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GENETICS BEHIND MOOD DISORDERS

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Genetics behind Mood Disorders

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Abstract – The principal goal of this paper will be to survey functionally relevant candidate genes for mood disorders and risk variants revealed from the first GWA studies in clinical cohorts for mood disorders. One is that rare variants play a more important role in the aetiology of mood disorders than previously thought and these variants might be distinct in different populations and families. That might also explain the huge variety and expansion of linkage peaks throughout the genome in the traditional linkage studies. Another possibility is that the heterogeneity of the genetic component contributes to the aetiology of mood disorders, even within one predisposing gene. While all of these can be true, the most plausible explanation is that the phenotypes of MDD and BD are too broad, which leads to the confounding results seen in genetic studies, since the different aspects of broad mood disorder phenotypes are affected by distinct genetic susceptibility genes. Thus, analysis of huge sets of genotyped individuals in future GWA studies might not necessarily lead to the discovery of the missing heritability, but instead to discovery of new low risk alleles. They will definitely reveal important etiological factors for the disease and might help to develop new, more efficient drugs, but they will not tell the whole story of genetics behind mood disorders.

Keywords: Genetics, Behind, Mood Disorders, Risk, Clinical, Important, Population, Families, Genetic, Different, Genes, Discovery, Disease, Develop, Drugs, etc.

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INTRODUCTION

Mood disorders are common in the population and they are the most prevalent psychiatric disorders. Mood disorders are the leading cause of morbidity, thus their economic impact is huge since they are also the leading cause of disability to work. The high suicide rate also makes them fatal disorders; up to 15 % of people suffering from mood disorders will eventually commit suicide (Guze and Robins 1970). Mood disorders are divided to major depressive disorder (MDD) and bipolar disorder (BD). Common to these two disorders are the fluctuation of mood. In MDD, the fluctuation is unipolar, comprising only depressive episodes of mood. In BD, the fluctuation ranges from extreme elation of mood, mania (BD type I, BDI) or hypomania (BD type II, BDII), to depression. The life-time prevalence of MDD is 6.5 % and of BD is 0.24 % (Perala et al 2007).

REVIEW OF LITERATURE:

Mood disorders, also known as affective disorders and manic-depressive illnesses, are defined by abnormal fluctuation of mood. They include BD and MDD, which is also known as unipolar disorder, and BD. MDD is characterized by major depressive episodes that affect patients' ability to function. BD patients have had at least one episode of abnormally elevated mood, which can be either hypomania (BDII) that does not affect social or occupational functioning, or mania (BDI) that either affects social and occupational functioning, requires hospitalization, or contains psychotic features (Goodwin and Jamison 2007). MDD and BD can be seen either as two different disease entities (the categorical view) or as the ends of the same manic-depressive disease spectrum (the spectrum view). Both categorical and spectrum views have supporting findings in the literature (Benazzi 2007). The categorical view is supported by findings such as: gender distribution of MDD and BD differs (female dominance in MDD, equal prevalence in BD) (Angst and Marneros 2001); brain structure abnormalities of MDD are different to those of BD (Kempton et al); and the family distribution of BD and MDD cases differs between mania and depressive patients (Winokur et al 1995). The spectrum view is supported by the fact that in both, the depression is present either with or without hypomania or mania. In addition, the existence of hypomania and the mood continuum from normal to manic, the existence of fluctuation of mood in both disorders (recurrent-MDD, rMDD and BD), high rate of MDD diagnoses shifting to BD, and similarities in cognitive performance

(Benazzi 2007) support the spectrum view of mood disorders.

1- Genetics of complex diseases:

The field of genetics has evolved enormously within the last decade after the complete sequencing of the whole human genome. Before the availability of the whole human genome sequence, genetic research was concentrated on mapping of risk areas by linkage and positional cloning of candidate regions. A number of so-called classical monogenic traits were successfully characterized by linkage studies taking advantage of the Mendelian inheritance model and family structures. However, the more common multifactorial diseases, such as diabetes and psychiatric illnesses, have not been proven to be as successful in genetic vulnerability research. New strategies of whole genome associations and sequencing are sought, but current approaches do not yet meet expectations in psychiatric genetics.

2- Genetics of mood disorder:

❖ **Linkage findings:**

The linkage peaks of mood disorder are spread all over the genome and also contain few replications and some shared linkage peaks for MDD and BD. Figure 1 summarizes the genome wide significant linkage findings of both MDD and BD.

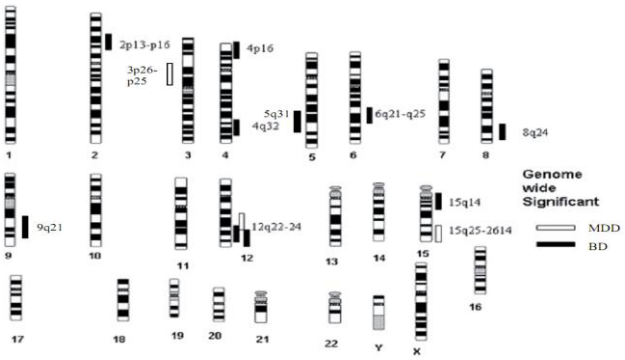

Figure 1 Genome wide significant linkage findings of MDD and BD

Only few genome-wide linkage studies of MDD have been performed with a sufficient number of affected individuals, i.e. over 100 per study, by the end of May 2012. Their findings are not consistent with each other and the linkage peaks are spread throughout the genome. In the first linkage study, the collected families contained individuals affected for both MDD and alcoholism. The strongest linkage peak was gained with phenotype MDD or alcoholism and it was located in chromosome 1. The best linkage peak for depression only was located in chromosome Holman's described linkage peak in the 15q25.3-26.2 in an initial analysis of 297 families (Holmans et al 2004) and when they expanded it to 359 families, the linkage peak of 15q was further supported and also suggestive evidence of linkage was observed in chromosomes 8p and 17p (Holmans et al 2004). A study made in a sample of 81 families containing early-onset r-MDD cases contains many confusing points, like the use of many covariates in the analyses, so the comparison of the results to other studies is highly difficult, as summarized in the review article of MDD (Levinson 2006).

3- Brain derived neurotrophic factor:

Brain derived neurotrophic factor (BDNF) is a widely studied candidate gene, both for MDD and BD. Its function makes it a very potential susceptibility gene for mood disorders since it regulates neurogenesis and mediates neuronal plasticity. There are many arguments that support the role of BDNF behind MDD. Its expression in brain was first shown to be altered by antidepressant treatment in 1995, when it was shown that both chronic anti-depressant drugs and electroconvulsive seizure (ECS) treatments increase the expression of BDNF in different parts of the rat brain. Its expression is decreased by stress and this reduction is restored by antidepressant treatments. The effect of the stress is located mainly to the hippocampus, a brain area that is known to be relevant in depression and emotionality in general. Stress promotes cellular death and atrophy, and the same is seen in MDD patients that have shown to have smaller hippocampal volume compared to controls. The simplified model of stress and antidepressant effect to the BDNF function and mood is illustrated in Figure 2. The delayed antidepressant effect on mood has also given rise to the theory that brain structure and plasticity dysfunction is the leading cause of depression, and it is a BDNF recovery and its effects on brain plasticity that leads to the antidepressant effects of medication. Recent meta-analysis of plasma BDNF levels have shown that they are dependent on the state of disease, i.e. the levels are decreased in both depression and mania, but not in euthymic when compared to controls. Therefore, there is a wealth of biological evidence that BDNF plays a major role in depression and mood disorders.

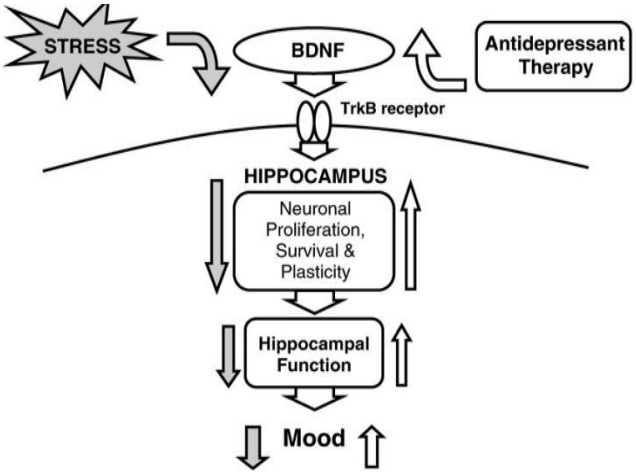

Figure 2 Model of stress and antidepressant effect on BDNF function in hippocampus

The most studied genetic variant within the BDNF gene is rs6263, a functional variant that changes amino acid valine to methionine (val66met). The first positive association findings of this val66met variant and BD were made in 2002, and after that there have been positive replications for both MDD and BD. The meta-analysis of val66met and MDD found supporting evidence of BDNF association with MDD among males, but the meta-analyses of BD studies did not find evidence for association The activation of BDNF receptor, NTRK2, is known to mediate the effects of BDNF in the cell, i.e. the plasticity function. Thus, the NTRK2 gene is also a good candidate gene for MDD and there are positive association findings for MDD and BD, as well as other common co morbid disorders of mood disorders. CREB1 is also a potential candidate gene, because it enhances the transcription of BDNF via a regulatory loop with BDNF. It regulates the transcription of BDNF target genes in cells after NTRK2 activation (Figure 3). A recent sophisticated study has shown that many environmental factors known to associate with MDD (such as smoking, age, alcohol abuse), together with genetic vulnerability genes (such as BDNF), affect disease susceptibility.

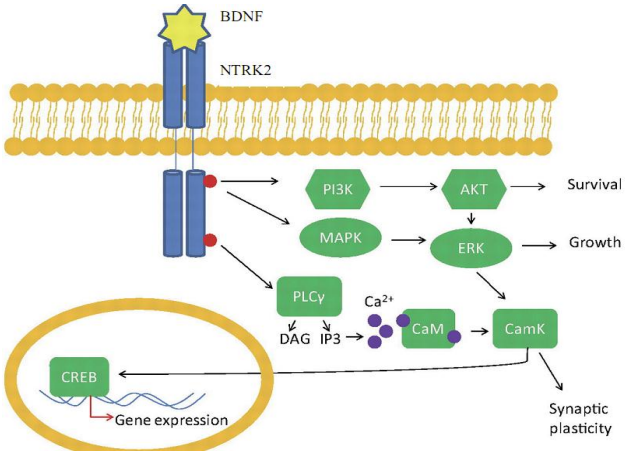

Figure 3 Simplified model of BDNF action in the cell after binding to the receptor NTRK2

The interaction of post-traumatic stress and val66met polymorphism of BDNF has also been shown to increase the risk for MDD (Rakofsky et al 2012). The BDNFCREB1-NTRK2 pathway, together with cognitive and neural intermediate phenotypes, has been shown to increase the risk for depression.

CONCLUSION:

The principal goal of this paper will be to survey functionally relevant candidate genes for mood disorders and risk variants revealed from the first GWA studies in clinical cohorts for mood disorders. One is that rare variants play a more important role in the aetiology of mood disorders than previously thought and these variants might be distinct in different populations and families. Accordingly, in our mood disorder cohort study, the association signal of vanished completely when analyses were performed using cases with no familial loading. The importance of selection of cases was seen also in linkage studies of MDD, where findings from linkage studies in cases with both r-MDD and single episode MDD, as well as BD cases, were completely different from those in cases with early onset r-MDD as well as anxiety disorder cases. They will definitely reveal important etiological factors for the disease and might help to develop new, more efficient drugs, but they will not tell the whole story of genetics behind mood disorders.

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