 years). Two other studies failed to find an association between pre-pubertal and early-adolescent BD and the 5-HTTLPR polymorphism (Geller and Cook, 1999; Mick et al., 2009).

Among other serotonin-related genes, Massat et al. (2007) found an association between early-onset BD (<16 years) and Cys23Ser polymorphism of the serotonin 2C receptor gene (*HTR2C*). In 151 Kurdish–Iranian BD-I patients, however, Mohammadi et al. (2015) did not find a significant overrepresentation of the *HTR2C* Ser allele in early-onset cases (<19 years). Massat, Souery et al. (2000) did not find an association between polymorphisms in the serotonin 2A receptor gene (*HTR2A*) and early-onset BD (<25 years), or with BD in general. Ni et al. (2002) also failed to find a significant association between *HTR2A* and age-of-onset among 286 BD trios. Kim et al. (2014) found no association between the functional polymorphism C(−1019)G (rs6295) of the serotonergic 1A receptor (*HTR1A*) and BD, including subset analysis for age-of-onset. Only one study has studied early-onset BD and the gene for tryptophan hydroxylase 2 (*TPH-2*), which encodes the rate-limiting step in the biosynthesis of serotonin. In 190 BD-I patients, Grigoriu-Serbanescu et al. (2008) found significant associations for four *TPH-2* SNPs in an early-onset BD group (<25 years, $n=107$), but not for BD in general. Taken together, there is little convincing evidence that serotonin-related genes play a significant role in the etiology of early-onset BD.

4.5. Genes related to immunity, inflammation, and oxidative stress

In the past 10 years, immune function, inflammation, and oxidative stress have been increasingly implicated in the etiology of psychiatric illnesses, including BD (e.g. Andreazza, 2012; Goldstein et al., 2009; Kim et al., 2007). Only a small number of studies have investigated these genes in relation to BD and early-onset BD, but this is a growing area of research.

The Toll-like receptors (TLR) are pattern recognition receptors that play an important role in innate immunity against microbial pathogens and trigger pro-inflammatory pathways (Moresco et al., 2011). Two recent papers have implicated the role of TLR-2 and TLR-4 in the pathogenesis of early-onset BD (<22 years). Oliveira et al. (2014) found two SNPs in the *TLR4* gene that were associated with BD and early-onset BD (rs1927914 and rs11536891). Oliveira et al. (2014) investigated the presence of candidate polymorphisms in the *TLR2* gene among 229 early-onset and 342 late-onset BD cases. The authors found that TLR2 rs3804099 TT and TLR2 rs4696480 TT were significantly associated with the early-onset BD group.

Xu et al. (2009) linked early-onset BD (< 24 years) to two haplotypes in the nonselective calcium ion permeable transient receptor potential melastatin type 2 gene (*TRPM2*) in 300 families with a bipolar spectrum disorder proband. This gene is involved in immune-system function, oxidative stress, and apoptosis (Nilius et al., 2007), and has been inconsistently implicated in adults with BD (McQuillin et al., 2006). In 183 BD subjects, Roh et al. (2007) failed to find any relationship between BD, age-of-onset, and the cytokine gene monocyte chemoattractant protein-1 (MCP-1), which is involved in immune function, the regulation of neurotransmission, and the regulation of other proteins implicated in BD, like NMDA receptor 1 and glycogen synthase kinase 3 (GSK-3) (see Roh et al., 2007).

Three studies have investigated the relationship between age-of-onset in BD and *X-box binding protein 1 (XBP1)*, which encodes a transcription factor involved in the regulation of MHC class II genes, T cell genes, and the endoplasmic reticulum (ER) stress response. A large meta-analysis found a significant association between the *XBP1* and BD among Asians, but not among BD in Caucasians (Cheng et al., 2014). Findings in the early-onset BD population have also been mixed: Kakiuchi et al. (2003) found an association with age-of-onset and *XBP1*, while Cichon et al. (2004) and Hou et al. (2004) failed to find an association.

Finally, two papers have investigated the relationship between early-onset BD and genes involved in oxidative stress, specifically the genes for the glutathione *S*-transferases. Glutathione *S*-transferases (GSTs) help neutralize reactive oxygen species, which can cause damage to biomolecules and lead to cell death. Oxidative stress has been implicated in the etiology of BD (Andreazza et al., 2008; Andreazza, 2012), and serum levels of glutathione have been associated with age-of-onset (Rosa et al., 2014). Mohammadynejad et al. (2011) investigated genes for GSTs in 228 patients with BD and found that neither *GSTM1* nor *GSTT1* were associated with risk for the disorder. However, a combination of the positive genotype for *GSTM1* and the null genotype of *GSTT1* significantly increased risk of BD among the early-onset, but not late onset, group (OR=2.28). A 2012 study by Rezaei, Saadat, and Saadat looked for associations with polymorphisms for glutathione *S*-transferase Z1 among 228 individuals with BD. They found that early-onset BD (< 19 years) was associated with polymorphisms at Glu32Lys and G-1002A in GSTZ1, along with the haplotype “-1002G, 32Glu, 42Gly”.

4.6. Circadian rhythm and clock genes

There has been consistent evidence linking disruptions in circadian and social rhythms to the onset of BD (Murray and Harvey, 2010). A handful of studies have investigated polymorphisms in genes related to biological clocks and circadian rhythms in adult BD (Milhiet et al., 2011, 2014; see Murray and Harvey, 2010) and in the early-onset subtype, but the findings are conflicting and unconvincing.

One oft-studied gene is that of glycogen synthase kinase 3- β (GSK3- β), which has a diverse range of functions including the regulation of transcription factors and involvement in the biological clock (Grimes and Jope, 2001). GSK3- β is also inhibited by lithium and valproate (Gould and Manji, 2005). Two studies found that the -50T/T (rs334558) genotype in the effective promoter region for the gene encoding GSK3- β was associated with age-of-onset in

185 Italian patients with BD-I, but not with BD in general (Benedetti et al., 2004a, 2004b). Most studies published after this initial finding have not replicated it (Lee and Kim, 2011; Lin et al., 2012; Szczepankiewicz et al., 2006), including a meta-analysis of six studies involving 649 BD-I patients (Chen et al., 2014). In 118 patients with BD, Lee and Kim (2011) found that the $-172A/T$ polymorphism was associated with age-of-onset. Lin et al. (2012) investigated a sample of 138 Taiwanese BD-I patients and found that $-157C/T$ (rs6438552) was associated with older onset BD in females. Both of these studies did not find an association with the polymorphisms and BD in general.

In regards to other circadian-rhythm genes, Benedetti et al. (2008) found that age-of-onset was associated with a variable-number tandem repeat (VNTR) polymorphism in the Period 3 (Per3) gene, which is involved in the biological clock. Artioli et al. (2007) found that two exonic polymorphisms in Per3 were associated with age-of-onset (T/G in exon 15 and T/C in exon 18). Severino et al. (2009) investigated SNPs in the REV-ERB α gene (NR1D1) in 300 bipolar patients of Sardinian ancestry. REV-ERB α interacts with GSK3- β to synchronize the biological clock (Yin et al., 2006). One haplotype was associated with late-onset BD (>38 years) and one SNP (rs12941497) was associated with the early-onset group, but no associations were found for BD in general. McGrath et al. (2009) found associations between *RORB* and BD, but not for early-onset BD. Lee et al. (2010) found an association between the $-3111T/C$ SNP (rs1801260) in the CLOCK gene and BD, but not with age-of-onset in BD.

4.7. Linkage-analysis driven candidate gene-association studies

With the evidence that the vast majority of candidate gene-association studies have returned null or conflicting findings, a number of papers have pointed out that the candidate gene approach necessarily relies on current (and inherently speculative) theories of the neurobiology of mental disorders (Barnett and Smoller, 2009; Craddock and Sklar, 2013; Seifuddin et al., 2012). In recent years, research groups have attempted to avoid the limitations of the theory-driven selection of candidate genes by using the results of linkage studies to locate candidate genes. Three studies have used this technique to study early-onset BD, which has led to the implication of three genes: *ADRB2* (encoding the beta-2-adrenergic receptor OMIM 109690; Dizier et al., 2012); *SNAP25* (encoding the synaptosomal-associated protein of 25 kDa; Etain et al., 2010); and the SNP rs1156026 (perhaps related to *Diacylglycerol kinase eta* [*DGKH*] or the *serotonin receptor 2A* [*HTR2A*]; Bureau et al., 2013). Given that none of these studies has been replicated, these results can only be interpreted cautiously. Still, the use of atheoretical methods to identify candidate genes in small populations is a positive step for the field.

5. Genome-wide association studies

Genome-wide association studies (GWAS) enable the detection of common SNPs (typically in >5% of the population) across the vast majority of the genome. Despite the substantial evidence that BD is highly heritable, GWAS have implicated only a very small number of polymorphisms, including ones in genes for calcium ion channel subunits (e.g. *CACNA1C*) and cell-surface or extracellular matrix proteins involved in inter-cellular communication

(e.g., *ODZ4*, *ANK3*, *NEK4-ITIH1,3,4*, and *NCAN*; see Shinozaki and Potash, 2014; Sklar et al., 2011). The paucity of findings is almost certainly due to the fact that the common SNPs involved in complex mental illnesses have very small effects, meaning that *extremely* large samples are required to identify any causal polymorphisms (Gratten et al., 2014). Nonetheless, there is compelling evidence that common SNPs constitute a large fraction of susceptibility to BD (roughly 25%) and can be identified in GWAS with extremely large samples (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

We identified only two GWAS that have examined age-of-onset in BD (Jamain et al., 2014; Mahon et al., 2011). Both investigated the early-onset subtype primarily to reduce the heterogeneity of the sample rather than to identify differences between early- and late-onset BD. Neither found any SNPs that achieved the stringent genome-wide statistical significance but both were underpowered: Jamain and colleagues included a total of 370 early-onset cases and over 2400 controls while Mahon et al. included 2744 controls and 2836 BD cases with information about age-of-onset and psychotic symptoms. With such small sample sizes, it was very unlikely that either study could have detected a causal variant in early-onset BD. Nevertheless, these negative results suggest that the genetic architecture of early-onset BD is likely composed of many common variants with small effects, similar to adult BD. Moreover, these studies cast doubt on the idea that the early-onset subtype has enough genetic homogeneity to require significantly fewer participants than conventional GWAS on adult BD.

6. Copy number variants (CNVs)

Since the completion of the Human Genome Project, researchers have primarily investigated the role of common SNPs in the etiology of psychiatric disorders. Recently, there has been growing interest in the role of structural variations in mental illness, primarily the rare but large (>1000 bp) duplications and deletions called copy number variants (CNVs). Although CNVs are far less common than SNPs, each CNV tends to be much more pathogenic, given its greater size and functional impact on the genome. Gratten et al. (2014) reported that common SNPs will typically have odds-ratios of ~1.05–1.2 while rare CNVs will have odds-ratios of ~2 to >20. Interest in CNVs has also stemmed from evidence that common SNPs are responsible for roughly 17–29% of variance in liability for common mental illnesses (24–26% in BD; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Lee and Chow, 2014; Yang et al., 2011), meaning that a substantial proportion of liability must not come from common SNPs. Rare SNPs and rare CNVs could represent two major sources of this liability. A number of studies have investigated the role of CNVs in early-onset BD, and can be grouped into two categories: the total number (burden) of CNVs in the genome and the frequency of *de novo* CNVs.

6.1. Total number (burden) of CNVs

There is compelling evidence that the burden of CNVs in the genome (total number of both *de novo* and inherited CNVs) is elevated in a number of psychiatric disorders, particularly autism (Pinto et al., 2010; Sanders et al., 2011), schizophrenia (Rees et al., 2014; Sebat et

al., 2009; Walsh et al., 2008), intellectual disability/developmental delay (Coe et al., 2014; Girirajan et al., 2012), and ADHD (Williams et al., 2010).

A small number of studies have investigated the burden of total CNVs in BD. The majority have not found an elevated number of CNVs in BD compared to controls (Grozeva et al., 2010, 2013; McQuillin et al., 2011; Noor et al., 2014; Priebe et al., 2012). In fact, at least three studies have found lower rates of CNVs in BD than in controls, especially for very large (>1 Mb) CNVs (Georgieva et al., 2014; Grozeva et al., 2013; McQuillin et al., 2011). Two studies have found an increased burden of CNVs in cases of early-onset BD, one of which focused on singleton deletions (Priebe et al., 2012; Zhang et al., 2009). However, two studies with comparable sample sizes failed to replicate this result (Grozeva et al., 2013; Noor et al., 2014). Even in the studies that associated CNVs with early-onset BD, the effect size was fairly small (OR around 1.5), suggesting that these CNVs are not the major source of liability that some rare variant models predicted.

6.2. De novo CNVs

There is inconsistent evidence that the frequency of *de novo* CNVs (variants in a child's DNA that are not in either parent's) is increased in BD or early-onset BD. The earliest report of increased *de novo* CNVs in BD came from Malhotra et al. (2011) who found *de novo* CNVs in 4.3% of 185 BD probands (OR=4.8), 4.5% of schizophrenia probands (OR=5.0), and 0.9% of 426 healthy controls. The rate of *de novo* CNVs was 5.6% (OR=6.3) among individuals with an onset before 18. A recent meta-analysis of 768 parent-child trios, however, only found a significant difference in CNVs between BD patients and controls for the less stringent CNV threshold (>10 kb) and not for the more stringent one (>100 kb) (Georgieva et al., 2014). Furthermore, no study has found an association between the frequency of *de novo* CNVs and age of onset (Georgieva et al., 2014; Noor et al., 2014), although most of these studies are likely underpowered given the rarity of *de novo* CNVs.

7. Discussion

The findings from this review highlight the nascent status of genetics research on early-onset BD. Across four major molecular genetics methods, there is little convincing evidence of differences in the genetic architecture of early- and late-onset subtypes of BD. In one sense, the lack of findings from this research is not surprising. Thus far, most genetics research on complex mental illnesses (including adult BD) has had only limited success in identifying causal genetic variants, particularly when using linkage analysis and candidate gene-association studies. There is a growing consensus among researchers that heightened vulnerability for BD is associated with thousands of common SNPs with small effects and by a small number of rare variants with larger effects (Craddock and Sklar, 2013; Gratten et al., 2014; Shinozaki and Potash, 2014; for disagreement see Cirulli and Goldstein, 2010). Currently, most common variants can only be detected by using GWAS with extremely large sample sizes that are relatively homogenous. Rare variants are most easily detected by using high-resolution techniques like whole-exome or whole-genome sequencing (or with GWAS, in the case of CNVs). Genetics research on early-onset BD has typically been vastly underpowered and has employed techniques that are ill-equipped to detect common and rare

variants, like low-resolution linkage studies. As this review indicates, they have primarily offered negative, conflicting, and irreproducible findings.

Candidate gene-association studies of early-onset BD have also been plagued by inconsistent and irreproducible results. While dozens of studies have been conducted on a wide-range of polymorphisms, these studies have generally been underpowered and have employed varying methodologies (e.g. defining early-onset differently, using mixed BD-MDD populations, using mixed ethnicities, etc.) which have hindered efforts at generalizing or replicating findings. In general, there have been too few attempts to replicate polymorphisms that have previously been implicated, especially in much larger populations. As a result, there are now a large (and growing) number of genes that have been tentatively associated with BD but few that have been robustly implicated or excluded. Before testing new theories of candidate genes, a concerted effort should be made to identify a very large population of early-onset BD patients who can be enrolled in GWAS or gene-association studies that test all of the currently-implicated polymorphisms. The largest GWAS on schizophrenia, for instance, has uncovered 128 polymorphisms at 108 loci after using over 36,000 cases and 113,000 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Assembling sample sizes this large will require coordinated effort of many research groups at many institutions or nation-wide initiatives. Although this undoubtedly will be an difficult a task, it is increasingly apparent that a small number of large-scale studies are far more valuable than a large number of underpowered studies that neither prove nor disprove an hypothesis (as the null and conflicting findings reviewed in this paper serve to demonstrate).

Research on CNVs is another place where larger sample sizes are needed to determine the role of CNVs in early onset BD. Despite the discrepancies between some studies, current evidence indicates that there does not seem to be a major difference in the burden of total CNVs or *de novo* CNVs in early-onset cases. It seems possible that the very rare variants with large effect-sizes are not CNVs, but very rare SNPs that are not detectable on current microarrays. These would require detection by whole exome or whole genome sequencing. Despite being a relatively new field, exome sequencing has already been applied to adult BD to search for highly penetrant rare variants (in <1% of population) with some success (e.g. Kato, 2015).

In future studies on early-onset BD, efforts should be made to standardize methodology. There is a pressing need for genetics studies to use a consistent definition of “early-onset” and “late-onset.” It is difficult to compare studies or to conduct meta-analyses when the definition of “late-onset” or “early-onset” varies by as much as 10 or 15 years between studies. Participants who are classified as “early-onset” in one study are often defined as “late-onset” by a different study looking at the same polymorphisms. While age is only a rough estimate of development, a greater consensus in the field about these issues would be optimal.

Similarly, efforts to standardized methodology will require a closer look at diagnostic considerations. It may be advisable to restrict the sample to a single type of BD (e.g. BD-I). Although there is still considerable debate regarding the relationship between DSM

classifications and genetic homogeneity, it is likely that homogeneity gained by studying the early-onset phenotype will be negated by including the full range of BDs, especially when there is evidence of substantial genetic heterogeneity among the bipolar disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). This discussion about diagnostic inclusion criteria has been especially salient when the focus is on a population who is continuing to undergo development, leading to ongoing, lively debates in the field about what features of BD are represented early in development, how these characteristics change across development, and methods of altering the probabilistic risk trajectories (Klimes-Dougan et al., in press).

It is also possible that phenotypic and endophenotypic features may be better markers of genetic homogeneity, especially when one considers the significant variation in the symptom profile of those with early-onset BD (e.g. Coryell et al., 2013). Such phenotypic features include measures of affective temperament (Greenwood et al., 2012), dimensional analysis of symptoms (Labbe et al., 2012), analysis of multi-dimensional phenotypes like brain structure/function relationships (Schumann, 2014), and endophenotypes like cognitive deficits and resting state brain activity (Gottesman and Gould, 2003; Hall and Smoller, 2010; Hasler et al., 2006; Hasler and Northoff, 2011). One study combined GWAS with fMRI of amygdala activation in a small sample of youth with BD and identified a SNP in the gene DOK5 that accounted for 33% of the variation in amygdala activation in the BD sample compared to 12% of the variance in the controls (Liu et al., 2010). On the other hand, a large study conducted at the University of Minnesota cast doubt on the idea that endophenotypes can simplify genetics research by showing that endophenotypes are “massively polygenic” and are “not sufficiently simpler genetically to aide in gene discovery” in a sample of nearly 5000 participants (Iacono et al., 2014).

Although it is clear that the heterogeneity and genetic complexity of BD has hindered the elucidation of the genetic etiology of BD, molecular genetics research has not offered compelling evidence that early-onset BD has sufficient genetic homogeneity to be advantageous in research. Currently, none of the papers reviewed convincingly shows that the use of the early-onset subtype allowed for the detection of associations that would not be present in a mixed-age-of-onset population. Neither is there evidence that the use of an early-onset group enabled the detection of polymorphisms with smaller sample sizes than in a conventional study. The null findings even raise the question of whether early-onset bipolar disorder is qualitatively different from the adult-onset disorder. If nothing else, the negative findings indicate that the early-onset subtype has sufficiently genetic overlap with adult BD that their differences cannot be detected with low-resolution probes and small samples. When we recognize that environmental and developmental factors could help account for the age-of-onset clusters (Alloy et al., 2006), it is very possible that early-onset BD is a (quantitatively) more severe form of BD, and that both disorders can be best situated along the bipolar spectrum. If there are major genetic differences between early-onset and late-onset BD, it seems that the use of GWAS and high-resolution techniques will be needed to identify them. At a minimum, GWAS could definitively calculate the genetic heterogeneity between patients with different ages-of-onset and the proportion of common SNPs that comprise each subtype, much as it has for adult BD (see Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

In total, the idea that early-onset BD has a large degree of homogeneity and a unique genetic etiology is an interesting theory but one that has not yet been successful in practice. Small sample sizes and varying methodologies have hindered the progress of this research. Nonetheless, the attempt to use narrow phenotypic features to study an illness is a positive direction for the field to take and there have already been very interesting preliminary studies conducted on candidate genes involved in a wide range of biological pathways, including oxidative stress, immune function, and inflammation. For assurance that these results are true-positives, however, these studies should be replicated in GWAS with large sample sizes. Large-scale collaborative efforts employing atheoretical genetics research (e.g. GWAS, whole exome sequencing, and whole genome sequencing) are the most promising way forward.

8. Limitations

The central limitation of this review is the small sample sizes of the studies included, many of which evaluated early-onset BD through subset analysis. In some cases, this led to very small samples ($N < 30$) which have difficulty implicating many causal polymorphisms. These studies were included to show where preliminary genetics research has been conducted on early-onset BD. A second limitation is that meaningful meta-analysis could not be conducted on this research, given the varying methods used by the studies. Thus, for some genetics methods, this review explores the state of the field more than it can definitively implicate genetic variants in early-onset BD.

Acknowledgments

The authors express their deep gratitude to Irving Gottesman for offering feedback on the paper. They also thank Brian Aplan for help compiling references and Kristen Doucette for proof-reading the paper. There were no funding sources for this review.

References

- Akiskal HS, Downs J, Jordan P, Watson S, Daugherty D, Pruitt DB. Affective disorders in referred children and younger siblings of manic-depressives: mode of onset and prospective course. *Arch Gen Psychiatry*. 1985; 42(10):996–1003. <http://dx.doi.org/10.1001/archpsyc.1985.01790330076009>. [PubMed: 4037989]
- Alloy LB, Abramson LY, Walshaw PD, Keyser J, Gerstein RK. A cognitive vulnerability-stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. *Dev Psychopathol*. 2006; 18:1055–1103. <http://dx.doi.org/10.1017/S0954579406060524>. [PubMed: 17064429]
- Andreazza AC, Kauer-Sant'Anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, Yatham LN. Oxidative stress markers in bipolar disorder: a meta-analysis. *J Affect Disord*. 2008; 111(2–3):135–144. <http://dx.doi.org/10.1016/j.jad.2008.04.013>. [PubMed: 18539338]
- Andreazza AC. Combining redox-proteomics and epigenomics to explain the involvement of oxidative stress in psychiatric disorders. *Mol Biosyst*. 2012; 8:2503. <http://dx.doi.org/10.1039/c2mb25118c>. [PubMed: 22710408]
- Artioli P, Lorenzi C, Pirovano A, Serretti A, Benedetti F, Catalano M, Smeraldi E. How do genes exert their role? Period 3 gene variants and possible influences on mood disorder phenotypes. *Eur Neuropsychopharmacol*. 2007; 17:587–594. <http://dx.doi.org/10.1016/j.euroneuro.2007.03.004>. [PubMed: 17512705]
- Barnett JH, Smoller JW. The genetics of bipolar disorder. *Neuroscience*. 2009; 164(1):331–343. <http://dx.doi.org/10.1016/j.neuroscience.2009.03.080>. [PubMed: 19358880]

- Bellivier F, Leroux M, Henry C, Rayah F, Rouillon F, Laplanche J-L, Leboyer M. Serotonin transporter gene polymorphism influences age at onset in patients with bipolar affective disorder. *Neurosci Lett*. 2002; 334:17–20. [http://dx.doi.org/10.1016/S0304-3940\(02\)01029-7](http://dx.doi.org/10.1016/S0304-3940(02)01029-7). [PubMed: 12431765]
- Benedetti F, Bernasconi A, Lorenzi C, Pontiggia A, Serretti A, Colombo C, Smeraldi E. A single nucleotide polymorphism in glycogen synthase kinase 3-B promoter gene influences onset of illness in patients affected by bipolar disorder. *Neurosci Lett*. 2004a; 355:37–40. <http://dx.doi.org/10.1016/j.neulet.2003.10.021>. [PubMed: 14729229]
- Benedetti F, Dallaspesza S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian clock gene *Per3* influences age at onset of bipolar disorder. *Neurosci Lett*. 2008; 445:184–187. <http://dx.doi.org/10.1016/j.neulet.2008.09.002>. [PubMed: 18789374]
- Benedetti F, Dallaspesza S, Locatelli C, Radaelli D, Poletti S, Lorenzi C, Smeraldi E. Recurrence of bipolar mania is associated with catechol-*O*-methyltransferase Val(108/158)Met polymorphism. *J Affect Disord*. 2011; 132(1–2):293–296. <http://dx.doi.org/10.1016/j.jad.2011.02.022>. [PubMed: 21397335]
- Benedetti F, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E. A glycogen synthase kinase 3-B promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. *Neurosci Lett*. 2004b; 368:123–126. <http://dx.doi.org/10.1016/j.neulet.2004.06.050>. [PubMed: 15351432]
- Brisch R. The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. *Front Psychiatry*. 2014; 5(May):1–11. <http://dx.doi.org/10.3389/fpsy.2014.00047>. [PubMed: 24478729]
- Bureau A, Chagnon YC, Croteau J, Fournier A, Roy MA, Paccalet T, Merette C, Maziade M. Follow-up for a major psychosis linkage site in 13Q13-Q14 reveals significant associations in both case-control and family samples. *Biol Psychiatry*. 2013; 74:444–450. [PubMed: 23602252]
- Cate Carter TD, Mundo E, Parikh SV, Kennedy JL. Early age at onset as a risk factor for poor outcome of bipolar disorder. *J Psychiatr Res*. 2003; 37:297–303. [http://dx.doi.org/10.1016/S0022-3956\(03\)00052-9](http://dx.doi.org/10.1016/S0022-3956(03)00052-9). [PubMed: 12765852]
- Chen, G., Tang, J., Yu, G., Chen, Y., Wang, L., Zhang, Y. Meta-analysis demonstrates lack of association of the GSK3B –50C/T polymorphism with risk of bipolar disorder; *Mol Biol Rep*. 2014. p. 5711–5718. <http://dx.doi.org/10.1007/s11033-014-3441-x>
- Cheng D, Zhang K, Zhen G, Xue Z. The –116C/G polymorphism in XBP1 gene is associated with psychiatric illness in Asian population: a meta-analysis. *Am J Med Genet Part B: Neuropsychiatr Genet*. 2014; 165:665–672. <http://dx.doi.org/10.1002/ajmg.b.32271>.
- Cichon S, Buervenich S, Kirov G, Akula N, Dimitrova A, Green E, Craddock N. Lack of support for a genetic association of the XBP1 promoter polymorphism with bipolar disorder in probands of European origin. *Nat Genet*. 2004; 36(8):783–784. <http://dx.doi.org/10.1038/ng0804-784>, author reply 784–785. [PubMed: 15284840]
- Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. *Nat Rev Genet*. 2010; 11(6):415–425. <http://dx.doi.org/10.1038/nrg2779>. [PubMed: 20479773]
- Coe BP, Witherspoon K, Rosenfeld Ja, van Bon BWM, Vulto-van Silfhout AT, Bosco P, Eichler EE. Refining analyses of copy number variation identifies specific genes associated with developmental delay. *Nat Genet*. 2014; 46(10) <http://dx.doi.org/10.1038/ng.3092>.
- Coryell W, Fiedorowicz J, Leon AC, Endicott J, Keller MB. Age of onset and the prospectively observed course of illness in bipolar disorder. *J Affect Disord*. 2013; 146(1):34–38. <http://dx.doi.org/10.1016/j.jad.2012.08.031>. [PubMed: 23062746]
- Craddock N, Sklar P. Bipolar disorder 1—genetics of bipolar disorder. *Lancet*. 2013; 381(9878):1654–1662. [http://dx.doi.org/10.1016/S0140-6736\(13\)60855-7](http://dx.doi.org/10.1016/S0140-6736(13)60855-7). [PubMed: 23663951]
- Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013; 45(9):984–994. [PubMed: 23933821]
- Dizier MH, Etain B, Lajnef M, Lathrop M, Grozeva D, Craddock N, Mathieu F. Genetic heterogeneity according to age at onset in bipolar disorder: a combined positional cloning and candidate gene

- approach. *Am J Med Genet Part B: Neuropsychiatr Genet.* 2012; 159B:653–659. <http://dx.doi.org/10.1002/ajmg.b.32069>.
- Dmitrzak-Weglarz M, Rybakowski JK, Slopian A, Czerski PM, Leszczynska-Rodziewicz A, Kapelski P, Hauser J. Dopamine receptor D1 gene –48A/G polymorphism is associated with bipolar illness but not with schizophrenia in a polish population. *Neuropsychobiology.* 2006; 53:46–50. <http://dx.doi.org/10.1159/000090703>. [PubMed: 16397404]
- Ernst CL, Goldberg JF. Clinical features related to age at onset in bipolar disorder. *J Affect Disord.* 2004; 82:21–27. <http://dx.doi.org/10.1016/j.jad.2003.10.002>. [PubMed: 15465573]
- Etain B, Dumaine a, Mathieu F, Chevalier F, Henry C, Kahn JP, Jamain S. A SNAP25 promoter variant is associated with early-onset bipolar disorder and a high expression level in brain. *Mol Psychiatry.* 2010; 15(7):748–755. <http://dx.doi.org/10.1038/mp.2008.148>. [PubMed: 19125158]
- Etain B, Mathieu F, Rietschel M, Maier W, Albus M, McKeon P, Leboyer M. Genome-wide scan for genes involved in bipolar affective disorder in 70 European families ascertained through a bipolar type I early-onset proband: supportive evidence for linkage at 3p14. *Mol Psychiatry.* 2006; 11(May 2005):685–694. <http://dx.doi.org/10.1038/sj.mp.4001815>. [PubMed: 16534504]
- Faraone SV, Glatt SJ, Su J, Tsuang MT. Three potential susceptibility loci shown by a genome-wide scan for regions influencing the age at onset of mania. *Am J Psychiatry.* 2004; 161(15):625–630. <http://dx.doi.org/10.1176/appi.ajp.161.4.625>. [PubMed: 15056507]
- Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. *Biol Psychiatry.* 2003; 53:970–977. [http://dx.doi.org/10.1016/S0006-3223\(02\)01893-0](http://dx.doi.org/10.1016/S0006-3223(02)01893-0). [PubMed: 12788242]
- Faraone SV, Lasky-Su J, Glatt SJ, Eerdekewegh PV, Tsuang MT. Early onset bipolar disorder: possible linkage to chromosome 9q34. *Bipolar Disord.* 2006; 8(2):144–151. [PubMed: 16542184]
- Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* 2004; 161(September):1698–1700. <http://dx.doi.org/10.1176/appi.ajp.161.9.1698>. [PubMed: 15337662]
- Geller B, Cook EH. Ultradian rapid cycling in prepubertal and early adolescent bipolarity is not in transmission disequilibrium with val/met COMT alleles. *Biol Psychiatry.* 2000; 47:605–609. [http://dx.doi.org/10.1016/S0006-3223\(99\)00251-6](http://dx.doi.org/10.1016/S0006-3223(99)00251-6). [PubMed: 10745052]
- Geller B, Cook EH. Serotonin transporter gene (HTTLPR) is not in linkage disequilibrium with prepubertal and early adolescent bipolarity. *Biol Psychiatry.* 1999; 45(1996):1230–1233. [http://dx.doi.org/10.1016/S0006-3223\(98\)00362-X](http://dx.doi.org/10.1016/S0006-3223(98)00362-X). [PubMed: 10331118]
- Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 1997; 36(9):1168–1176. <http://dx.doi.org/10.1097/00004583-199709000-00008>. [PubMed: 9291717]
- Geoffroy PA, Etain B, Scott J, Henry C, Jamain S, Leboyer M, Bellivier F. Reconsideration of bipolar disorder as a developmental disorder: importance of the time of onset. *J Physiol —Paris.* 2013; 107(4):278–285. [PubMed: 23542544]
- Georgieva, L., Rees, E., Moran, JL., Chambert, KD., Milanova, V., Craddock, N., Kirov, G. De novo CNVs in bipolar affective disorder and schizophrenia; *Hum Mol Gen.* 2014. p. 1-7. <http://dx.doi.org/10.1093/hmg/ddu379>
- Girirajan S, Rosenfeld JA, Coe BP, Parikh S, Friedman N, Goldstein A, Eichler EE. Phenotypic heterogeneity of genomic disorders and rare copy-number variants. *N Engl J Med.* 2012; 367:1321–1331. <http://dx.doi.org/10.1056/NEJMoa1200395>. [PubMed: 22970919]
- Glatt JM, Burton KL, Williams LM, Schofield PR. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. *J Psychiatr Res.* 2015; 60:1–13. [PubMed: 25287955]
- Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry.* 2009; 70:1078–1090. [PubMed: 19497250]
- Goodwin, FK., Jamison, KR. Manic-depressive Illness: Bipolar Disorders and Recurrent Depression. Oxford University Press; New York: 2007.

- Gonçalves VF, Tiwari AK, de Luca V, Kong SL, Zai C, Tampakeras M, Kennedy JL. DRD4 VNTR polymorphism and age at onset of severe mental illnesses. *Neurosci Lett*. 2012; 519:9–13. <http://dx.doi.org/10.1016/j.neulet.2012.04.027>. [PubMed: 22543114]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; 160(4):636–645. [PubMed: 12668349]
- Gould TD, Manji HK. Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs Official Publication of the American College of Neuropsychopharmacology. *Neuropsychopharmacology*. 2005; 30:1223–1237. <http://dx.doi.org/10.1038/sj.npp.1300731>. [PubMed: 15827567]
- Gratten J, Wray NR, Keller MC, Visscher PM. Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nat Neurosci*. 2014; 17(6):782–790. <http://dx.doi.org/10.1038/nn.3708>. [PubMed: 24866044]
- Greenwood TA, Akiskal HS, Akiskal KK, Kelsoe JR. Genome-wide association study of temperament in bipolar disorder reveals significant associations with three novel loci. *Biol Psychiatry*. 2012; 72(4):303–310. <http://dx.doi.org/10.1016/j.biopsych.2012.01.018>. [PubMed: 22365631]
- Grigoriou-Serbanescu M, Diaconu CC, Herms S, Bleotu C, Vollmer J, Mühleisen TW, Cichon S. Investigation of the tryptophan hydroxylase 2 gene in bipolar I disorder in the Romanian population. *Psychiatr Genet*. 2008; 18:240–247. <http://dx.doi.org/10.1097/YPG.0b013e3283053045>. [PubMed: 18797398]
- Grigoriou-Serbanescu M, Martinez M, Nöthen MM, Grinberg M, Sima D, Propping P, Hrestic M. Different familial transmission patterns in bipolar I disorder with onset before and after age 25. *Am J Med Genet—Neuropsychiatr Genet*. 2001; 105(1983):765–773.
- Grigoriou-Serbanescu M, Rietschel M, Hauser J, Czerski PM, Herms S, Sun X, Elston RC. Commingling analysis of age-of-onset in bipolar I disorder and the morbid risk for major psychoses in first degree relatives of bipolar I probands. *J Affect Disord*. 2014; 168:197–204. <http://dx.doi.org/10.1016/j.jad.2014.06.054>. [PubMed: 25063958]
- Grimes, Ca, Jope, RS. The multifaceted roles of glycogen synthase kinase 3beta in cellular signaling. *Prog Neurobiol*. 2001; 65:391–426. [http://doi.org/S0301-0082\(01\)00011-9](http://doi.org/S0301-0082(01)00011-9) [pii]. [PubMed: 11527574]
- Grozeva D, Kirov G, Ivanov D, Jones IR, Jones L, Green EK, Craddock N. Rare copy number variants: a point of rarity in genetic risk for bipolar disorder and schizophrenia. *Arch Gen Psychiatry*. 2010; 67(4):318–327. [PubMed: 20368508]
- Grozeva D, Kirov G, Conrad DF, Barnes CP, Hurles M, Owen MJ, Craddock N. Reduced burden of very large and rare CNVs in bipolar affective disorder. *Bipolar Disord*. 2013; 15:893–898. <http://dx.doi.org/10.1111/bdi.12125>. [PubMed: 24127788]
- Gutierrez B, Arranz MJ, Collier Da, Valles V, Guillamat R, Bertranpetit J, Fanas L. Serotonin transporter gene and risk for bipolar affective disorder: an association study in Spanish population. *Biol Psychiatry*. 1998; 43(1996):843–847. [PubMed: 9611675]
- Hall MH, Smoller JW. A new role for endophenotypes in the GWAS Era: functional characterization of risk variants. *Harvard Rev Psychiatry*. 2010; 18(1):67–74. <http://dx.doi.org/10.3109/10673220903523532>.
- Hasler G, Drevets WC, Gould TD, Gottesman II, Manji HK. Toward constructing an endophenotype strategy for bipolar disorders. *Biol Psychiatry*. 2006; 60(2):93–105. [PubMed: 16406007]
- Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. *Mol Psychiatry*. 2011; 16(6):604–619. <http://dx.doi.org/10.1038/mp.2011.23>. [PubMed: 21602829]
- Ho LW, Furlong Ra, Rubinsztein JS, Walsh C, Paykel ES, Rubinsztein DC. Genetic associations with clinical characteristics in bipolar affective disorder and recurrent unipolar depressive disorder. *Am J Med Genet—Neuropsychiatr Genet*. 2000; 96(May 1999):36–42. [http://dx.doi.org/10.1002/\(SICI\)1096-8628\(20000207\)96:1<36::AID-AJMG8>3.0.CO;2-6](http://dx.doi.org/10.1002/(SICI)1096-8628(20000207)96:1<36::AID-AJMG8>3.0.CO;2-6).
- Hou SJ, Yen FC, Cheng CY, Tsai SJ, Hong CJ. X-box binding protein 1 (XBP1) C-116G polymorphisms in bipolar disorders and age of onset. *Neurosci Lett*. 2004; 367:232–234. <http://dx.doi.org/10.1016/j.neulet.2004.06.012>. [PubMed: 15331160]

- Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci.* 2001; 24:677–736. <http://dx.doi.org/10.1146/annurev.neuro.24.1.677>. [PubMed: 11520916]
- Iacono WG, Vaidyanathan U, Vrieze SI, Malone SM. Knowns and unknowns for psychophysiological endophenotypes: integration and response to commentaries. *Psychophysiology.* 2014; 51:1339–1347. <http://dx.doi.org/10.1111/psyp.12358>. [PubMed: 25387720]
- Jamain S, Cichon S, Etain B, Mühleisen TW, Georgi A, Zidane N, Leboyer M. Common and rare variant analysis in early-onset bipolar disorder vulnerability. *PLoS ONE.* 2014; 9(8):e104326. <http://dx.doi.org/10.1371/journal.pone.0104326>. [PubMed: 25111785]
- Javadi N, Kennedy JL, De Luca V. Ethnicity and age at onset in bipolar spectrum disorders. *CNS Spectr.* 2011; 16:127–134. <http://dx.doi.org/10.1017/S1092852912000296>. [PubMed: 24725455]
- Jiang HY, Qiao F, Xu XF, Yang Y, Bai Y, Jiang LL. Meta-analysis confirms a functional polymorphism (5-HTTLPR) in the serotonin transporter gene conferring risk of bipolar disorder in European populations. *Neurosci Lett.* 2013; 549:191–196. [PubMed: 23756178]
- Juli G, Juli MR, Juli L. Involvement of genetic factors in bipolar disorders: current status. *Psychiatr Danub.* 2012; 24:112–116. [PubMed: 22706407]
- Kakiuchi C, Iwamoto K, Ishiwata M, Bundo M, Kasahara T, Kusumi I, Kato T. Impaired feedback regulation of XBP1 as a genetic risk factor for bipolar disorder. *Nat Genet.* 2003; 35(2):171–175. <http://dx.doi.org/10.1038/ng1235>. [PubMed: 12949534]
- Kato T. Whole genome/exome sequencing in mood and psychotic disorders. *Psychiatry Clin Neurosci.* 2015; 69:65–76. <http://dx.doi.org/10.1111/pcn.12247>. [PubMed: 25319632]
- Kennedy N, Everitt B, Boydell J, van Os J, Jones PB, Murray RM. Incidence and distribution of first-episode mania by age: results from a 35-year study. *Psychol Med.* 2005; 35:855–863. [PubMed: 15997605]
- Kim Y, Xia K, Tao R, Giusti-Rodriguez P, Vladimirov V, van den Oord E, Sullivan PF. A meta-analysis of gene expression quantitative trait loci in brain. *Transl Psychiatry.* 2014; 4(10):e459. <http://dx.doi.org/10.1038/tp.2014.96>. [PubMed: 25290266]
- Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord.* 2007; 104:91–95. <http://dx.doi.org/10.1016/j.jad.2007.02.018>. [PubMed: 17434599]
- Kirov G, Jones I, McCandless F, Craddock N, Owen MJ. Family-based association studies of bipolar disorder with candidate genes involved in dopamine neurotransmission: DBH, DAT1, COMT, DRD2, DRD3 and DRD5. *Mol Psychiatry.* 1999; 4(February):558–565. <http://dx.doi.org/10.1038/sj.mp.4000565k>. [PubMed: 10578238]
- Klimes-Dougan, B., Kennedy, KP., Cullen, KR. Bipolar disorder from a developmental psychopathology perspective: focusing on phenomenology, etiology and neurobiology. In: Cicchetti, D., editor. *Developmental Psychopathology.* 3. Vol. IV. New York, N.Y: John Wiley & Sons; (in press)
- Kroon JS, Wohlfarth TD, Dieleman J, Sutherland AL, Storosum JG, Denys D, Sturkenboom MC. Incidence rates and risk factors of bipolar disorder in the general population: a population-based cohort study. *Bipolar Disord.* 2013; 15:306–313. <http://dx.doi.org/10.1111/bdi.12058>. [PubMed: 23531096]
- Kunugi H, Iijima Y, Tatsumi M, Yoshida M, Hashimoto R, Kato T, Yoshikawa T. No association between the Val66Met polymorphism of the brain-derived neurotrophic factor gene and bipolar disorder in a Japanese population: a multicenter study. *Biol Psychiatry.* 2004; 56:376–378. <http://dx.doi.org/10.1016/j.biopsych.2004.06.017>. [PubMed: 15336520]
- Labbe A, Bureau A, Moreau I, Roy M-A, Chagnon Y, Maziade M, Merette C. Symptom dimensions as alternative phenotypes to address genetic heterogeneity in schizophrenia and bipolar disorder. *Eur J Hum Genet.* 2012; 20(February):1182–1188. <http://dx.doi.org/10.1038/ejhg.2012.67>. [PubMed: 22535187]
- Leboyer M, Bellivier F, McKeon P, Albus M, Borrmann M, Perez-Diaz F, Maier W. Age at onset and gender resemblance in bipolar siblings. *Psychiatry Res.* 1998; 81:125–131. [http://dx.doi.org/10.1016/S0165-1781\(98\)00087-0](http://dx.doi.org/10.1016/S0165-1781(98)00087-0). [PubMed: 9858030]

- Lee KY, Song JY, Kim SH, Kim SC, Joo EJ, Ahn YM, Kim YS. Association between CLOCK 3111T/C and preferred circadian phase in Korean patients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010; 34(7):1196–1201. <http://dx.doi.org/10.1016/j.pnpbp.2010.06.010>. [PubMed: 20600471]
- Lee YJ, Kim YK. The impact of glycogen synthase kinase 3 β gene on psychotic mania in bipolar disorder patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35(5):1303–1308. <http://dx.doi.org/10.1016/j.pnpbp.2011.04.006>. [PubMed: 21549170]
- Lee JJ, Chow CC. Conditions for the validity of SNP-based heritability estimation. *Hum Genet*. 2014; 133(8):1011–1022. <http://dx.doi.org/10.1007/s00439-014-1441-5>. [PubMed: 24744256]
- Leibenluft E, Rich BA. Pediatric bipolar disorder. *Annu Rev Clin Psychol*. 2008; 4:163–187. <http://dx.doi.org/10.1146/annurev.clinpsy.4.022007.141216>. [PubMed: 17716034]
- Leszczyńska-Rodziewicz A, Hauser J, Dmítrzak-Węglarz M, Skibińska M, Czerski P, Zakrzewska A, Rybakowski JK. Lack of association between polymorphisms of dopamine receptors, type D2, and bipolar affective illness in a Polish population. *Med Sci Monit: Int Med J Exp Clin Res*. 2005; 11(6):CR289–R295.
- Lin P-I, McInnis MG, Potash JB, Willour VL, Mackinnon DF, Miao K, Zandi PP. Assessment of the effect of age at onset on linkage to bipolar disorder: evidence on chromosomes 18p and 21q. *Am J Hum Genet*. 2005; 77:545–555. <http://dx.doi.org/10.1086/491602>. [PubMed: 16175501]
- Lin PI, McInnis MG, Potash JB, Willour V, MacKinnon DF, DePaulo JR, Zandi PP. Clinical correlates and familial aggregation of age at onset in bipolar disorder. *Am J Psychiatry*. 2006; 163(2):240–246. <http://dx.doi.org/10.1176/appi.ajp.163.2.240>, doi: DOI. [PubMed: 16449477]
- Lin Y-F, Huang M-C, Liu H-C. Glycogen synthase kinase 3 β gene polymorphisms may be associated with bipolar I disorder and the therapeutic response to lithium. *J Affect Disord*. 2012; 147(1–3): 401–406. <http://dx.doi.org/10.1016/j.jad.2012.08.025>. [PubMed: 23021822]
- Liu X, Akula N, Skup M, Brotman MA, Leibenluft E, McMahon FJ. A genome-wide association study of amygdala activation in youths with and without bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2010; 49(1):33–41. [PubMed: 20215924]
- Mahon, PB., Pirooznia, M., Goes, FS. NIH Public Access. 2011. <http://dx.doi.org/10.1002/ajmg.b.31172>. Genome-wide
- Malhotra D, McCarthy S, Michaelson JJ, Vacic V, Burdick KE, Yoon S, Sebat J. High frequencies of de novo CNVs in bipolar disorder and schizophrenia. *Neuron*. 2011; 72:951–963. <http://dx.doi.org/10.1016/j.neuron.2011.11.007>. [PubMed: 22196331]
- Manchia M, Zai CC, Squassina A, Vincent JB, De Luca V, Kennedy JL. Mixture regression analysis on age at onset in Bipolar Disorder patients: investigation of the role of serotonergic genes. *Eur Neuropsychopharmacol*. 2010; 20(9):663–670. <http://dx.doi.org/10.1016/j.euroneuro.2010.04.001>. [PubMed: 20452754]
- Mann JJ. Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. *Neuropsychopharmacology*. 1999; 21:99S–105S. [PubMed: 10432495]
- Massat I, Lerer B, Souery D, Blackwood D, Muir W, Kaneva R, Mendlewicz J. HTR2C (cys23ser) polymorphism influences early onset in bipolar patients in a large European multicenter association study. *Mol Psychiatry*. 2007; 12:797–798. <http://dx.doi.org/10.1038/sj.mp.4002018>. [PubMed: 17767148]
- Massat I, Souery D, Lipp O, Blairy S, Papadimitriou G, Dikeos D, Mendlewicz J. A European multicenter association study of HTR2A receptor polymorphism in bipolar affective disorder. *Am J Med Genet*. 2000; 96:136–140. [http://dx.doi.org/10.1002/\(SICI\)1096-8628\(20000403\)96:2<136::AID-AJMG2>3.0.CO;2-S](http://dx.doi.org/10.1002/(SICI)1096-8628(20000403)96:2<136::AID-AJMG2>3.0.CO;2-S). [PubMed: 10893484]
- Massat I, Kocabas NA, Crisafulli C, Chiesa A, Calati R, Linotte S, Mendlewicz J. COMT and age at onset in mood disorders: a replication and extension study. *Neurosci Lett*. 2011; 498(3):218–221. <http://dx.doi.org/10.1016/j.neulet.2011.05.012>. [PubMed: 21600957]
- Massat I, Souery D, Del-Favero J, Van Gestel S, Serretti A, Macciardi F, Mendlewicz J. Positive association of dopamine D2 receptor polymorphism with bipolar affective disorder in a European Multicenter Association Study of affective disorders. *Am J Med Genet*. 2002; 114:177–185. <http://dx.doi.org/10.1002/ajmg.10118>. [PubMed: 11857579]

- Mathieu F, Dizier M-H, Etain B, Jamain S, Rietschel M, Maier W, Bellivier F. European collaborative study of early-onset bipolar disorder: evidence for genetic heterogeneity on 2q14 according to age at onset The Official Publication of the International Society of Psychiatric Genetics. *Am J Med Genet Part B: Neuropsychiatr Genet*. 2010; 153B(September):1425–1433. <http://dx.doi.org/10.1002/ajmg.b.31121>.
- McGrath CL, Glatt SJ, Sklar P, Le-Niculescu H, Kuczenski R, Doyle AE, Tsuang MT. Evidence for genetic association of RORB with bipolar disorder. *BMC Psychiatry*. 2009; 9:70. <http://dx.doi.org/10.1186/1471-244X-9-70>. [PubMed: 19909500]
- McQuillin, a, Bass, NJ., Kalsi, G., Lawrence, J., Puri, V., Choudhury, K., Gurling, HMD. Fine mapping of a susceptibility locus for bipolar and genetically related unipolar affective disorders, to a region containing the C21ORF29 and TRPM2 genes on chromosome 21q22. *Mol Psychiatry*. 2006; 11:134–142. <http://dx.doi.org/10.1038/sj.mp.4001759>. [PubMed: 16205735]
- McQuillin A, Bass N, Anjorin A, Lawrence J, Kandaswamy R, Lydall G, Gurling H. Analysis of genetic deletions and duplications in the University College London bipolar disorder case control sample. *Eur J Hum Genet : EJHG*. 2011; 19(5):588–592. <http://dx.doi.org/10.1038/ejhg.2010.221>. [PubMed: 21206513]
- Mendlewicz J, Massat I, Souery D, Del-Favero J, Oruc L, Nöthen MM, Van Broeckhoven C. Serotonin transporter 5HTTLPR polymorphism and affective disorders: no evidence of association in a large European multi-center study. *Eur J Hum Genet : EJHG*. 2004; 12(October 2003):377–382. <http://dx.doi.org/10.1038/sj.ejhg.5201149>. [PubMed: 14735161]
- Mick E, Faraone SV. Family and genetic association studies of bipolar disorder in children. *Child Adolesc Psychiatr Clin N Am*. 2009; 18:441–453. <http://dx.doi.org/10.1016/j.chc.2008.11.008>. [PubMed: 19264272]
- Mick E, Wozniak J, Wilens TE, Biederman J, Faraone SV. Family-based association study of the BDNF, COMT and serotonin transporter genes and DSM-IV bipolar-I disorder in children. *BMC Psychiatry*. 2009; 9:2. <http://dx.doi.org/10.1186/1471-244X-9-2>. [PubMed: 19193231]
- Milhiet V, Etain B, Boudebessé C, Bellivier F. Circadian biomarkers, circadian genes and bipolar disorders. *J Physiol —Paris*. 2011; 105(4–6):183–189. <http://dx.doi.org/10.1016/j.jphysparis.2011.07.002>. [PubMed: 21767641]
- Milhiet V, Boudebessé C, Bellivier F, Drouot X, Henry C, Leboyer M, Etain B. Circadian abnormalities as markers of susceptibility in bipolar disorders. *Front Biosci*. 2014; 6:120–137.
- Miller S, Hallmayer J, Wang PW, Hill SJ, Johnson SL, Ketter TA. Brain-derived neurotrophic factor val66met genotype and early life stress effects upon bipolar course. *J Psychiatr Res*. 2013; 47(2): 252–258. [PubMed: 23182421]
- Mohammadi S, Khazaie H, Rahimi Z, Vaisi-raygani A, Zargooshi N, Rahimi Z. The serotonin transporter (5-HTTLPR) but not serotonin receptor (5-HT2C Cys23Ser) variant is associated with bipolar I disorder in Kurdish population from Western Iran. *Neurosci Lett*. 2015; 590:91–95. [PubMed: 25596490]
- Mohammadynejad P, Saadat I, Ghanizadeh A, Saadat M. Bipolar disorder and polymorphisms of glutathione *S*-transferases M1 (GSTM1) and T1 (GSTT1). *Psychiatry Res*. 2011; 186:144–146. [PubMed: 20674986]
- Moresco EMY, LaVine D, Beutler B. Toll-like receptors. *Curr Biol*. 2011; 21(13):R488–R493. <http://dx.doi.org/10.1016/j.cub.2011.05.039>. [PubMed: 21741580]
- Müller DJ, de Luca V, Sicard T, King N, Strauss J, Kennedy JL. Brain-derived neurotrophic factor (BDNF) gene and rapid-cycling bipolar disorder: family-based association study. *Br J Psychiatry: J Ment Sci*. 2006; 189:317–323. <http://dx.doi.org/10.1192/bjp.bp.105.010587>.
- Murray G, Harvey A. Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord*. 2010; 12:459–472. <http://dx.doi.org/10.1111/j.1399-5618.2010.00843.x>. [PubMed: 20712747]
- Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am J Hum Genet*. 2002; 71(LD):651–655. <http://dx.doi.org/10.1086/342288>. [PubMed: 12161822]

- Ni X, Trakalo JM, Mundo E, Lee L, Parikh S, Kennedy JL. Family-based association study of the serotonin-2A receptor gene (5-HT2A) and bipolar disorder. *Neuromolecular Med.* 2002; 2:251–259. <http://dx.doi.org/10.1385/NMM:2:3:251>. [PubMed: 12622403]
- Ni X, Trakalo JM, Mundo E, Maciardi FM, Parikh S, Lee L, Kennedy JL. Linkage Disequilibrium between Dopamine D1 Receptor Gene (DRD1) and Bipolar Disorder. *Biol Psychiatry.* 2002; 52:1144–1150. [PubMed: 12488059]
- Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease. *Physiol Rev.* 2007; 87(1):165–217. [PubMed: 17237345]
- Noble EP. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes The Official Publication of the International Society of Psychiatric Genetics. *Am J Med Genet Part B: Neuropsychiatr Genet.* 2003; 116B:103–125. <http://dx.doi.org/10.1002/ajmg.b.10005>.
- Noor A, Lionel AC, Cohen-Woods S, Moghimi N, Rucker J, Fennell A, Vincent JB. Copy number variant study of bipolar disorder in Canadian and UK populations implicates synaptic genes. *Am J Med Genet Part B: Neuropsychiatr Genet.* 2014; 165(April):303–313. <http://dx.doi.org/10.1002/ajmg.b.32232>.
- O'Mahony E, Corvin a, O'Connell R, Comerford C, Larsen B, Jones R, Gill M. Sibling pairs with affective disorders: resemblance of demographic and clinical features. *Psychol Med.* 2002; 32:55–61. <http://dx.doi.org/10.1017/S0033291701004986>. [PubMed: 11883730]
- Oliveira J, Busson M, Etain B, Jamain S, Hamdani N, Boukouaci W, Tamouza R. Polymorphism of Toll-like receptor 4 gene in bipolar disorder. *J Affect Disord.* 2014; 152–154:395–402. <http://dx.doi.org/10.1016/j.jad.2013.09.043>.
- Oliveira J, Hamdani N, Busson M, Etain B, Bennabi M, Amokrane K, Tamouza R. Association between toll-like receptor 2 gene diversity and early-onset bipolar disorder. *J Affect Disord.* 2014; 165:135–141. <http://dx.doi.org/10.1016/j.jad.2014.04.059>. [PubMed: 24882191]
- Ospina-Duque J, Duque C, Carvajal-Carmona L, Ortiz-Barrientos D, Soto I, Pineda N, Freimer N. An association study of bipolar mood disorder (type I) with the 5-HTTLPR serotonin transporter polymorphism in a human population isolate from Colombia. *Neurosci Lett.* 2000; 292:199–202. Retrieved from c:\pdf\xc14734.pdf. [PubMed: 11018311]
- Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Nierenberg Aa. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry.* 2004; 55:875–881. <http://dx.doi.org/10.1016/j.biopsych.2004.01.022>. [PubMed: 15110730]
- Pinto C, Souza RP, Lioult D, Smeralul M, Kennedy JL, Warsh JJ, De Luca V. Parent of origin effect and allelic expression imbalance of the serotonin transporter in bipolar disorder and suicidal behaviour. *Eur Arch Psychiatry Clin Neurosci.* 2011; 261:533–538. <http://dx.doi.org/10.1007/s00406-011-0192-8>. [PubMed: 21290142]
- Pinto D, Pagnamenta A, Klei L, Anney R. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature.* 2010; 466(7304):368–372. <http://dx.doi.org/10.1038/nature09146.Functional>. [PubMed: 20531469]
- Priebe L, Degenhardt Fa, Herms S, Haenisch B, Mattheisen M, Nieratschker V, Mühleisen TW. Genome-wide survey implicates the influence of copy number variants (CNVs) in the development of early-onset bipolar disorder. *Mol Psychiatry.* 2012; 17:421–432. <http://dx.doi.org/10.1038/mp.2011.8>. [PubMed: 21358712]
- Sklar P, Ripke S, Scott LJ, Andreassen OA, Cichon S, Craddock N, Mahon PB. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet.* 2011; 43(10):977. [PubMed: 21926972]
- Rees E, Walters JTR, Georgieva L, Isles AR, Chambert KD, Richards AL, Kirov G. Analysis of copy number variations at 15 schizophrenia-associated loci. *Br J Psychiatry.* 2014; 204:108–114. <http://dx.doi.org/10.1192/bjp.bp.113.131052>. [PubMed: 24311552]
- Roh MS, Lee KY, Joo EJ, Lee N, Kim YS. No association of the MCP-1 promoter A-2518G polymorphism with bipolar disorder in the Korean population. *Neurosci Lett.* 2007; 427:1–5. <http://dx.doi.org/10.1016/j.neulet.2007.04.038>. [PubMed: 17928143]

- Rosa, R., Singh, N., Whitaker, E., de Brito, M., Lewis, M., Vieta, E., Goodwin, GM. Altered plasma glutathione levels in bipolar disorder indicates higher oxidative stress; a possible risk factor for illness onset despite normal brain-derived neurotrophic factor (BDNF) levels; *Psychol Med*. 2014. p. 1-10. <http://dx.doi.org/10.1017/S0033291714000014>
- Rybakowski JK, Borkowska A, Czerski PM, Skibi ska M, Hauser J. Polymorphism of the brain-derived neurotrophic factor gene and performance on a cognitive prefrontal test in bipolar patients. *Bipolar Disord*. 2003; 5(8):468–472. <http://dx.doi.org/10.1046/j.1399-5618.2003.00071.x>. [PubMed: 14636373]
- Rybakowski JK, Suwalska a, Skibinska M, Szczepankiewicz a, Leszczynska-Rodziewicz a, Permoda a, Hauser J. Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. *Pharmacopsychiatry*. 2005; 38:166–170. <http://dx.doi.org/10.1055/s-2005-871239>. [PubMed: 16025419]
- Sanders SJ, Ercan-Sencicek aG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, State MW. Multiple recurrent de novo CNVs, including duplications of the 7q11.3 Williams syndrome region, are strongly associated with autism. *Neuron*. 2011; 70:863–885. <http://dx.doi.org/10.1016/j.neuron.2011.05.002>. [PubMed: 21658581]
- Saunders EH, Scott LJ, McInnis MG, Burmeister M. Familiality and diagnostic patterns of subphenotypes in the National Institutes of Mental Health bipolar sample. *Am J Med Genet Part B*. 2008; 147B:18–26. [PubMed: 17525972]
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014; 511(7510):421–427. [PubMed: 25056061]
- Schulze TG, Hedeker D, Zandi P, Rietschel M, McMahon FJ. What is familial about familial bipolar disorder?: resemblance among relatives across a broad spectrum of phenotypic characteristics. *Arch Gen Psychiatry*. 2006; 63:1368–1376. [PubMed: 17146011]
- Schumann G. Are we doing enough to extract genomic information from our data? *Psychophysiology*. 2014; 51:1335–1336. <http://dx.doi.org/10.1111/psyp.12357>. [PubMed: 25387718]
- Schürhoff F, Bellivier F, Jouvent R, Mouren-Siméoni MC, Bouvard M, Allilaire JF, Leboyer M. Early and late onset bipolar disorders: two different forms of manic-depressive illness? *J Affect Disord*. 2000; 58:215–221. [PubMed: 10802130]
- Scola G, Andreazza AC. The role of neurotrophins in bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015; 56:122–128. <http://dx.doi.org/10.1016/j.pnpbp.2014.08.013>. [PubMed: 25193130]
- Sebat J, Levy DL, McCarthy SE. NIH Public Access. 2009; 25(12):528–535. <http://dx.doi.org/10.1016/j.tig.2009.10.004>. *Rare*.
- Seifuddin F, Mahon PB, Judy J, Pirooznia M, Jancic D, Taylor J, Zandi PP. Meta-analysis of genetic association studies on bipolar disorder. *Am J Med Genet Part B: Neuropsychiatr Genet*. 2012; 159B:508–518. <http://dx.doi.org/10.1002/ajmg.b.32057>.
- Serretti A, Malitas PN, Mandelli L, Lorenzi C, Ploia C, Alevizos B, Smeraldi E. Further evidence for a possible association between serotonin transporter gene and lithium prophylaxis in mood disorders. *Pharmacogenomics J*. 2004; 4:267–273. <http://dx.doi.org/10.1038/sj.tpj.6500252>. [PubMed: 15111989]
- Serretti A, Benedetti F, Colombo C, Lilli R, Lorenzi C, Smeraldi E. Dopamine receptor D4 is not associated with antidepressant activity of sleep deprivation. *Psychiatry Res*. 1999a; 20:107–114.
- Serretti A, Lilli R, Lorenzi C, Gasperini M, Smeraldi E. Tryptophan hydroxylase gene and response to lithium prophylaxis. 1999b; 33:371–377.
- Severino G, Manchia M, Contu P, Squassina A, Lampus S, Ardau R, Del Zompo M. Association study in a Sardinian sample between bipolar disorder and the nuclear receptor REV-ERB α gene, a critical component of the circadian clock system. *Bipolar Disord*. 2009; 11(3):215–220. <http://dx.doi.org/10.1111/j.1399-5618.2009.00667.x>. [PubMed: 19267705]
- Shinozaki, G., Potash, JB. New developments in the genetics of bipolar disorder; *Curr Psychiatry Rep*. 2014. p. 16 <http://dx.doi.org/10.1007/s11920-014-0493-5>
- Skibinska M, Hauser J, Czerski PM, Leszczynska-Rodziewicz A, Kosmowska M, Kapelski P, Rybakowski JK. Association analysis of brain-derived neurotrophic factor (BDNF) gene

- Val66Met polymorphism in schizophrenia and bipolar affective disorder. *World J Biol Psychiatry*. 2004; 5:215–220. <http://dx.doi.org/10.1080/15622970410029936>. [PubMed: 15543516]
- Somanath CP, Jain S, Janardhan Reddy YC. A family study of early-onset bipolar I disorder. *J Affect Disord*. 2002; 70:91–94. [http://dx.doi.org/10.1016/S0165-0327\(00\)00372-4](http://dx.doi.org/10.1016/S0165-0327(00)00372-4). [PubMed: 12113924]
- Souery D, Lipp O, Rivelli SK, Massat I, Serretti a, Cavallini C, Mendlewicz J. Tyrosine hydroxylase polymorphism and phenotypic heterogeneity in bipolar affective disorder: a multicenter association study. *Am J Med Genet—Neuropsychiatr Genet*. 1999; 88:527–532. [http://dx.doi.org/10.1002/\(SICI\)1096-8628\(19991015\)88:5<527::AID-AJMG17>3.0.CO;2-4](http://dx.doi.org/10.1002/(SICI)1096-8628(19991015)88:5<527::AID-AJMG17>3.0.CO;2-4).
- Squassina, a, Manchia, M., Costa, M., Chillotti, C., Ardau, R., Del Zompo, M., Severino, G. Age at onset in bipolar disorder: investigation of the role of TaqIA polymorphism of DRD2 gene in a Sardinian sample. *Eur Psychiatry*. 2011; 26(3):141–143. <http://dx.doi.org/10.1016/j.eurpsy.2010.09.013>. [PubMed: 21292452]
- Szczepankiewicz A, Skibinska M, Hauser J, Slopian A, Leszczynska-Rodziewicz A, Kapelski P, Rybakowski JK. Association analysis of the GSK-3beta T-50C gene polymorphism with schizophrenia and bipolar disorder. *Neuropsychobiology*. 2006; 53:51–56. <http://dx.doi.org/10.1159/000090704>. [PubMed: 16397405]
- Tang J, Xiao L, Shu C, Wang G, Liu Z, Wang X, Bai X. Association of the brain-derived neurotrophic factor gene and bipolar disorder with early age of onset in mainland China. *Neurosci Lett*. 2008; 433:98–102. <http://dx.doi.org/10.1016/j.neulet.2008.01.001>. [PubMed: 18242852]
- Taylor MA, Abrams R. Early-and late-onset bipolar illness. *Arch Gen Psychiatry*. 1981; 38:58–61. [PubMed: 7458569]
- Tozzi F, Manchia M, Galwey NW, Severino G, Del Zompo M, Day R, Muglia P. Admixture analysis of age at onset in bipolar disorder. *Psychiatry Res*. 2011; 185:27–32. <http://dx.doi.org/10.1016/j.psychres.2009.11.025>. [PubMed: 20580841]
- Visscher PM, Yazdi MH, Jackson aD, Schalling M, Lindblad K, Yuan QP, Blackwood DH. Genetic survival analysis of age-at-onset of bipolar disorder: evidence for anticipation or cohort effect in families. *Psychiatr Genet*. 2001; 11(3):129–137. <http://dx.doi.org/10.1097/00041444-200109000-00004>. [PubMed: 11702054]
- Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Sebat J. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science (New York, NY)*. 2008; 320:539–543. <http://dx.doi.org/10.1126/science.1155174>.
- Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R, Thapar A. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet*. 2010; 376(9750):1401–1408. [http://dx.doi.org/10.1016/S0140-6736\(10\)61109-9](http://dx.doi.org/10.1016/S0140-6736(10)61109-9). [PubMed: 20888040]
- Wu R, Fan J, Zhao J, Calabrese JR, Gao K. The relationship between neurotrophins and bipolar disorder. *Exp Rev Neurother*. 2014; 14(1):51–65. <http://dx.doi.org/10.1586/14737175.2014.863709>.
- Xu C, Li PP, Cooke RG, Parikh SV, Wang KS, Kennedy JL, Warsh JJ. TRPM2 variants and bipolar disorder risk: confirmation in a family-based association study. *Bipolar Disord*. 2009; 11(3):1–10. <http://dx.doi.org/10.1111/j.1399-5618.2008.00655.x>.
- Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet*. 2011; 88(1):76–82. <http://dx.doi.org/10.1016/j.ajhg.2010.11.011>. [PubMed: 21167468]
- Yen FC, Hong CJ, Hou SJ, Wang JK, Tsai SJ. Association study of serotonin transporter gene VNTR polymorphism and mood disorders, onset age and suicide attempts in a Chinese sample. *Neuropsychobiology*. 2003; 48(201):5–9. <http://dx.doi.org/10.1159/000071821>. [PubMed: 12886033]
- Yin L, Wang J, Klein PS, Lazar MA. Nuclear receptor Rev-erba is a critical lithium-sensitive component of the circadian clock. *Science*. 2006; 311(5763):1002–1005. [PubMed: 16484495]
- Zandi PP, Badner JA, Steele J, Willour VL, Miao K, MacKinnon DF, Potash JB. Genome-wide linkage scan of 98 bipolar pedigrees and analysis of clinical covariates. *Mol Psychiatry*. 2007; 12:630–639. <http://dx.doi.org/10.1038/sj.mp.4002027>. [PubMed: 17505464]

Zhang Z, Lindpaintner K, Che R, He Z, Wang P, Yang P, Shi Y. The Val/Met functional polymorphism in COMT confers susceptibility to bipolar disorder: evidence from an association study and a meta-analysis. *J Neural Transm.* 2009; 116:1193–1200. <http://dx.doi.org/10.1007/s00702-009-0260-7>. [PubMed: 19578924]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript