

GENE ENVIRONMENT INTERACTIONS IN BIPOLAR DISORDER

Peter Pregelj

Medical Faculty, University of Ljubljana, Slovenia
University Psychiatric Hospital, Ljubljana, Slovenia

SUMMARY

It has been estimated that the heritable component of bipolar disorder ranges between 80 and 90%. However, even genome-wide association studies explain only a fraction of phenotypic variability not resolving the problem of »lost heritability«. Although direct evidence for epigenetic dysfunction in bipolar disorder is still limited, methodological technologies in epigenomic profiling have advanced, offering even single cell analysing and resolving the problem of cell heterogeneity in epigenetics research. Gene overlapping with other mental disorders represents another problem in identifying potential susceptibility genes in bipolar disorder. Better understanding of the interplay between multiple environmental and genetic factors involved in the pathogenesis of bipolar disorder could provide relevant information for treatment of patients with this complex disorder. Future studies on the role of these factors in psychopathological conditions, subphenotypes and endophenotypes may greatly benefit by using more precise clinical data and a combined approach with multiple research tools incorporated into a single study.

Key words: bipolar disorder – epigenetics – neurobiology - environmental factors - suicidal behaviour

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INTRODUCTION

Family and twin studies revealed that like other mental disorders bipolar disorder aggregates in families suggesting a heritable basis (Shih et al. 2004). It is known that the lifetime prevalence of bipolar disorder in the general population is around 1–2%, multiple studies have reported that the lifetime morbidity risk for bipolar disorder in a first-degree relative of a patient with bipolar disorder is much higher, between 10 to 20% (Shih et al. 2004). It has been further calculated that the heritable component of bipolar disorder is ranging between 80 and 90%. Regarding environmental influences, adoption studies indicate that genetic factors contribute substantially more to the etiology of bipolar disorder than environmental factors (Shih et al. 2004). However, most linkage studies were not supported by subsequent studies (Schulze & McMahon 2003). It was summarized that methodological problems associated with these early linkage studies were manifold (Schulze, 2010). Even genome-wide association studies explain only a fraction of phenotypic variability not resolving the problems of »lost heritability« (Schulze, 2010). The locus heterogeneity of bipolar disorder may be so high that it is not possible to dissect it by means of linkage analysis, even with very large sample sizes (Schulze, 2010). Also a meta-analysis of the widely reported interaction between variation in the serotonin transporter gene and stressful life events provides no additional evidence for the complex interplay between genes and environmental factors involved in the pathogenesis of bipolar disorder (Risch et al. 2009).

Although direct evidence for epigenetic dysfunction in bipolar disorder is still limited, methodological technologies in epigenomic profiling have advanced (Rutten & Mill 2009). It is known that epigenetic

processes like DNA methylation and histone modulation are essential for normal cellular development and differentiation and allow the long-term regulation of gene function through nonmutagenic mechanisms (Henikoff 1997). Phenotypic discordance between monozygotic twins with bipolar disorder is often attributed to nonshared environmental factors, although the empirical evidence for such environmental contribution is still lacking, with no specific environmental risk factors being conclusively linked to etiology. The partial stability of epigenetic signals provides an alternative explanation for phenotypic discordance between monozygotic twins (Rutten & Mill 2009). Genome-wide approaches to identify DNA methylation changes associated with bipolar disorder revealed DNA methylation differences between monozygotic twins discordant for bipolar disorder (Kuratomi et al. 2008). Increased methylation in affected twins upstream of the spermine synthase gene (SMS) and lower methylation upstream of the peptidylprolyl isomerase E-like gene (PPIEL) were observed (Kuratomi et al. 2008).

SUICIDAL BEHAVIOUR AND BIPOLAR DISORDER

Bipolar spectrum from mild to more severe cases in combination with suicidal behaviour prevents the formation of phenotypically homogenous groups. Gene overlapping with other mental disorders represents another problem in identifying potential susceptibility genes in bipolar disorder. Further, subphenotypic analyses identified a history of suicide attempts as a familial phenotypic characteristic in bipolar disorder (Potash et al. 2007). It seems that similar genes are involved in the pathogenesis of bipolar disorder and suicidal behaviour. Replications across several candidate gene

association studies at the allelic level for the identical allele of a particular single nucleotide polymorphism (SNP) in bipolar disorder revealed genes encoding: serotonin transporter (SLC6A3), D-amino acid oxidase activator (G72) (DAOA), brain-derived neurotrophic factor (BDNF), disrupted-in-schizophrenia-1 (DISC-1) and tryptophan hydroxylase 2 (TPH 2) (Schulze, 2010). It seems that the same genes are involved in suicidal behaviour. Associations between BDNF (Pregelj et al. 2011) and TPH2 (Zupanc et al. 2011) polymorphisms and completed suicide were observed in suicide victims in a population with high suicide risk. Indeed, several lines of evidence link the special role of BDNF as a mediator of neuroplasticity in bipolar disorder (Grandel et al. 2010) and suicidal behaviour (Kim et al. 2010). It is also known that BDNF influences a variety of neural processes during the development like neurogenesis, neuronal survival, and maturation of neural development pathways (Post 2007). In adulthood, BDNF is important for synaptic plasticity, dendritic growth and also for long-term memory consolidation (Post 2007). Recent evidence suggests that BDNF might be a potential state marker also in bipolar disorder (Kapczinski et al. 2008, Grandel et al. 2010).

SINGLE CELL APPROACH

Single cell approach is more and more important in evaluating neurobiology of bipolar and other severe mental disorders focusing on apoptosis on the one hand and neuroprotection on the other. Similar to neurobiology of bipolar disorder, little is known about the neuronal correlates of the mental processes like negative emotions involved in suicidal behaviour on the cellular level. It was hypothesised that von Economo neurons (VENs) may have a specific functional role in the evaluation of these complex emotions, based on the findings that VENs are uniquely located in the brain regions involved in emotion processing (Craig 2009). Even though the precise functional properties of the VENs are unknown (Watson et al. 2006), it has been shown that these cells express dopamine, serotonin and vasopressin receptors (Allman et al. 2005), neurotransmitters involved in emotion regulation and pathophysiology of bipolar disorder. Indeed, it was reported that VENs density in the anterior cingulate cortex is increased in suicide victims with bipolar disorder or schizophrenia. New research approaches like restriction enzyme-based single-cell methylation assay (RSMA) are addressing the problems of cell heterogeneity in epigenetic mechanisms research (Kantlehner et al. 2011).

CONCLUSION

Research of epigenetic mechanisms could provide a better understanding of gene environmental interactions in patients with bipolar disorder with or without suicidal

behaviour. The dynamic nature of the epigenetic mechanisms could be involved in the cycling clinical picture of bipolar disorder. The potential reversibility of epigenetic modifications could be important for the management of patients with bipolar disorder offering the opportunity to influence aberrant gene expression by modifying environmental factors with methods such as psychotherapy. The field of pharmacogenomics may also emerge as an important part of the improved, more individualised management of bipolar patients (Schulze, 2010). Better understanding of the interplay between multiple environmental and genetic factors involved in the pathogenesis of bipolar disorder and suicidal behaviour could provide relevant information for treatment of this complex disorder. Future studies on the role of these factors in psychopathological conditions, subphenotypes and endophenotypes may greatly benefit by using more precise clinical data and a combined approach with multiple research tools incorporated into a single study. Research focusing on the functioning and survival of a single neuron involved in the pathogenesis of bipolar disorder seems to be a reasonable but difficult way in the further exploration of the bipolar spectrum.

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Correspondence:

Peter Pregelj
University Psychiatric Hospital
Študenec 48, 1000 Ljubljana, Slovenia
E-mail: peter.pregelj@psih-klinika.si