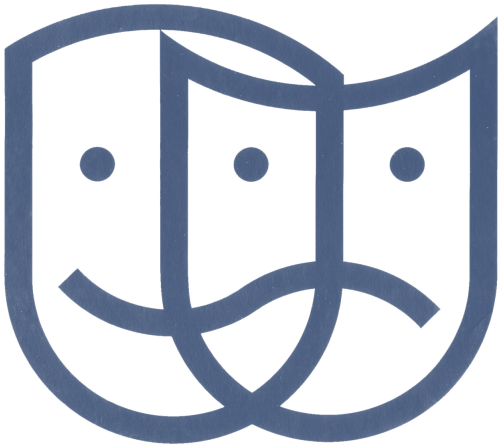
GENETIC FACTORS OF BIPOLAR DISORDER

BACHELOR THESIS



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Genetic factors of bipolar disorder

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ABSTRACT

Bipolar disorder is one of the most severe mental illnesses worldwide where it affects approximately 1% of the population. It is a disease where patients experience episodes of extreme mania and depression and for this reason, suicide attempts are very high among these patients. It is evidenced that bipolar disorder is highly heritable (60%-80%) providing the evidence that there is a strong genetic component in this disorder. Researchers investigated different genes and polymorphisms that could be important in the higher risk of developing BD. However, environmental factors play a crucial role as well. Different aspects of environmental factors are found to be important, from prenatal stress exposure to the experience of events in the late adolescence. This thesis provides an overview of the different risk factors of BD, in which the genetic risk factors are highlighted.

Keywords: Bipolar disorder – mental illness – genetic risk factors – environmental exposure – polymorphisms – miRNA – risk genes

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ABBREVIATIONS

BD – Bipolar Disorder
QoL – Quality of Life
BPS – Bipolar spectrum disorder
PTSD – Posttraumatic stress disorder
GWAS – Genome-wide Association Studies
SNP- Single Nucleotide Polymorphism
ANK3 – Ankyrin-G
WM – White matter
PFC – Prefrontal Cortex
GSK3ß – Glycogen synthase kinase-3 ß isoenzyme
BDNF – Brain-derived neurotrophic factor
ADM – Adrenomedullin
NO- Nitric Oxide
HPA – Hypothalamic Pituitary Axis
NCAN – Neurocan
miRNA – MicroRNA

INTRODUCTION

BIPOLAR DISORDER

Bipolar disorder (BD) is a mood disorder that manifests itself in patients experiencing episodes of severe mania and depression. Depressive episodes include lower levels of energy, mood and less feeling of enjoyment. These problems often go hand in hand with disturbances in sleep and other problems. On the other hand, mania is the opposite of depression, which causes patients to feel extremely energetic and experience much happiness or irritations. Between these episodes, there is an emotional state of euthymia which is a neutral state of emotion (Sagar & Pattanayak, 2016). The pathogenesis of bipolar disorder is often characterized by increasing number of episodes with shorter intervals between these episodes. Moreover, there will be a higher cognitive dysfunction when there will be shorter, more frequent intervals between these episodes (Kessing et al., 2017). The quality of life (QoL) is reduced in patients with bipolar disorder as well (Madhav et al., 2017). Many studies found that 11% of the patients with BD have died by the cause of suicide. Most of these suicide attempts happen during the depressive episodes and the mixed states as they call it in the article of Pallaskorpi et al., 2017.

Normally, the age of onset of BD is when the patients are in their early 40s, so when they are in their late adolescence. But BD also has its onset during early adulthood, so begin 20s. The onset occurs in the most critical periods of life, during educational and social development. Therefore, the consequences and the disease will be chronic across the life span (Merikangas et al., 2011). Moreover, recent studies found an increase in BD in childhood. They showed that children with BD would experience more periods of mixed states and that they would feel more irritated and aggressive, in comparison with the symptoms of the adult version of BD. In fact, the findings of the study of Ryles et al. also confirmed some conclusions of another recent study, where they stated that irritability is the second most frequent symptom of manic periods in BD in childhood. Despite the finding that irritability is increased in children with BD, it should be noted that irritability could be a common feeling when children are in their developmental phase. Moreover, irritability as well as a higher energy level, could be a symptom of another disorder like ADHD. Ryles et al. also found a difference in cognitive dysfunction associated with BD between children and patients who are in their adulthood. They found that cognitive dysfunctions like speed and content of thought, were of increased prominence. Furthermore, the frequency of BD symptoms seems to differ between adult patients with BD and children or young adolescents (Ryles, Meyer, Manes, Macmillan, & Scott, 2017).

PREVALENCE

Bipolar disorder affects approximately 1% to 2% of the worldwide population. However, several studies indicate that nowadays, the prevalence of bipolar disease is increasing. In the article of Merikangas et al., 2012, a study was described where the prevalence of BD differed from 0,1% in Nigeria to 3,3% in the United States, with a mean of 1,2%. In the same study, a worldwide survey has been performed, which is called the World Mental Health survey. In this survey, the prevalence of bipolar spectrum disorder (BPS) worldwide was investigated. They estimated the prevalence of BPS at 2,4%, where India scored the lowest and the US the highest. Another study from 2000 described that studies at that time indicated a prevalence of BD that varies from 0,3% to 1,5% (Lewinsohn et al., 2000). Thus, in thirteen years the prevalence of BD would be increased over the past years.

Finally, studies tried to find differences in BD occurrence across genders but it is evidenced that there are no gender differences in the prevalence of BD (Cipriani, Reid, Ah, Macritchie, & Geddes, 2013).

FAMILIAR RISKS

Research demonstrated that the risk of getting bipolar disease is higher when you are a biological relative of someone with bipolar disease. This might be one of the biggest predictors of getting BD (Scott et al., 2016). So, there is a strong indication of a relation between BD and genetics, which will be discussed later on in this thesis (Sagar & Pattanayak, 2016).

COMORBIDITIES

The article of Merikangas et al., 2012 described that more than half of the patients with BD also have a history with other psychiatric disorders. These other disorders include mainly anxiety or panic disorders. It was evidenced that the chance of comorbidity of anxiety disorder in combination with BD also increases after the age of 30 (Bajor et al., 2013). Anxiety disorders are a very common comorbidity for BD. More specifically, around 60% of the adult patients with BD also suffer from an anxiety disorder (Duffy et al., 2013). A possible reason for that could be that the depressive episodes that are seen in BD and depression together are often associated with anxiety. Furthermore, a low self-esteem co-occurs in BD, even in euthymia, with anxiety. This could be another reason why the prevalence of BD and anxiety disorder are as high as they are. Lastly, it is found that anxiety disorders occur more often in people that are relatives of the BD patients (Pavlova, Perlis, Alda, & Uher, 2015). Offspring of parents where at least one parent suffers from BD, are at higher risk for developing an anxiety disorder and for developing mood disorders like BD later in life (Duffy et al., 2013). Comorbidities like personality disorder and substance abuse disorder are associated with bipolar disorder as well (Marangoni, Hernandez, & Faedda, 2016).

Medical comorbidities play a role too in the association with BD, like diabetes and obesity (Kim, Santos, Gage, Marchetto, & Kesby, 2017). Moreover, patients with BD develop a higher risk for getting cardiovascular diseases when they suffer from metabolic pathologies as well (Vancampfort et al., 2013).

A study has shown that people with bipolar disorder have an elevated risk for posttraumatic stress disorder (PTSD), more than people without BD. The patients with BD and PTSD also have a decreased QoL. These reductions in QoL were highest when a patient found himself in a depressive episode (Bajor et al., 2013).

SYMPTOMS

People with BD often experience different episodes of depression and mania. During these episodes, many psychotic features occur. During manic periods, hallucinations and delusions are often experienced by patients with BD. A so-called thought disorder can also occur during a manic episode. This disorder expresses with symptoms like pressure of speech and illogical thoughts. Thought disorder is common in patients with Schizophrenia as well (Dunayevich & Keck, 2000). Many patients also experience another form of mania, which is called ‘delirious mania’. This type of mania is stated when the patient’s symptoms cannot be distinguished from the symptoms of schizophrenia (Carlson

et al., 2017). Delirious mania is typically described by the loss of appetite in patients, severe insomnia and bizarre delusions and hallucinations (Dunayevich & Keck, 2000).

According to the DSM, a guideline in which all psychiatric disorders are described, depressive episodes of bipolar disorder are characterized by loss of energy, melancholia and withdrawal of social interactions (Marangoni et al., 2016).

MISDIAGNOSIS

BD is often misdiagnosed. Many patients with bipolar disorder frequently experience episodes of depression. Therefore, almost 40% of the patients with bipolar disorder were first diagnosed with depression or major depressive disorder. However, when sudden manic episodes occur, the diagnosis is reformed into bipolar disorder, but only if this was reported as pathological by the patient himself (Kim et al., 2017). Because of the delay in the correct diagnosis, there is a delay in treatment. Even more specific, the time between the 'wrong' and the 'right' diagnosis could last for almost a decade. Therefore, patients are diagnosed with depression, only to be re-diagnosed with bipolar disorder after ten years. During these years, patients with BD do not receive the right treatment. Many factors play a role in this misdiagnosis. Firstly, when the onset of depression is before their 30s, the conversion to bipolar disorder diagnosis doubles in comparison with patients whose onset was later in life. Furthermore, misdiagnosed BD patient will probably show resistance to antidepressant medication. As a result, after this is concluded by the treating doctor, it could mean that patients do not actually have a depression but they might be suffering of bipolar disease. Fritz et al. described that an earlier detection of BD when the symptoms are early recognized, should cause better diagnosing and earlier treatment of BD (Fritz et al., 2017).

CURRENT THERAPIES

Mood stabilizers are the most commonly used therapeutic treatments in bipolar disorder. These type of medicines stabilizes the amplitude of the depressive and manic episodes (Cipriani et al., 2013). Periods of mania and depression are reduced to the euthymic state. Furthermore, treatment also has its maintenance goals. Some of these are targeting the prevention of relapse and reduction of episode symptoms and elevating the social level (Geddes & Miklowitz, 2013).

One of the best well-known mood stabilizers of bipolar disorder is lithium. It has also been the only mood stabilizer for many years. Lithium upregulates the neurotrophic and protective responses. These responses could be therapeutic for the impairments in psychiatric disorders (De-Paula, Gattaz, & Forlenza, 2016). However, studies demonstrated that 40% of the patients with BD does not respond very adequately to lithium. Over the past few years, studies showed that some new therapies are popping up. Therefore, researchers started to investigate these new therapies. One of them is valproate. Valproate could be a good therapy for long-term treatment in BD. Valproate is similar to lithium, because lithium and valproate are suitable therapeutic agents when BD relapses need to be prevented (Cipriani et al., 2013). However, the research of Cipriani et al. did not find any favored effect of valproate when compared with lithium. What they did find was that a combination therapy of lithium and valproate are more likely to prevent relapse than therapy where just valproate was given.

BRAIN PATHOLOGIES

Brain pathologies are still poorly understood in bipolar disorder and it is currently a hot topic in neuroscience. Research evidenced that during depressive episodes in a patient with BD, the volume of neuronal densities were decreased in dentate gyrus areas, which are subfields of the hippocampus in depressive episodes (Maletic & Raison, 2014). Furthermore, researchers demonstrated that oxidative stress is involved in the pathogenesis of BD. High levels of oxidative damage were found in the blood and brain. Oxidative stress can damage neurons and therefore, may cause the reductions in volume of the hippocampal subfields (Elvsashagen et al., 2016). More neuroimaging studies showed that neural abnormalities in gray matter are common in BD patients. Decreased white matter density are also found in the PFC of BD patients. Genetic markers are demonstrated that could be involved in the impaired neural development in bipolar disorder (Lippard et al., 2016). This will be described later on.

There are some results that provide possible biomarkers for bipolar disorder, which could provide targets for therapy development (Kessing et al., 2017).

CAUSES

The underlying causes of bipolar disorder are thought to be mostly genetic. Moreover, it is stated that BD has the highest rates of heritability among all psychiatric disorders (Hanford, Nazarov, Hall, & Sassi, 2016). Twin studies estimated heritability is around 70% to 80% (Uher, 2014). Furthermore, there are some environmental risks and possible causes of BD, which will be discussed later on (Bortolato et al., 2017).

ENVIRONMENTAL RISK FACTORS OF BD

Mental disorders are caused by environmental exposure as well as genetic predispositions (Uher, 2014). Uprising evidence states that the interaction between genes and environment plays a big role in the pathology of BD. Because the heritability is close to 80%, there must be some sort of role of the environment. For there are many comorbidities that go with BD, researchers are assuming that environmental risk factors will increase the chance of comorbidities. Life expectancy will be lower because of this (Bortolato et al., 2017).

It is estimated that 50% of the patients with BD were maltreated in various ways in their childhood. Moreover, this maltreatment could also result in an earlier onset of BD in these patients and it may also result in a higher risk of attempting suicide and experiencing more relapses during pathogenesis (Pavlova et al., 2016). Familiar associations play a role in the risk of developing BD as well. It was proven that children of parents with psychiatric disorders like BD are more sensitive to environmental exposure, prenatal and postnatal (Uher, 2014). This could mean that genes and environment interact with each other. Experiencing a severe infection during pregnancy can result in a higher risk of offspring that develop psychotic illnesses (Uher, 2014). However, these results are not consistent in every research. Some studies found a 6-fold increased risk for developing BD after having an infection during pregnancy and for example, the study of Marangoni et al., 2016 did not find any correlations at all. Smoking during pregnancy could also increase the risk, but this is only found in one study, so no real conclusions could be made from that. Furthermore, preterm birth seems to increase the risk as well (Uher, 2014).

As said before, the risk of developing an anxiety disorder is elevated in patients with BD. Patients with BD were very often exposed to maltreatment, stressful or even traumatic events in their childhood (Pavlova et al., 2016). One example of a traumatic event could be the exposure of a child with their parent who suffers from bipolar disorder. Children who were exposed to maternal neglect or other exposures during early childhood when at least one of their parents has BD have an increased risk of developing BD (Doucette et al., 2014). Stressful experiences are correlated with a polymorphism in BDNF, which results in stress triggering BD in people with this specific polymorphism (Uher, 2014) These exposures are also risk factors for developing an anxiety disorder (Pavlova et al., 2015).

During childhood, when a child loses one of their parents before their fifth there is an increased risk of developing BD with a 2,4-fold (Marangoni et al., 2016).

Later in life, drug abuse like usage of cannabis and other types of drug exposure during adulthood shows a strong positive correlation with BD in several studies. Another study from Marangoni et al., 2016 showed the investigation of the environmental risk factors of BD. Head injury was found to elevate the risk of a BD pathology later in life.

GENETIC RISK FACTORS OF BD

Genome-wide association studies (GWAS) were conducted to determine that genes or genetic factors could play an important role in developing bipolar disorder. However, many articles stated that genetic research about bipolar disorder did not make any hard evidence. Mainly because of the sample sizes. Studies that were conducted worked with small sample sizes so very often there could not be made valid conclusions (Escamilla & Zavala, 2008).

Despite this, many researchers wanted to investigate genes to find out if these genes make a link with bipolar disorder. They analyzed genes that were associated with neurophysiological processes which contribute to or are also impaired in BD pathologies. Analyzed genes that play a role in circadian rhythms, in the dopaminergic and serotonergic pathway, brain development and neurotropism. Moreover, genes that were associated with schizophrenia were also investigated whether the same genes associate with BD. (Escamilla & Zavala, 2008).

RISK GENES

Bipolar disorder is often being correlated with genetic causalities. As said before, BD is heritable for almost 80%. So, when genetic relatedness decreases, the risk of getting BD also diminishes (Craddock & Sklar, 2013).

Many studies were performed to find polymorphisms that could have an association with bipolar disorder. They found that multiple genes would be involved in BD where each of the genes contributes for a small part in the pathogenesis of BD (Lett et al., 2011) . Some of the most investigated risk genes are described below.

ANK3

The polymorphism (SNP) rs9804190 of the ANK3 gene is found to be associated with bipolar disorder (Lippard et al., 2016). ANK3 is an adaptor protein which encodes for Ankyrin-G. It is localized in axons and supports the maintenance of sodium channels and adhesion molecules (Schulze et al., 2009, Ferreira et al., 2009) but it is also involved in the motility, activation, proliferation and contact of the cell (Lett et al., 2011). It is thought that ANK3 is involved in the abnormalities in neural development in BD. Gray and white matter densities are changed in BD. White matter (WM) is decreased in the prefrontal cortex (PFC) in BD patients. ANK3 is involved in WM changes in BD. As said before, ANK3 is involved in the regulation of stabilization and localization of ion channels and adhesion molecules. They fulfill this role in the nodes of Ranvier. Similarly, they play a role in the development of the cortex and the onset of myelination (Lippard et al., 2016). Furthermore, ANK3 is targeted by miR-34. This is a microRNA which also is involved in BD. An elevated expression of miR-34 results in decreased levels of ANK3 (Bavamian et al., 2015). This will be discussed later on. ANK3 expression was tested in mice and they found decreased levels of ANK3 in BD and after lithium treatment these levels would increase again. Therefore, ANK3 could be a possible therapeutic target for bipolar disorder (Lippard et al., 2016).
Another SNP, that lies about 340kb apart from the rs9804190 in the ANK3 gene, seems to be

important in bipolar disorder and it is called rs10994336. The research of Schulze et al., 2009 found a significant association of the rs10994336 and BD. Given the fact that more polymorphisms of the ANK3 gene, it is becoming clear that ANK3 is an important risk gene in the pathogenesis of BD.

CACNA1C

Another gene that is involved in BD is CACNA1C. CACNA1C is a risk allele for BD but it has a very frequent occurrence in humans, of around 30%. When a person is carrying the risk allele, the chance of developing BD is increased with 18%. However, not all people who carry the gene do get the disorder, so many other (non-)genetic factors play a role here (Craddock & Sklar, 2013). CACNA1C is a gene that encodes for the alpha subunit of L-type voltage-dependent calcium channel (Fiorentino et al., 2016). CACNA1C is involved in the regulation of dendritic development, neuronal survival, synaptic plasticity and memory and learning as said in the article of (Zhang et al., 2013). Zhang et al., investigated the role of three polymorphisms of CACNA1C. They found significant association between the rs1051375 polymorphism and BD. Patients with this SNP were found to have a lower age of onset in the development of BD. Another SNP they studied, called rs1006737, was found to be associated with brain pathologies of BD. An elevated response in the amygdala after emotional stimuli was found and facial emotional recognition was impaired. The amygdala is the target of this risk allele rs1006737. These impairments increase the risk of BD (Zhang et al., 2013).

Moreover, treatment with lithium is shown to downregulate the CACNA1C gene in the mouse brain (Ferreira et al., 2008). Ferreira et al., 2009 stated that impairments in ion channels could be involved in bipolar disorder psychopathology. It is also found that CACNA1C as well as ANK3 is associated with not only BD but also with schizophrenia (Lett et al., 2011).

GSK3ß

GSK3ß (glycogen synthase kinase-3 ß isoenzyme) is a serine threonine kinase that acts in the ATK/WNT neuronal signaling pathway, where it regulates cell growth, cell survival, gene expression and microtubule formation (Lett et al., 2011). This kinase is found to be associated with bipolar disorder and more specifically, it is an important target when it comes to lithium treatment due to the inhibitory function of lithium on GSK3ß (Oedegaard et al., 2016).

Research also demonstrated that brain-derived neurotrophic factor (BDNF) is associated with GSK3ß. BDNF stimulates neuronal cell growth and repair. Increased GSK3ß impairs BDNF by inhibiting the protein phosphorylation. Lithium treatment causes higher levels of BDNF in the brain.

Jiménez et al., 2014 investigated the association between GSK3ß and impulsivity. Impulsivity is often increased in BD patients, during acute phases and euthymia. Because of this impulsive behavior, BD patients will be more sensitive to abuse substances and attempting suicide, as told before. Jiménez et al., 2014 stated that variability in the GSK3ß gene alleles causes increased impulsive behavior in BD patients, in specific attentional impulsivity. Lithium inhibits impulsive behavior by inhibiting GSK3ß. GSK3ß is shown to be a mediator in the serotonergic pathway. This pathway is involved in mood disorders which means it is also involved in the pathogenesis of BD. In the study of Jiménez et al., 2014, they found that the risk allele of GSK3ß causes increased impulsive behavior, measured as difficulties in maintain attention and tolerating cognitive complex behavior. These worsened

performances in impulsivity tasks were also correlated with the number of suicide attempts in patients with BD (Jiménez et al., 2014).

ADM

ADM stands for adrenomedullin and it functions as a neuropeptide (Savas et al., 2002). It is also found that ADM plays a role within cardiovascular functions of the body and in the homeostasis of body fluid electrolytes. Adrenomedullin is involved in the hypothalamic-pituitary-adrenal axis (HPA) and mood disorders are often associated with dysregulation in the HPA axis (Savas et al., 2002). Huang et al., 2014 found an association between single nucleotide polymorphisms (SNPs) that are located near the ADM gene on chromosome 11p. The SNPs near ADM should be associated with BD according to the marker model of Huang et al. Adrenomedullin is widely expressed in the brain. Elevated levels of plasm ADM are reported to occur in the brain of BD patients (Huang et al., 2010). In the study of Savas, levels of ADM were found 2-fold higher in manic BD patients which suggests that ADM could serve as an indicator in the severity of the manic episode.

Additionally, ADM is associated with NO (nitric oxide) in a way that ADM stimulates the release of NO. NO causes vasorelaxation. Savas et al. also studied the specific role of NO in BD and they found that levels of NO similarly to ADM, were elevated in patients with BD.(Savas et al., 2002).

NCAN

Another gene that seems to be involved in BD is the NCAN gene, the neurocan gene. Neurocan is an extracellular matrix glycoprotein where it functions in the regulation of cell adhesion and migration (Cichon et al., 2011). It was found by a GWAS study that this risk gene is located on chromosome 19p13.11 (Muhleisen et al., 2014). In the study of Mu et al., they found a SNP called rs1064395 and they showed that genetic variations of NCAN play a significant role in the pathogenesis of bipolar disorder. Levels of NCAN where decreased in patients with BD and in patients with depression. In BD mice, NCAN is localized in cortical and hippocampal brain areas, which are also regions were BD has its implications. NCAN is also expressed in the hippocampus of the human brain and in BD patients it is suggested that the underlying mechanisms of NCAN are disturbed (Cichon et al., 2011). Moreover, expression of NCAN is reduced in two Brodmann areas in BD patients (Muhleisen et al., 2014)

MIRNA

Recent studies showed that microRNA's (miRNA) play an important role in neuronal development, differentiation and plasticity, dendritic spine morphology and circadian-clock periods. All these processes are thought to contribute in the pathogenesis of bipolar disorder (Rong et al., 2011). In postmortem studies, differences in expression of miRNAs were found in cortical brain areas that were associated with BD (Fiorentino et al., 2016). In this sub chapter, some miRNAs are described, which are all involved in bipolar disorder in some way.

MIR-34A

One of the studied miRNA's is miR-34a. MiR-34a is a miRNA that belongs to the miR-34 family. It has already been shown that miR-34a levels are reduced after lithium or valproate treatment, the two therapies which were described earlier in this thesis. The article of Bavamian et al., 2015 provided evidence that miR-34a levels are increased in the cerebellum of patients with bipolar disorder.

With the help of GWAS studies, Bavamian et al. identified 25 targets of miR-34a. miR-34a overexpression caused the targeting and silencing of the already known to be associated with BD, ANK3, DDN, CACNB3 genes. Overexpression of miR-34a causes decreased levels of ANK3 and CACNB3 which are negatively correlated which means that there will be an impairment of neuronal differentiation and morphology. These target genes are all involved in neurodevelopment which suggests that miR-34a is important in the pathogenesis of BD through the effects on neurodevelopment (Bavamian et al., 2015).

MIR-708

miR-708 is an miRNA that is located on the first intron of ODZ4 where it is found to be co-expressed with ODZ4 itself in the human nervous system (Bavamian et al., 2015; Fiorentino et al., 2016; Woo, Yu, Kumar, & Reifman, 2017). Fiorentino et al., 2016 also performed a gene-based analysis where they found that nine miRNAs including miR-708 showed significant difference in BD. A postpartum study of women with BD showed that expression of miR-708 was different in monocytes compared to healthy controls. In mouse models, expression of miR-708 was found to be upregulated in hippocampal neurons. The binding sites of miR-708 respond to antipsychotic drugs (Fiorentino et al., 2016). However, more research is needed to find out more about the miR-708 risk allele contributing in BD.

MIR-134

Another mi-RNA that is involved in the neuronal remodeling after synaptic activity, is miR-134 (Schratt et al., 2006). This miRNA is involved in the regulation of the dendritic spine size. Since BD is associated with impairments in neuronal development, it is possible that miR-134 is associated with the pathophysiology of BD. Rong et al., 2011, found that miR-134 levels were significantly lower in the manic periods of BD patients compared to healthy controls. In the same research, the BD patients were treated and their plasma levels of miR-134 were measured. After four weeks of treatment they found that the miR-134 levels were significantly increased and were almost completely normalized

when compared to the plasma levels of healthy controls. The researchers of the article suggest that miR-134 could be an important marker for the pathogenesis of BD, mainly in manic episodes which could be associated with mood stabilizing treatment (Rong et al., 2011).

CONCLUSION

Bipolar disorder is a psychopathological disease in which patients experience severe periods of mania and depression. In these manic episodes, people experience extreme levels of energy and in depressive episodes there are lower levels of energy. Many suicide attempts occur during these episodes. Consequently, the quality of life is also reduced in BD patients.

Around 1% or 2% of the population worldwide are diagnosed with BD. This prevalence differs for many countries. Research demonstrated that Nigeria has a BD prevalence of 0,1% while the USA has a BD prevalence of 3,3%. This prevalence is thought to be caused by higher risk factors such as genetic predisposition or environmental factors. BD has its onset between the age of 20 to 40 but there are individual differences. Moreover, BD has its onset in the most critical periods in life, during educational, social and thus neural development. However, BD is found to occur during childhood as well. Controversially, many misdiagnosis take place when BD develops itself. Estimations were made that around 40% of the people, who actually suffer from BD are first being diagnosed with major depressive disorder because of the high frequency of depressive episodes.

BD occurs with many comorbidities. The most common comorbidity seems to be anxiety disorder. Almost 60% of the adult patients with BD suffer from an anxiety disorder as well. Moreover, comorbidities like substance use disorder, personality disorder and post-traumatic stress syndrome are at high risk for people with BD.

Brain pathologies in BD mostly occur in the white and gray matter. Reduced densities in these matters are found in different brain areas like the hippocampus, the prefrontal cortex and other cortical areas.

The current therapies of bipolar disorder mainly consist of lithium treatment. This is the most well-known mood stabilizer a patient with BD can receive nowadays. However, researchers found that lithium does not function well in all patients with BD. More studies are conducted to develop new possible therapies for BD. One of them is valproate, which is a mood stabilizer as well. But further research is still needed to find a better treatment for BD.

It is evidenced that bipolar disorder is heritable for 60-80%. However, other factors that play a role are environmental influences. There are many comorbidities associated with BD, which means that environmental exposures certainly play a role. Firstly, familiar associations are important. Children whose parents were diagnosed with mental illness develop a higher sensitivity for pre- and postnatal environmental exposure. Furthermore, early exposure to stressful, traumatic events or maltreatment could elevate the risk of BD as well. Finally, drug abuse could also raise the sensitivity for developing bipolar disorder.

Many studies tried to find possible genetic markers to explain why some people develop an increased risk of getting bipolar disorder. Genome-wide association studies were conducted. Some of these studies found risk genes or alleles where variations could be involved in BD.

First, the ANK3 gene is described. A polymorphism called rs9804190 was found to be associated with BD. ANK3 is involved in neural development and abnormalities in this development were found in BD. In the disorder, white matter density is decreased because ANK3 levels are decreased. However, after treatment with lithium, ANK3 levels would be restored to relatively normal levels. Therefore, ANK3 is a good treatment target.

Next, the risk allele CACNA1C was found to be very common in people with BD. If a person carries this gene, the risk of developing BD will increase with 18%. CACNA1C is involved in dendritic development, neuronal survival, plasticity and in memory and learning. Three polymorphisms of CACNA1C seemed to play a role in BD pathogenesis. These polymorphisms were all increased in the brains of BD patients. Lithium treatment causes downregulations of the CACNA1C.

Next, GSK3ß was studied to be a risk gene in BD. GSK3ß causes for the expression of the kinase that is involved in the regulation of cell growth, survival, gene expression and microtubule formation. Increased levels of GSK3ß were found and it is shown that this gene plays an important role in the impulsive behavior in BD patients. Lithium treatment inhibits GSK3ß.

Another gene that is known to be important in BD pathogenesis is the NCAN gene which expresses neurocan. Neurocan is a glycoprotein which functions in the regulation of cell adhesion and migration. A polymorphism was found in BD patients which causes levels of NCAN to be decreased in patients who suffer from BD.

Studies also focused on miRNAs that are involved in the risk of developing BD, because many miRNAs are involved in brain development, plasticity and more. These processes are all involved in the pathogenesis of BD. This thesis described three types of miRNA which were found to be involved in BD.

Firstly, the miRNA called miR-34a. This is one of the most widely studied type of miRNA. This miRNA is expressed with elevated levels in BD patients. MiR-34a causes the expression of ANK3 for example, to lower. 25 targets of miR-34a were discovered of which they all seem to play an important role in the neuronal development deficits in bipolar disorder (Bavamian et al., 2015).

The second miRNA type is called miR-708. This miRNA caused some controversial results. Many studies found significant results between miR-708 and BD. Despite this, no clear results came out of these researches so all the studies that were mentioned in this thesis, gave the implication that future studies certainly are needed.

MiR-134 is the third miRNA that is described. Studies demonstrated that miR-134 is involved in neuronal developments and that miR-134 levels were lowered in brains of patients that suffer from bipolar disorder. Furthermore, treatment of lithium showed significant increases in the levels of miR-134, which shows that targeting this type of miRNA is used for therapeutic goals.

To summarize, bipolar disorder is a severe mental disorder that manifests through manic and depressive episodes. During depressive episodes, the suicide rate is extremely high compared to control groups. The disorder affects around 1% or 2% of the worldwide population. Bipolar disorder finds its causes in genetic disposition and environmental factors. This thesis was mainly focused on the genetic risk factors. Many GWAS studies were conducted to find out wat genes contribute to the pathogenesis of BD. These studies all provide possible targets to use in treatment and prevention of BD. However, more replications of these studies need to be conducted to provide the medical world with possible new targets for treatment.

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