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Review Article

# Effects of Brain-Derived Neurotrophic Factor (BDNF) and Ankyrin 3 (ANK3) in Bipolar Disorder

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## ABSTRACT

Bipolar Disorder (BD) is a mental disorder with emotional highs (euphoria) and lows, diagnosed especially in teenage years and early adulthood, which can cause cyclings containing manic (hypomanic) episodes and major depressive episodes. Nowadays, the suicide death rate of BD increases dramatically, thus BD has attracted more attention of society.

So far, numerous studies have argued that it is heavily influenced by genetics, and BDNF (Brain-Derived Neurotrophic Factor) and ANK3 (Ankyrin 3) are regarded as the most important risk factors to BD susceptibility. Furthermore, *BDNF* and *ANK3* both play a key role in central nervous system, which means a small mutation or change of them will induce some significant consequences.

This article summarizes some researches about the association between BDNF and BD and its typical rapid cycling, as well as the potential effects of ANK3's cis-regulation and its variants. In addition, it introduces some information about how cis-regulation of ANK3 affects the susceptibility of BD and how some remarkable variants of ANK3 may contribute to BD. But also noteworthy is the fact that existing research results are far from enough, and there are still a great deal of effort that should be devoted to figure out the exact mechanism of BD, which must be beneficial for human health and improvement for relevant treatment and medicine.

**Keywords:** Bipolar Disorder (BD), Brain-Derived Neurotrophic Factor (*BDNF*), Ankyrin 3 (ANK3), Rapid cycling

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## ABBREVIATIONS

BD: Bipolar Disorder; BDNF: Brain-Derived Neurotrophic Factor; NGF: Nerve Growth Factor; CNS: Central Nervous System; ANK3: Ankyrin-3; ANK-G: Ankyrin-G; RHF: Relative Hybridization Factor; LD: Linkage Disequilibrium; SNP: Single Nucleotide Polymorphisms

## INTRODUCTION

### *Bipolar Disorder (BD)*

Bipolar Disorder (also known as manic depression) is a recurrent chronic mental disorder that contains an extreme mood swings between mania or hypomania and depression. It has impacts on more than 1% of the world's population (Grande I, *et al*., 2016). Additionally, BD can be diagnosed in any age, especially in teenage years and early adulthood. In manic episodes, patients will experience emotional highs like over activity with less need of sleep and talkativeness with racing thoughts, etc. (Belmaker RH, 2004). In contrast, in major depressive episodes, patients may suffer a range of symptoms same as depression, like sleep disturbance and lack of energy and so on. Even though most people may go through with episodes, there are a few people may not experience any.

There are many risk factors that may be involved, such as biological differences, environmental effects, and genetic causes. Biological differences mean that patients appear to have physical changes in their brains. There are many factors belonging to environmental impacts. For instance, some people who experience periods of high stress like the death of a loved one or other traumatic event, or who abuse drug or alcohol tend to increase the risk of BD. And there is evidence that vulnerability to BD is markedly increased by traumatic life events. Genetic reasons refer to people who have a first-degree relative with BD would be more likely to have BD. Today, many studies have shown that some genes such as *BDNF* and *ANK3* have a significant effect on BD (Berk M, *et al*., 2011).

### *Brain-Derived Neurotrophic Factor (BDNF) and Ankyrin-3 (ANK3)*

*BDNF* presents in small amounts in the central nervous system of an adult, a member of the NGF family (Hyman C, *et al*., 1991). BDNF is expressed in many regions in the CNS of adults, like striatum (Hofer M, *et al*., 1990). In this case, BDNF appears to be a factor that provides mesencephanic dopaminergic neurons with nutrition in order to support their survival. Nowadays, many studies show that BDNF has played an important role in BD, based on its functions in CNS (Post RM, 2007). In addition, BDNF also benefits the growth and maintenance of intercellular connections, acts as a neurotransmitter modulator, and plays a key role in plasticity mechanisms. Therefore, abnormal BDNF level can have negative effects on neuronal differentiation and synaptic function leading to brain alterations (Palomino A, *et al*., 2006).

ANK3 is also known as ANK-G, a member of ankyrins family. Ankyrins are a protein family, whose functions are connecting the integral membrane proteins to the underlying spectrin-actin cytoskeleton. Moreover, ANK3 is significant in activities like cell contact, motion, proliferation, etc. ANK3 is composed of three structural domains: An amino-terminal domain containing multiple ankyrin repeats, a central region with a highly conserved spectrin binding domain, and a carboxy-terminal regulatory domain which is the least conserved and subject to variation. ANK3 was originally found at the axonal initial segment and nodes of Ranvier of neurons in the central and peripheral nervous systems. In recent research, more and more discoveries reveal that ANK3 would be a risk factor of BD.

## LITERATURE REVIEW

### *Brain-Derived Neurotrophic Factor (BDNF) and Bipolar Disorder (BD)*

In fact, the real reason of BD is still unknown. However, numerous experiments aim to work out that changes of BDNF levels

may contribute to risks of BD, and many different hypotheses have been put forward.

On the one hand, numerous researchers have found that higher BDNF levels have something to do with it. Barbosa IG and his colleagues have done some experiments about this and they draw a conclusion that BDNF levels rise in the circulation of BD patients, because patients in manic episodes presented a 1.90-fold increase in BDNF levels (p=0.001), while patients in remission presented a 1.64-fold increase in them (p=0.03) (Barbosa IG, *et al*., 2013). Their experiment gives evidence to a hypothesis that higher BDNF plasma levels may cause BD. Another experiment was conducted by Munkholm K, and they got a similar result. Compared with healthy control subjects, levels of BDNF were significantly elevated in BD patients in euthymic-($p<0.05$), depressed-($p<0.005$) and manic or hypomanic ($p<0.005$) states. Within BD patients, adjusting for medication, there was no significant difference in BDNF levels between affective states, with equally elevated levels present in euthymic, depressive and manic or hypomanic patients. On the other hand, levels of BDNF were higher in patients with longer duration of illness compared with patients with shorter duration of illness (Munkholm K, *et al*., 2014).

On the other hand, many studies also argue that lower BDNF levels would be a remarkable factor of BD. Lin PY gives information about recent studies, which illustrate that reduced BDNF levels are a state-dependent biomarker in manic and major depressive states of BD, because levels grow after treatment. Researcher's meta-analysed blood BDNF levels between BD patients with different emotional states and healthy controls. The result indicated that, overall, BD patients had a lower levels of BDNF than healthy ones ($p=1 \times 10.4$). In this study, we should pay attention to that the stark difference existed only when making a comparison between patients in manic (p=0.0008) or depressed (p=0.02) state and controls, but not in healthy state (p=0.25). Also noteworthy is the fact that after pharmacological treatment of manic episode, BDNF levels were dramatically increased (p=0.01) (Lin PY, 2009).

As shown in *Figure 1*, all the figures in those experiments have revealed that abnormal BDNF levels would be discovered in patients' brains, and this phenomenon indicates that changes in BDNF level will influence BD, regardless of higher levels or lower levels. Noteworthy is the fact that lower BDNF levels would be reduced dramatically in manic episodes, and this might be a biological marker for BD, which deserves more experiments to explore powerful evidence.

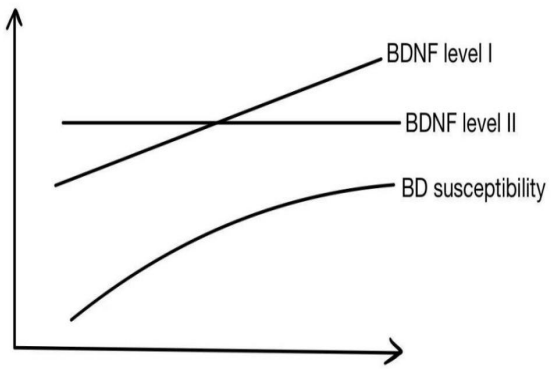


**Figure 1: Brain-Derived Neurotrophic Factor (BDNF) level I means higher levels of BDNF in BD patients' brains, and this would cause a higher chance for Bipolar Disorder (BD), to some extent. BDNF level II means lower levels of BDNF, and this would also contribute to a higher susceptibility of BD. As shown in this figure, with levels of BDNF changing, BD susceptibility increases to some degree**

However, there are also small scales of studies strongly suggesting that the BDNF gene is unlikely to confer susceptibility to BD. For instance, Nakata and his colleagues used matched case-control association design in a Japanese population, and found there was no evidence for an allelic or genotypic association of two polymorphisms of the BDNF gene with BD. Furthermore, no significant association was observed between these polymorphisms and either of two diagnostic subtypes (BD type I and BD type II). In this case, these results show that the association between BDNF and BD susceptibility is still not explicit, meaning more experiments are urgently needed (Nakata K, *et al*., 2003).

### *BDNF and rapid cycling*

Recently, there are a bunch of articles reporting an idea that SNP of BDNF has play a significant role in rapid cycling of BD. Based on this hypothesis, more and more researchers start to devote themselves to this work.

In this field, most experiments aim to detect the association between those genes and BD by testing some markers at different levels and by testing the illness categories of BD type I and II and rapid cycling. Method researchers performed a family-based association study and haplotype analyses using four single SNPs and the *Val66Met* and GT(n) repeat polymorphisms. In the results, the *Val66Met* and GT(n) were significantly linked with BD using transmission disequilibrium analyses (p=0.02, 0.009, 0.001 and 0.008 respectively). According to DSM-IV, noteworthy is the fact that the effect at these markers was mainly caused by the rapid-cycling patients. In conclusion, BDNF variants seem to predict risk for developing rapid cycling (Liu L, *et al*., 2008).

Furthermore it is interesting to note that SNP *rs7127507* is associated with rapid cycling, and no other SNP gives any information about association with rapid cycling (Müller DJ, *et al*., 2006). In addition, Muller and his colleagues also published an article that several markers on the gene BDNF has an important association with BD and rapid cycling, and this finding came from a large number of rapid cycling patients in their samples (Müller DJ, *et al*., 2006).

By way of conclusion, BDNF has been proved to be an important aspect in BD susceptibility and its levels' changes would have many impacts on BD. Moreover, rapid cycling is a remarkable symptom or as a symbol in BD, because most BD patients tend to have rapid cycling during this process. Therefore, findings about the association between BDNF and rapid cycling in BD are rather valuable, and mutation in BDNF or some variants of *BDNF* gene may have considerable effects on rapid cycling. But on the other hand, the exact mechanism of how BDNF affects rapid cycling is in vague, which means more efforts should be invested. In addition, this will benefit the patients who are bothered by BD and build up an awareness of this field.

### *Ankyrin-3 (ANK3) and Bipolar Disorder (BD)*

**Cis-regulation of Ankyrin-3 (ANK3) and Bipolar Disorder (BD):** ANK3 and its protein may have some significant effects on cognitive functions or neuronal activities in ways which can cause more chance for BD susceptibility (Rueckert EH, *et al*., 2013). Consequently, making sure whether ANK3 is a risk factor of BD or not is significant. There are many spliced transcripts encoded by ANK3 can be chosen, containing more than 50 known exons (mRNA lengths ranging from 5 kb to 17 kb), thus mutation in ANK3 or variants of ANK3 can be easy to have some negative effects on BD patients, or increase the chance to BD (Kordeli E, *et al*., 1995; Hopitzan AA, *et al*., 2005).

Many studies have tested cis-regulatory impacts on ANK3, in order to investigate a more exact association between ANK3 and BD susceptibility. Researchers made use of a more sensitive, exon-specific custom expression assay of mRNA, and qualified splice variants in some brain circumstances. What is more, they depicted an association between cerebellar levels of ex-

pressions of a certain brain-specific ANK3 isoform and gene variants at ANK3 correlated with BD, which would be powerful to prove that ANK3 has an important impact on BD. Additionally, they have examined distinguished regulations of start sites of different ANK3 transcription, BD-correlated SNP (*rs1938526*) allelic variation linked to a valuable difference in cerebellar expression of this brain-specific transcript of ANK3, which suggests that BD susceptibility may be related to a brain-specific transcriptional effects of ANK3 cis-regulation.

By way of conclusion, it remains unclear whether the cis-regulatory effects on ANK3 transcripts are specific to the cerebellum or discovered in other brain domains possibly involved in BD. Alternatively, researchers found that exon1b-initiated ANK3 transcripts in the cerebellum was dominant so the signal may be evident, while another reason was the limited degree of cellular diversity (Rueckert EH, *et al*., 2013). But what can be ensured is that cis-regulatory effects on ANK3 transcripts would influence BD susceptibility, thus more researches are required in order to figure out if ANK3 has played a key role in BD. In this case, it would be beneficial for an improvement for BD treatment or medicine.

### *Impacts of Ankyrin-3 (ANK3) variants*

Some researchers made use of Genome-Wide Association Studies (GWASs) to explore whether ANK3 is a promising candidate of a susceptibility gene of BD. Other than that, there are some studies have indicated that there are much evidence to support an allelic heterogeneity and show how important ANK3 for BD, which means this is relevant with ANK3 variants (Ruberto G, *et al*., 2011).

In recent years, cognitive disorders have been examined in BD patients and their parents or siblings, indicating that processes of cognition may be influenced by those susceptibility genes. *ANK3* codes for Ankyrin-3, which is a kind of proteins. These proteins regulate sodium gated ion channels to play a key role in facilitating the spreading of action potentials. As the efficiency of the transmission of numerous neuronal impulses would be affected by ANK3, possible cognitive influences caused by relevant variations of this gene cannot be ignored (Hatzimanolis A, *et al*., 2012). Because of ANK3's functions, mutations in ANK3 or any variant will induce numerous cognitive changes in patients' brains, and this may be the main reason to explain why most BD patients have cognitive disorders more or less.

Recently, a Single Nucleotide Polymorphism (SNP) of *ANK3* gene (*rs10994336*) has been detected by many independent genome-wide association studies. In this case, *rs10994336* was established as a significant marker to be a genetic candidate predisposing factor for BD. Moreover, the latest studies suggest that those effects of ANK3 variation on cognition of BD patients, their first degree but healthy relatives, and relevant controls by affecting sustained attention (Hori H, *et al*., 2014).

On the one hand, Hori H and his colleagues have analyzed almost 50 BD patients (a sample) and hundreds of healthy controls, detecting two risk variants' potential influences on many different neurocognitive domains related to ANK3 (*rs10761482* and *rs10994336*). When analyzing the results of it, compared with healthy subjects, in most neurocognitive domains tested, significantly worse performance has been observed. This poorer performance on verbal comprehension or memory with logic or speed of thoughts was linked to a risk C-allele of *rs10761482*. About visual memory and functions of executive capacity, bad performance mentioned above had a significant correlation with the allele. However, this poorer performance in this experiment has been found that researchers had not observed any valuable correlation in *rs10994336* (Schulze TG, *et al*., 2009). Therefore, in these two genes, which one is more important is still unknown, more powerful evidence needs to be examined.

On the other hand, Ferreira has reported a research that approximately 145 kb region around ANK3 was found to be contained by several SNPs. In some samples of United States and the British Isles, researchers did a meta-analysis in 6,000 healthy subjects and 4,000 cases and discovered a possible relationship between this region and BD. During this process, the strongest signal was examined in *rs10994336*, and its genotypes were imputed (Ferreira MA, *et al*., 2008). Therefore, researchers figure out if the connection signals of *rs10994336* and *rs9804199* can repeat in independent samples and if the two ANK3 markers which are divided by nearly 340 kb, affect risk of BD independently (Schulze TG, *et al*., 2009).

In order to work out more about how each SNP individually contribute to BD susceptibility in those various samples, those researchers examined influences of every SNP and possible correlation between PLINK with SNPs independently (Dudbridge F, 2008).

Through numerous samples and relevant analysis, researchers discovered an important excess of the C-allele. Moreover, the meta-analysis gave some information to support this observation. By way of conclusion, *rs10994335* and *rs9804190* alike were congruously correlated with BD in many samples they had analyzed, and both of them produced dramatic whole association through meta-analysis. And this result suggests that an association results that can be replicate are achievable in BD, with suitable sample sizes.

Furthermore, based on experiments conducted by Ferreira, they concluded that the risk factor of BD can be each of the two markers. It is hardly tested a LD which can be detected in both markers, which are located over 340 kb apart. And because they had found nothing about an interaction between two markers, their results may belong to true allelic heterogeneity, in which contributions of more than one remarkable variant in the same locus were implicated to risks of BD (Purcell S, *et al*., 2007).

One of other researches genotyped several SNPs of ANK3 originally discovered to be correlated with BD (*rs1938526*, *rs9804190* and *rs10994336*). Combining about 11,491 healthy controls and 435 BD cases, *rs9804190* and *rs10994336* have been observed to have the strongest association with BD. These analyses give further information about that BD involves more than one locus of risks and that BD has a specific susceptibility gene which is *ANK3* (Dudbridge F, 2008).

Another research conducted in Asia focused on the genetic association of some SNPs of ANK3 (*rs10994336* and *rs1938526*), and in previous meta-analysis of GWASs, researchers made use of some data of GWASs from Taiwan in Han-Chinese and numerous data coming from Japanese and Korean samples including cases and controls to prove a connection in the two genes' genome-wide. When researchers mixed those data sets and did a meta-analysis, *rs1938526* performed a strong association. What was reported in Caucasian GWASs had no difference with the allele which was over-represented. Nonetheless, researchers found no significant phenomenon in *rs10994336* (Tesli M, *et al*., 2011; Takata A, *et al*., 2011).

By way of conclusion, ANK3 has been proved by numerous experiments and researches that are significantly associated with BD susceptibility, even though its exact mechanism is not explicit. In the future, more information is needed to make sure the effects of ANK3 on the whole BD process, or to confirm whether *ANK3* is the key gene to activate some potential pathways and induce this disorder.

## DISCUSSION AND CONCLUSION

Considering that the suicide rate of BD and other many side effects, there is an urgent need to understand and the relevant gene mechanism and some potential risk factors, which can be beneficial for the improvement for a more effective treatment. So far, many studies have paid attention to the impacts of BDNF and ANK3, seen as the most important risk factors of BD susceptibility. In this case, studies have shown that the level of BDNF would influence BD, whether it is high or low. In addition, researchers found that BDNF is related to rapid cycling in BD, which means an potential pathway of rapid cycling may be discovered. Furthermore, ANK3 is regarded as a significant risk factor in BD. On the one hand, in recent years, more and more researchers start to explore the possible influences

of cis-regulation of ANK3. Cis-regulatory effects of ANK3 transcripts have been found, and there is an association between it and BD susceptibility. On the other hand, ANK3's variants have been detected how they affect BD and found that *rs10994336* might be the most valuable one, because most relevant studies have proved there is a relationship between *rs10994336* and BD, which may contribute to the exploration in BD treatment.

However, almost all studies have not illustrated an exact mechanism about how relevant genes contribute to BD, and because of this, there is not a rather effective treatment for BD patients. This article gathers some key information about recent studies, which may be helpful to those who are specialized in drug or medicine. Additionally, as BD has become an important disease in a modern society, how to set up a high-efficient therapy is necessary for future investigation. Therefore, it is apparent that massive efforts should be devoted in the future to figure out a clearer association between BD and BDNF or *ANK3* or other risk genes.

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