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Genetics in bipolar disorder

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Vorwort

Mood disorders are widespread and devastating diseases. Since affective disorders harm many people effort must put into elucidation of the exact pathogenesis of bipolar disorder. Molecular psychiatry might help to achieve this aim. Maybe one day psychiatric genetics will help to draw exact lines between the different psychiatric diagnoses. This could lead to restructuring of nosology. Furthermore molecular genetics will give inview in exact disease mechanisms and therefore targets for development of new medication and laboratory markers. In addition the knowledge of inheritance could lead to strategies to prevent the outbreak of a mental disease. However one has to illuminate the gene-environment-interactions to detect strategies against disease onset. Although molecular psychiatry still has to overcome teething troubles, this is an attempt to review the genetics of bipolar affective disorder, an important psychiatric disease.

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Zusammenfassung

Die bipolare Depression hat einen starken, polygenetischen Erbgang. Obwohl die molekulare Psychiatrie noch in den Kinderschuhen steckt, wurden bereits viele Suszeptibilitätsgene gefunden, jedoch mit widersprüchlichen Resultaten. Kandidaten gehören zur Ionen-Kanal-Familie, besonders ANK und CACNA1C seien als Favoriten erwähnt. BDNF, das für den "brain derived neurotrophic factor" kodiert, scheint mit der bipolaren Störung in Kaukasiern assoziiert zu sein, jedoch nicht in Asiaten. BDNF könnte als Labor Marker dienen, da Serum Spiegel in manisch depressiven Patienten erniedrigt sind. Eine weitere prädisponierende Gruppe sind die „clock genes", die unter anderem ARNTL, CRY1 und CRY2, PER1-3 beinhaltet. Entgegen aller Erwartungen spielen die Serotonin Rezeptor Gene keine sehr große Rolle. Jedoch scheinen die gut untersuchten Serotonin Transporter Polymorphismen in der Pathogenese der bipolaren Erkrankung involviert zu sein. Auch Gene des Dopamin-und Noradrenalin-Systems zeigen keine überwältigenden Resultate. Die Gene des GABA und Glutamat Systems wurden bisher noch nicht intensiv erforscht, allerdings gab es einige positive Ergebnisse. Neben diesen sehr gut untersuchten Gen Gruppen existiert noch eine lange Liste neu detektierter Gene. Eine detaillierte Beschreibung all dieser Kandidaten Gene und ihrer Polymorphismen wird in dieser Diplomarbeit gegeben. Die Entdeckung all dieser Suszeptibilitätsgene hat großen Einfluss auf die zukünftige Nosologie und Therapie. Grenzen zwischen bipolarer Depression und verwandten Krankheiten, wie Depression und Schizophrenie, sind verwaschen. Viele Suszeptibilitäts Gene der bipolaren Erkrankung überlappen mit den beliebtesten Kandidaten Genen der Schizophrenie (z.B. DISC1, COMT, DTNBP1, NRG1 und DAOA). Die bipolare Krankheit überschneidet sich auch mit der unipolaren Depression. Besonders Gene des Serotonin Systems, wie Serotonin Transporter Genvarianten, werden von beiden Erkrankungen geteilt. Die „molecular psychiatry" wird in Zukunft auch Therapie Entscheidungen beeinflussen. Viele Genotypen von Suszeptibilitätsgenen führen zu unterschiedlichem Therapieerfolg. Das kurze Allel des Serotonin Transporters führt beispielsweise zu schlechter Therapieantwort. Genotypen haben ebenso einen starken Einfluss auf Umwelteinflüsse. Manche Genvarianten mildern den Effekt von Misshandlungen in der Kindheit, während andere Genvarianten die depressive Reaktion auf negative Lebensereignisse sogar verstärken. Alle Gen-Umwelt-Interaktionen und ihre Folgen für die klinische Praxis sind in Tiefe in dieser Review erklärt.

Abstract

Bipolar disorder is a highly heritable disease with a polygenetic mode of inheritance. Although molecular psychiatry is still in its infancy, a huge amount of possible susceptibility genes have been discovered, but still with inconsistent results. Top candidates belong to the ion channel group- especially ANK3 and CACNA1C are favourite genes. BDNF, a gene coding for the brain derived neurotrophic factor, seems to be associated with bipolar disorder in Caucasians, but not in Asians. BDNF could be a laboratory marker for bipolar disorder, because serum levels are decreased in bipolar patients. Another promising predisposing group includes the "clock genes", like ARNTL, CRY1 and 2, PER1-3 and others. Although everybody would expect the serotonin system to play a major role, the serotonin receptor genes are not very likely to influence bipolar disorder a lot. The very well examined serotonin transporter polymorphisms are more likely to be involved in pathogenesis of manic depressive disease. Also other neurotransmitter systems, like the dopamine and noradrenaline systems, do not show overwhelming results. The genes of the GABA and glutamate systems have not been highly investigated yet, but show some positive results. Beside those well examined gene groups a huge list of new detected genes exists. A detailed description of all candidate genes and their polymorphism is given within this thesis. The detection of all these susceptibility genes has great impact on future nosology and therapy. Boundaries between bipolar disorder and related diseases, like unipolar depression and schizophrenia, are blurred. Many susceptibility genes for bipolar disorder overlap with top candidates for schizophrenia (DISC1, COMT, DTNBP1, NRG1, DAOA and others). Bipolar disorder overlaps with major depression too. Especially genes of the serotonin system, like serotonin transporter polymorphism, are shared between both affective disorders. Molecular psychiatry will also influence therapy decisions. Many genotypes of certain susceptibility genes lead to better or worse response to pharmacological treatment. The short allele of the serotonin transporter promoter polymorphism leads for example to bad antidepressant response. Genotypes have also an impact on the reaction toward environmental influences. Some gene polymorphism milden the effects of childhood maltreatment, while some gene variants aggravate depressive reaction after negative life events. All gene-environment-interactions and their implications for clinical practice are explained in depth in this review.

Inhaltsverzeichnis

1. Introduction

Many psychiatric diseases run within families and kinship. This high hereditary factor of mental disease was proven early by many family, twin and adoption studies. Important mental diseases like schizophrenia, depression, addiction, autism, chorea huntington and others have a strong genetic predisposition. Usually we do not handle with monogenetic pathogenesis, but with polygenetic inheritance. There are many susceptibility genes and they are not passed on in a Mendelian fashion as we learn at school. It is more likely that there are multiple, potentially interacting genes with small effects and incomplete penetrance. We do not even know all susceptibility genes for psychiatric diseases yet and we do not know how they interact exactly to lead to illness. Molecular psychiatry is still in its infancy. Maybe one day psychiatric genetics will help to draw exact lines between the different psychiatric diagnoses [Burmeister et al. 2008]. This could lead to restructuring of nosology. Furthermore molecular genetics gives inview in exact pathogenesis and therefore targets for development of new medication and laboratory markers. In addition the knowledge of inheritance could lead to strategies to prevent the outbreak of a mental disease. However one has to illuminate the gene-environment-interactions to detect strategies against disease onset. Although molecular psychiatry still has to overcome teething troubles, this is an attempt to review the genetics of bipolar affective disorder, an important psychiatric disease [Craddock et al. 2005].

1.1. Bipolar affective disorder

1.1.1. History and symptomatology of bipolar disorder

Over centuries psychiatric terminology was confusing. Emil Kraepelin was the first to introduce his dualism of schizophrenia ("dementia praecox") and bipolar disorder ("manic depressive insanity") in a clear way. Forerunners of the concept of Kraepelin's classical description were Araeteus from Cappadocia (50-130 after Christ) as well as Jean Pierre Falret (1794-1870) and Jules Baillarges (1809 –1890). However their concepts were not sufficiently defined and not discerned enough [Alexander and Selesnick 1969; Angst et al. 2001]. Nevertheless the essence of manic depressive insanity was typically explained in Falret's term "folie circulaire" and Bailarger's "folie a double forme" already 150 years ago [Benazzi et al. 2006; Haustgen et al. 2006]. But it was not before Emil Kraepelin that bipolar disorder is described as „manic depressive insanity" exactly in our sense over 100 years ago [Jablensky et al. 1999; Hippius et al. 2008]. Bipolar disorder is a mood disorder, which include depressive and manic episodes. Manic episodes are characterised by elevated or dysphoric

mood and raised energy level. Delusion of grandeur, logorrhoea, racing thoughts, loss of social inhibitions, reduced requirement of sleep, hyper-sexuality, increased goal-directed activity or agitation, impulsive or high-risk behaviours like reckless spending are other typical symptoms of mania. Manic episodes lead to marked impairment of social or occupational functioning, even psychosis or hospitalization. By contrast depressive episodes are characterized by vital sadness, low self-esteem and reduced activity- as well as loss of energy and concentration. Nevertheless elevated activity in line with agitated depression is possible. Disturbance of sleep, especially insomnia, early awaking and disruption of sleep, is another feature of depression. Typically appetite is reduced, whereas hyperphagia can occur in atypical depression or seasonal affective disorder. The ability of making decisions, loss of interests and social retraction, even social isolation, are further possible symptoms. Suicide ideation may occur in major depression, as well as suicide attempts and suicide in the last resort [Nabuco de Abreu et al. 2009; Hyong et al. 2008; Kapfhammer et al. 2008]. The change of depressive episodes with marked manic episodes is diagnosed as bipolar I disorder, while a change of hypomania and depression is classified as bipolar II disorder in DSM-IV. Hypomanic states are milder and do not cause impairment. Courses of manic disease without depressive episodes are rare [Schulte-Körne 2008; Barnett 2009]. A special subtype of bipolar disorder is called rapid cycling, which is defined by switching of mood episodes (depression, mania and hypomania) to remission or to the opposite pole within short time periods. Rapid cycling is characterised by at least 4 episodes within 12 months by DSM-IV. Patients with ultra rapid cycling switch even within days and ultra ultradian rapid cycler even within hours [Bauer et al. 2008; Barnett et al 2009].

1.1.2. Pharmacotherapy

1.1.2.1. Antidepressant therapy

Antidepressants helped to release many suffering people from the burden of depressive disorder. Although antidepressants lead to recoverment for the bigger part of patients, around 30-40 % of the individuals do not show full response. Detection of better responsive genotypes may help to create individual therapy plans. Besides it is also difficult to dose antidepressants in an ideal way, because bipolar patients are at risk to switch from depressive to manic states. So a genetic profile might help one day to create optimal individual treatment plans [Kato et al. 2009].

1.1.2.1.1. Selective Serotonin Reuptake Inhibitors (SSRI)

SSRI inhibit the serotonin transporter (SERT), which mediates the active transport of serotonin into neurons, enterochromaffin cells, platelets and other cells. In the central nerve system the transporters are located in perisynaptic membranes of nerve terminals and in dendritic arbors in close proximity to serotonin-containing cell bodies in the midbrain and brain stem raphe nuclei [Murphy et al. 2004]. SERT mediates the quick removal of serotonin in the synaptic gap after neuronal stimulation. Blockage of the transporter by SSRI leads to longer maintenance of serotonin in the gap, because reuptake into presynaptic vesicles is not possible. Highly potent serotonin reuptake inhibitors (SSRIs) include the following [Rothenhäusler et al. 2004; Kapfhammer et al. 2008]:

- Fluoxetine= Fluctine®
- Fluvoxamine= Floxyfral®
- Paroxetine= Seroxat®
- Sertraline= Tresleen®, Gladem®
- Citalopram= Seropram®
- Escitalopram = Cipralex®

1.1.2.1.2. NASSA (Noradrenaline and serotonin specific antidepressant)

- Mirtazapin= Remeron® and Mirtabene®

1.1.2.1.3. SNRI (Serotonin and noradrenaline reuptake inhibitor)

- Duloxetin= Cymbalta®
- Milnacipran= Ixel®
- Venlafaxin= Efectin®

1.1.2.1.4. NARI (Noradrenaline reuptake inhibitor)

NARI are a special group of antidepressants, which lead to reuptake inhibition of noradrenaline. Reboxetin (= Edronax®) is an example of this group.

1.1.2.1.5 . SRE (serotonin reuptake enhancer)

- Tianeptin (= Stablon®)

1.1.2.1.6. NDRI (noradrenaline and dopamine reuptake inhibitor)

- Bupropion= Wellbutrin®

1.1.2.1.7. Tricyclic antidepressants

- Amitriptylin= Saroten®
- Clomipramin= Anafranil®
- Dibenzepin= Noveril®

1.1.2.1.8. Tetracyclic antidepressants

- Maprotilin= Ludiomil®

1.1.2.1.9. MAO inhibitors

- Moclobemid= Aurorix®

1.1.2.1.10. Agomelatine

Agomelatine is a new antidepressant with a target far away from monoamine system. It is the first melatonergic antidepressant.

1.1.2.1.11. Others

- L-tryptophan= Kalma®
- Mianserin= Tolvon®
- Trazodon= Trittico®

1.1.2.1.12. Others

- L-tryptophan= Kalma®
- Mianserin= Tolvon®
- Trazodon= Trittico®

1.1.2.1.13. Sleep deprivation

Observed and therapeutic sleep deprivation leads to immediate brightening of the mood, but does not have long lasting effects.

1.1.2.1.14. Bright light therapy

Bright light in the morning leads to a phase advance in rhythms, while admission at night leads to a delay [McClung review]. Light administrated in the dark leads to phase delay or advances by activating the circadian oscillator in the suprachiasmatic nucleus in the hypothalamus [Hampp et al. 2008].

1.1.2.2. Mood stabilization, antimanic and phase prophylactic treatment

1.1.2.2.1. Lithium

Lithium is the golden standard of mood stabilization since 1949 [López-Muñoz F et al. 2007; Fountoulakis et al. 2010]. Lithium is efficient for acute and prophylactic treatment. It is a potent inhibitor of glycogen synthase kinase-3 (GSK3), which is a serine–threonine kinase that intermediates various intracellular signaling pathways [Bhat et al 2004]. GSK3b phosphorylates and stabilizes the orphan nuclear receptor Rev-erba, a negative component of the circadian clock. Lithium treatment of cells leads to rapid proteasomal degradation of Rev-erba and activation of the clock gene Bmal1. A form of Rev-erba that is insensitive to Lithium interferes with the expression of circadian genes [Yin et al. 2006]. The Wnt/GSK3b signaling pathway is also supposed to be involved in Lithium inhibited pathways [Lachman 2008]. Since mechanism of Lithium's antimanic effect are not totally clear a genome wide association study tried to discover genes involved in Lithium response. They found an involvement of GRIA2, a glutamate/alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionate (AMPA) receptor gene. Nevertheless further investigation is necessary [Perlis et al. 2009].

1.1.2.2.2. Antiepileptics

Antiepileptics are used for mood stabilization, here are listed some representatives [Fountoulakis et al. 2010]:

- Carbamazepin= Neurotop®, Tegretol®
- Lamotrigin= Lamictal®
- Valproinsäure= Convulex® and Depakine®

1.1.2.2.3. Antipsychotics

Antipsychotics are dopamine receptor inhibitors and are widely used in therapy of schizophrenia, but nowadays they are also established in mood stabilization in bipolar disorder. Here are some examples [Fountoulakis et al. 2010]:

- Aripiprazol=Abilify®
- Olanzapin= Zyprexa®
- Quetiapin= Seroquel®
- Risperidon= Risperdal®
- Ziprasidon= Zeldox®

1.1.3. Epidemiology of bipolar disorder

Bipolar disorder is a serious and devastating disease with a lifetime-risk as high as 1%, some argue even 4%. It is also a destructive disease, because life-time risk of suicide among bipolar patients is almost 20%. Suicide ideation is common in 14-59% of bipolar patients and 25-56% present at least one suicide attempt during lifetime [Abreu et al. 2009]. Mood disorders cause about 1% of all deaths and are one of the society's most important causes of days lost to disability [Michaud et al. 2006]. So manic-depressive disorder is a destroying disease and needs therefore intense research for better insight into biology to invent better strategies against it. In the following chapters I will therefore review the genetic insights of bipolar affective disorder up to now. First of all I want to give a quick look on the basic principles of genetics and molecular biology.

1.2. Basic principles of genetics

1.2.1. Structure of DNA

Heritable information lies within 46 chromosomes, which consist of DNA, the magic substance genes are made of, wrapped around histones. One can imagine DNA as a "spiral staircase" of coding base pair "steps" and a sugar-phosphate backbone. Thus the major three building blocks of DNA are deoxyribose, a five carbon sugar, phosphoric acid and nitrogenous bases. The treads of the "spiral staircase" are built by flat nitrogenous bases, which pair with each other on the inside of the right handed helix [Langridge et al. 1957; Watson and Crick 1974; Knippers et al. 2001; Lewin et al. 2004]. On one hand there are pyrimidine bases like uracil, thymine and cytosine and on the other hand derivatives of purine like adenine and guanine. Adenine pairs via two hydrogen bonds with thymine in DNA and with uracil in RNA. The only difference between uracil and thymine is one methyl substituent on position C_5. Cytosine and guanine make three hydrogen bridges. The ability of building hydrogen bonds between base pairs is the reason for hybridisation of two complementary DNA strands. The nitrogenous base is linked to position 1 on deoxyribose by a glycoside bond from N_1 of pyrimidines or N_9 of purines. This is how the "steps" are connected to the sugar-phosphate backbone of DNA. The backbone is built by phospho-diester-bridges between the deoxyribose molecules, which are the five carbon sugars of the DNA. This means that the 5'position of one pentose ring is connected to the 3' position of the next pentose ring via a phosphate group. This kind of linkage gives DNA a free 5' phosphate end and a free 3'OH end and therefore a direction. Recapitulatory DNA consists of two antiparallel and complementary DNA strands, which usually build a right handed double helix with linking

base pairs on the inside. Within this simple but creative construction lies the secret for coding genes and therefore the building plan for proteins, which functions build up the whole complex organism [Watson and Crick 1974; Knippers et al. 2001; Lewin et al. 2004]! Three base pairs, a triplet, code for one amino acid. Thus the key of life lies within the sequence of the bases [Crick et al. 1961]. The sequence of one gene codes for one protein or generally spoken for one polypeptide chain. To build the right protein we need a complex interaction of signal transduction, transcription and protein biosynthesis. Since those mechanisms are so important for the function of our body I want to explain all those central dogmas of molecular biology in the following pages [Lewin et al. 2004; Knippers et al. 2001].

1.2.2. Gene expression- from DNA to proteins

The first step in gene expression is making a transcript of the template DNA strand, which codes for the protein. This intermediate mRNA is then the matrix for converting the nucleotide sequence of DNA into the amino acid sequence of the protein in the second step of gene expression, which is called translation or protein biosynthesis [Knippers et al. 2001; Lewin et al. 2004]. Within those complex procedures are a lot of regulation points. Thus gene expression is not a rigid system. Lots of signal transduction signals lead to protein translation finally. Genes are the building plan for our organism, but the needs of our body influence how many and how often they are expressed. Genes can be transcribed very frequently or they can be silenced via methylation of regulatory elements [Lewin et al. 2004; Bogdanovic et al. 2009]. In this chapter I will explain the way from a gene sequence to the encoded protein, which carries out functions and helps to build up the whole organism together with other gene products. The start of transcription is associated with demethylation and the buildup of an initiation complex. Demethylation at the 5'end of the gene is necessary for transcription, because methylation near the promoter leads to absence of transcription. This is one of the regulatory events at the promoter. An active gene is undermethylated. CpG islands, which can be methylated, are especially located in regulatory targets. They surround some promoters and methylation of those GC repeats prevents transcription initiation [Knippers et al. 2001; Lewin et al. 2004; Yang et al. 2008; Bogdanovic et al. 2009].

1.2.2.1. Transcription

Transcription is the very first step of protein biosynthesis. The blueprint of a protein lies in the nucleotide sequence of its gene, as I mentioned before. Therefore the plan to construct the protein is conserved in the DNA. To express a gene the enzyme RNA polymerase is synthesising lots of copies of this DNA sequence. The resulting mRNA, a messenger RNA,

represents the coding strand (sense strand) and it is built by unwinding the DNA-double-helix and by complementation of the antisense strand with complementary ribonucleotides. The ribonucleotriphosphates get linked by a phosphodiester bond between the ribose units under elimination of pyrophosphate. RNA polymerase slides along the DNA matrix in the transcription bubble in 3'->5'direction of the antisense strand and adds the complementary ribonucleotide to the growing 3'OH end of the mRNA [Knippers et al. 2001; Lewin et al. 2004]. Eukaryotic mRNA must be modified after transcription to be protected during the transport from the nucleus into the cytoplasm. Thus mRNA gets a 5'methyl-guanosine-cap and a poly-(A)-tail. Beside the introns, the not coding sequences of eukaryotic mRNA, are eliminated during the process of splicing. Recapitulatory the processed and modified mRNA brings the information from the nucleus to the cytoplasm, namely to the protein synthesis apparatus at the ribosomes [Krainer 1988; Tarn et al. 1997; Knippers et al. 2001; Lewin et al. 2004]. The catalysing enzyme of transcription is called RNA polymerase. Eukaryotes have three types of RNA polymerases [Carter et al. 2009]. Type I catalyses the transcription of 28S-, 18S- and 5,8S rRNAs, RNA polymerase II transcribes mRNA and Type III synthesizes 5S-rRNAs. Those three enzymes differ in their response to α-amanitin and in their order in chromatography [Knippers et al. 2001; Brueckner et al. 2009]. The structure of eukaryotic RNA polymerases is more complex than those of bacterias. They have at least 12 subunits [Meyer et al. 2009; Carter et al. 2009]. One characteristic features of the largest subunit of RNA polymerase II are multiple repeats of typical heptapeptides at the carboxy terminal domain (CTD). Those heptapeptides contain serine (S) and threonine (T)-rests, which are phosphorylated in active enzymes. The phosphorylation is important for the release of the RNA polymerase in the initiation process [Chapman et al. 2004; Knippers et al. 2001; Lewin et al. 2004].

1.2.2.1.1. Initiation of transcription

Transcription can be subdivided into three parts- 1. initiation, 2. elongation and 3. termination [Brueckner et al. 2009]. Transcription initiation needs a promoter, the starting point for RNA polymerase, as well as helping transcription factors [Chen et al. 2003]. One common element of RNA polymerase II promoters is the TATA-box and it consists of an A-T-rich octamer about 25 bp upstream of the starting point of transcription [Juven-Gershon et al. 2008; Yang et al. 2008; Lewin et al. 2001]. The core sequence of the box is TATAA. Usually it is followed by three more AT pairs and the box is often surrounded by GC-rich sequences. Sometimes promoters do not contain a TATA-box. Then they have a DPE (downstream

promoter element) instead [Kadonaga et al. 2002; Yang et al. 2008; Lewin et al. 2004]. Another short conserved sequence at the starting point of the RNA polymerase II promoter is the initiator InR [Knippers et al. 2001; Yarden et al. 2009]. In general it can be described by Py_2CAPy_3. There is not extensive homology of sequence at the starting point, but there is a tendency for the first base of mRNA to be an adenine. The InR lies between -3 and +5. In front of constitutively expressed genes ("house keeping genes") are quite often GC-boxes (GpC islands) which can be methylated in silenced genes. Therefore CpG islands are regulatory targets. Methylation of those GC repeats prevents transcription initiation [Yang et al. 2008; Knippers et al. 2001; Lewin et al. 2004]. Beside the typical promoter sequences one can find other gene regulation elements with characteristic DNA motives. Some are around the transcription start and some far away. Regulation elements, which are far away of the startpoint, are called enhancer [Knippers et al. 2001; Lewin et al. 2004]. DNA-sequence motives are binding places for transcription factors or other regulating proteins. Thus transcription is one possible level of regulation in gene expression. Usually those regulating steps happen around the promoter. Summarized a promoter of RNA polymerase II consists either of a TATA-box plus InR or of an InR plus DPE [Lewin et al. 2004]. RNA polymerase II is not able to bind to its promotor by itself. The enzyme needs a positioning factor to bind to its promotor. The positioning factor is called $TF_{II}D$ and consists of TATA-binding protein (TBP) and multiple TBP-associated factors [Oelgeschläger et al. 1996; Green et al. 2000; Sanders et al. 2002; Knippers et al. 2001; Lewin et al. 2004]. TBP binds to the TATA box in the minor groove. It forms a saddle around the DNA and bends the DNA about 80˚. This leads to unwinding of about 1/3 of a turn and to a closer association of polymerase and transcription factors. The outside of the "saddle" is connected to TAFs. The largest TBP binding protein is TAF240. This largest TBP-associated factor (TAF) is a protein kinase and a histone-acetyl-transferase and it is important for recognition of TATA free promotors. TAF240 also represses TBP. Binding of TBP to the TATA box is the first step in the initiation of transcription. Then other transcription factors bind in a defined order! $TF_{II}A$ and $TF_{II}B$ join the positioning factor $TF_{II}D$ (= TBP and TAFs). They stabilize the binding of $TF_{II}D$ to DNA and complete the platform for RNA polymerase II. Actually $TF_{II}B$ builds the surface which is recognised by the RNA polymerase. So this factor is responsible for the directionality of the binding of the enzyme [Kostrewa et al. 2009]. $TF_{II}F$ is a heterotetramer with two types of subunits. One subunit of $TF_{II}F$ binds RNA polymerase II and leads the enzyme to the initiation complex, while the other $TF_{II}F$ subunit has an ATP-dependent DNA-helicase activity. Thus $TF_{II}F$ is involved in melting the DNA at initiation of transcription. But to really

unwind DNA two other factors are really important- namely $TF_{II}E$ and $TF_{II}H$. The factor $TF_{II}E$ leads the very important factor $TF_{II}H$ to the complex. This $TF_{II}H$ factor has several activities. It is a DNA helicase, which unwinds DNA at the promoter and it has protein-kinase-activity. With its kinase activity this factor phosphorylates the CTD (the tail of the polymerase with its heptapeptides), which is necessary to release RNA polymerase II from its transcriptionfactor platform and to start the transcription. Altogether this initiation process is quite complicated, but it helps the polymerase to find the promoter sequence, to melt the double strand and to start transcription [Parvin et al. 1994; Nikolov et al. 1997; Wu et al. 2001; Roeder 2003; Lewin et al. 2004; Knippers 2001].

1.2.2.1.2. Elongation of transcription

During elongation the polymerase moves along the DNA, unwinds its helix and extends the nascent RNA chain. Thus new ribonucleotides, which are complementary to the transiently exposed template strand, are linked covalently to the 3'OH end of the growing RNA. This ribonucleinacid is an exact copy of the sense strand and complementary to the template strand. There are only two differences to DNA. RNA contains ribose instead of deoxyribose and uracil instead of thymine. Behind the transcription bubble the two parental strands hybridize again [Knippers et al. 2001; Lewin et al. 2004; Brueckner et al. 2009].

1.2.2.1.3. Termination of transcription

Eukaryotic RNA polymerases, as well as bacterial, are at least terminated by two possible pathways. Usually RNA polymerase II termination is coupled to transcript cleavage and polyadenlyation for most mRNAs. To a smaller degree also the Nrd1/Nab3/Sen1-dependent pathway can occur. Sen1-dependent termination in eukaryotes is similar to rho dependant termination in bacteria [Peters et al. 2009].

1.2.2.2. Proteinbiosynthesis (translation):

Protein biosynthesis is the translation of the genetic code into the aminoacid sequence of a protein. This happens in the cytoplasm and needs a protein-synthesis-apparatus, which includes tRNA, mRNA, ribosomes, amino acids and enzymes. mRNA is the messenger, which brings the genetic information of the cell nucleus into the cytoplasm to the ribosomes. The ribosomes are the machinery of translation. Eukaryotic ribosomes consist of a 40S subunit and a 60S subunit. The small ribosomal subunit is the place where mRNA and tRNA meet, while the large subunit accommodates the place for knitting the peptide bond [Knippers

et al. 2001; Lewin et al. 2004]. tRNA is the adapter for amino acids and brings them to the right position on the mRNA via its anticodon. The secondary structure of tRNAs looks like a cloverleaf. It has one anticodon-arm, one acceptor-arm, one D-arm and a T-arm. The anticodon of a tRNA is complementary to the codon on the mRNA, which consists of three ribonucleotides and represents one amino acid. The acceptor-arm is the "stem" of the shamrock and it is built by the 5' and 3' ends of the RNA, whereas the 3'end overtops the 5'end with three ribonucleotides CCA. The very last ribose of this acceptor-arm-overlap is the binding position of the amino acid which corresponds to the codon in the mRNA. So the tRNA is the adapter for bringing the right amino acid to the right triplet in the mRNA [Knippers et al. 2001]. But the tRNA itself cannot decide which amino acid belongs to the adapter. For loading the right amino acid on the right vehicle aminoacyl-tRNA-synthetases are responsible. There is one enzyme for every single amino acid [Knippers et al. 2001; Lewin et al. 2004]. Summarized the tRNA brings the corresponding amino acid via its anticodon to the codon in the mRNA. For every codon there are at least 60 tRNAs in one cell, but only 20 amino acids. This means that some amino acids are coded by more than one triplet. This phenomenon is called redundancy or degeneration of the genetic code. This genetic code is universally valid in every creature of the world [Knippers et al. 2001]. Thus the tRNA anticodon with the very special amino acid docks to the codon of the mRNA in the small subunit. So the tRNA brings the corresponding amino acid to the mRNA and the amino acids are connected by a peptide bond. There are three sites at the ribosome- the A-site, the P-site and the E-site. The aminoacyl-tRNA enters the A-site which contains the piece of mRNA with the codon complementary to the anticodon of the tRNA. This makes sure that the right amino acid is at the right place. The peptidyl-tRNA is located at the P-site. The tRNA which is located at the P-site has the nascent peptide chain attached. Then the peptide bond is formed between the new amino acid in position A and the growing peptide on the peptidyl-tRNA in the P-site. So after the step of knitting the peptide bond the whole peptide chain is attached to the tRNA in site A. One can see the process of making the peptide bond like transferring the growing peptide chain to the new amino acid, alternatively to the tRNA with the new amino acid. The formation of the peptide bond is catalyzed by the large subunit. The empty tRNA of the P-site is released via the E-site. After peptide bond formation the ribosome moves one codon on the mRNA. The moving of the ribosomes is named translocation. Alternatively one can imagine the mRNA being pulled trough the ribosome. The process of translocation makes sure that there is always the next codon in the A-site and therefore a new amino acid (the neighbour acid of the amino acid which was knitted to the

chain before). So after translocation the tRNA, with the grown attached peptide, lies in the P-site and the A-site is free again. This makes sure that the order of the amino acids corresponds to the nucleotide sequence of the coding strand of the DNA double helix [Knippers et al. 2001; Lewin et al. 2004].

1.2.2.2.1. Initiation of protein biosynthesis in eukaryotes

Protein biosynthesis occurs in three stages: 1. initiation, 2.elongation and 3.termination. Protein biosynthesis starts with the special start codon AUG, which codes for methionine. In bacteria the very first methionine is formylated, whereas in eukaryotes only the tRNA of the first methionine differs compared to the carriers of the other methionines within the peptide chain. Beside the start codon twelve initiation factors are necessary to start translation in eukaryotes. On one hand those factors help the methionine-initiator-tRNA to reach the triplet AUG with its anticodon. While on the other hand the factors help the 40S and 60S ribosomal subunits to meet and connect to the functioning 80S ribosome. About six major steps lead to the complete 80S ribosome and a correctly positioned Met-$tRNA_i$. First of all the small 40S subunit gets prepared for initiation. This happens by binding of eIF1A and eIF3 to the 40S subunit, which blocks a too early attachment of the large subunit to the small one [Kolupaeva et al. 2005]. Then in the second step Met-$tRNA_i$ is placed on the mRNA. The methionine carrying initiaton-Met-$tRNA_i$ and the GTP-binding protein eIF2 build the "ternary complex", which places Met-$tRNA_i$ on the mRNA. This intermediate is called 43S complex, because now the small subunit is heavier and sediments in the ultracentrifuge at 43S. The next step prepares the mRNA for translation initiation. eIF4F, the "cap binding complex", binds to the 5'end of the mRNA. It contains eIF4E, which binds to the 7- methylguanosine cap, eIF4A a helicase and eIF4G the "scaffolding subunit". To find the AUG start codon the prepared small subunit binds the 5' end of the mRNA and scans the messenger RNA along the 5' non-coding-region until the small ribosomal subunit finds the start codon. AUG is only identified as the start codon, if it is in a special context, the so called "Kozak-sequence" CCRCCAUGG. The result of this scanning process is the positioning of the small subunit and the initiator Met-tRNA at the start codon. Sometimes this new complex is called 48S complex [Knippers et al. 2001]. The following reaction leads to the exact positioning of Met-$tRNA_i$. The procedure is dependent on the cleavage of GTP in the factor eIF2 within the ternary complex and is organized by eIF5 and eIF5B. Then the used and inactive eIF/GDP and the proteins eIF1A and eIF3 leave the small subunit. Now the blockade of eIF1A and eIF3 of the small subunit is released and the anticodon of the Met-$tRNA_i$ is paired with the start codon AUG. Finally the large subunit unites with the small subunit to form the active 80S ribosome. After

reunion of the 2 subunits all initiation factors are released and the first methionine lies in the P-site and the A-site is free for the following amino acid [Knippers et al. 2001; Lewin et al. 2004; Pestova et al. 2001; Siridechadilok et al. 2005; Jivotovskaya et al. 2006; Reibarkh et al. 2008].

1.2.2.2.2. Elongation

As i mentioned before the key process of peptide bond synthesis is based on 3major steps: First the new amino acid arrives at the A-site with the suiting tRNA-anticodon. Then in the second step the polypeptide attached to the tRNA in the P-site (or in the very first step the methionine) is transferred to the new amino acid in place A. The peptide bond is created under elimination of H_2O between the carboxy group and the amino group of two amino acids. And last but not least the ribosome moves one codon on the mRNA to generate a free A-site with a new free neighbour-codon and a P-site with the nascent peptide chain. Those steps are repeated until the whole protein-coding piece of the mRNA is translated into the corresponding amino acid sequence. Of course this part of translation needs helping factors again. The entry of aminoacyl-tRNAs to the A-site is mediated by the elongation factor eEF1α. Bringing the aa-tRNA to the A-site involves cleavage of the high energy bond in GTP. eEF1βγ regenerates the active form again with changing GDP to GTP. Translocation is coordinated by eIF2. Generally the translocation is catalyzed by the large subunit. eRF is responsible for recognising the stop codon [Knippers et al. 2001; Lewin et al. 2004].

1.2.2.2.3. Termination

Termination occurs at the stop codons UAA, UAG and UGA. The eRF1 protein is responsible for finding the stop codons in eukaryotes. The eRF1 factor mimics the structure of tRNA. There are not any real fitting tRNAs for the stop codon, thus the peptide chain is completed and released from the ribosomes [Lewin et al. 2004]

1.2.3. Replication

Before cell division DNA must be copied in the synthesis phase of the cell-cycle to give exactly the same genetic material to the daughter cells. Copying DNA happens semiconservatively. This means that the DNA of the daughter cell consists of one DNA-strand of the mother cell and one new synthesized strand. This happens because the mechanism of replication is opening and unwinding the mother-DNA-double-helix and completing each strand with the complementary corresponding deoxynucleotides. The reaction is catalyzed by the DNA-dependent DNA polymerase. This enzyme cannot start by

itself, so it needs a primer with a free 3'OH end. The free 3'OH is very important because the direction of DNA-synthesis is from 5' to 3'. This means that the DNA polymerase attaches a new nucleotide to the 3' OH end of the growing new strand, which is complementary to the mother strand. This is also the reason why the lagging strand synthesis is performed in short okazaki fragments. Since the DNA strands are antiparallel it is only possible on one strand to finish DNA synthesis with only one primer and without a stop. On the lagging strand the replication is discontinously because the direction of synthesis is reverse to the fork movement. But since the direction of synthesis is from 5' to 3' and the strands are antiparallel there is always only a short stretch of matrix exposed (from the fork to the next okazaki fragment). Thus DNA can only be synthesized in short okazaki fragments, which are connected after excision of the RNA primers and after refilling of the gaps with deoxyribonucleotides. On the leading-strand there is always the next necessary matrix of the mother strand (3' to 5') available for complementation, because the direction of synthesis is the direction of the fork movement. So the 3'end of the leading strand can grow along the fork in 5'-3' direction [Falaschi et al. 2000; Lewin et al. 2004; Kunkel et al. 2008].

1.2.3.1. Inititation of replication

Replication starts at the origin. Since the genome of eukaryotes is pretty large, there are multiple replication origins within the genome. The origin is recognised by the origin recognition complex (ORC). The next step is the addition of Cdc6 and other proteins. In the third step six Mcm (minichromosome maintenance proteins) are loaded on the chromatin. They build a ring around the chromatin, which can slide along double stranded DNA. The complex with ORC, Mcm2-7, Cdc 6 and Cdt1 is called prereplicative complex (pre-RC) then. The addition of the Mcm 2-7 is also called "licensing". A subcomplex of Mcm 4, 6 and 7 has DNA-helicase activity. This suggests a role in unwinding at the replication fork. The pre-RC adds other factors like Cdc45 and Sld3. Now the whole complex is called pre-initiation-complex. The main triggers for initiation are two protein-kinases. One of them is a cyclin-dependent kinase. In metazoes it is CDK2 and acts S-phase-specific together with cyclins A and E [Krude et al. 1997; Lewin et al. 2004; Baltin et al. 2006; Chen et al. 2007; Evrin et al. 2009; Remus et al. 2009].

1.2.4. Epigenetics

Enduring effects of early experience on neural function may be due to epigenetic changes of DNA. Those changes occur without changing the sequence of our genes. Functional changes

are created by means of methylation, acetylation and other chemical changes of DNA or histones, which lead to an alteration of transcription and gene expression in general. Thus epigenetic changes influence our body by modifying gene expression. Consequently the blueprint is not changed, but the frequency of reading it differs. Especially early childhood experiences influence signal cascades, which lead to a change of the "epigenome". This is a possibility how environment can influence our genome and gene expression [Oberlander et al. 2008].

1.2.5. Mutations

1.2.5.1. Gene mutations

1.2.5.1.1. Point mutations / Single nucleotide polymorphisms (SNPs)

Point mutations are gene mutations, which affect only one basepair. Substituition leads to an exchange of one single base in a triplet. Transversion is the process, when a purine base substitutes a pyrimidine base or the other way round. While an exchange of one base between the same kind of base, for example purine base against purine base, is called transition. Since the genetic code is degenerated it can occur, that the changed triplet still codes for the same amino acid. Thus the mutation does not have any effect. But a point mutation can also lead to a different amino acid. Deletions are more common than substituitions. The deletion of one base pair can lead to a frame shift and to a totally different amino acid constellation [Buselmaier 2004].

1.2.5.1.2. Insertions, deletions, duplications and repeat polymorphisms

Deletion of some base triplets leads to the loss of the coded amino acids. But if the deletion occurs exactly in triplets no frame shift occurs. Otherwise the frame-shift-mutation would lead to totally different amino acids. Duplications lead to doubled segment or doubled gene. This can happen during crossing over by mistake. Insertions are the opposite of deletions. Sometimes it happens that one or more basepairs are inserted. Repeat polymorphisms are the amplification of a certain motif, which usually consist of three basepairs [Buselmaier 2004].

1.2.5.2. Chromosomal mutations

1.2.5.2.1. Structural chromosomal mutations

Structural chromosomal mutations include deletions, duplications, insertions, inversions and translocations. Deletions can be terminal, then a part of the chromosome end breaks away, as well as interstitial, then a part in the middle of a chromosome gets lost. Large deletions are often lethal, since important genetic information is lost. Translocation describes the changing

of position and incorporation of a chromosomal fragment at another place. Inversions are mutations, which result by breaking out of a chromosome segment and reintegration at the same place, but in wrong direction [Buselmaier 2004].

1.2.5.2.2. Chromosome number aberrations

Whole chromosomes can get lost or additioned during meisosis. This results in trisomy or monosomy. The whole set of chromosomes can be doubled or tripled too [Buselmaier 2004].

1.2.6. Methods of molecular bipolar disorder research

1.2.6.1. Association studies

Association studies are important methods to investigate complex traits, like bipolar disorder. This method detects smaller effect sizes much better than linkage studies. Association studies are usually performed as case-control design. They search for association between an allele marker and disease within a population. The association approach includes comparing the frequency of a gene polymorphism in an unrelated affected individuals and a control sample that is representative of the allelic distribution in the general population or totally unaffected individuals, which would be a supernormal group. The case-control design bears the danger of spurious association, because of unsuspected population stratification. This can be avoided in family-based association designs. The non-transmitted alleles of the parents of a singly ascertained patient represent a random sample of alleles from the population and are used as a well-matched control sample. One popular family-based association study method is the transmission disequilibrium test (TDT). It is a test for excess transmission of a marker allele to affected individuals over and above that expected by chance. Family-based association studies have the disadvantage that gene-environment-interactions cannot be examined and that sample sizes are difficult to collect [Craddock et al. 2001]

1.2.6.2. Genome wide association studies (GWAS)

Genome wide association study (GWAS), also called whole genome association study (WGAS), is an examination of genetic polymorphism across the whole genome, designed to identify genetic associations with complex traits, like bipolar disorder. The human genome project made this approach possible. Usually it is performed as a case-control design. The genome of a group with the disease and of a group without the investigated disease is genotyped, in other words sequenced. Then the detected gene variant frequencies, the occurrence of special markers, are compared between cases and controls with special

software. If a certain gene polymorphism is more frequent in the case group, then this polymorphism is associated with the disease [Pearson et al. 2008].

1.2.6.3. Linkage disequilibrium analysis

Linkage disequilibrium analysis is a "positional approach in which a grid of tightly spaced markers is typed across a genomic region in the hope of identifying a region of allelic association that will allow a susceptibility gene to be localized" [Craddock et al. 2001]. A genome-wide study is an extreme example for a linkage disequilibrium analysis and needs a very dense net of markers, at least 30 000 [Craddock et al. 2001]. Genome wide approaches scan the whole genome for gene variants leading to disease. Even gene polymorphisms of very small effect can be detected. Since susceptibility genes for bipolar disorder are of modest effect, this approach is good for bipolar disorder research [Craddock et al. 2001; Glazier et al. 2002].

2. Methods

We searched Pubmed with the following key words:

History of bipolar disorder; History of schizophrenia; Kraepelin and bipolar disorder; Kraepelin and schizophrenia; Bipolar disorder genetics; genetics and bipolar disorder; pathogenesis bipolar disorder; DNA structure Watson and Crick; Triplet code; DNA is a double helix; eukaryotic transcription; eukaryotic translation; splicing mRNA; types of RNA polymerase; bdnf and bipolar disorder; neurotrophic factor and bipolar disorder; Val66Met allele; Val66Met and bipolar disorder; linkage studies bipolar disorder; BDNF and functions; BDNF and neurogenesis; BDNF and neuron growth; COMT and bipolar disorder; COMT and affective mood disorder; Catechol-O Methyltransferase and bipolar disorder; MAO gene and bipolar disorder; MAO-A gene bipolar disorder; MAO-A gene association studies bipolar affective disorder; clock genes and bipolar disorder; Arntl and bipolar disorder; Arntl and mood disorder; Bmal1 mania; Mop3 mania; Arntl mania; clock bipolar disorder; suprachiasmatic nucleus; circadian oscillator genes; mammalian circadian oscillator; NR1D1 and bipolar disorder; CLOCK gene and bipolar disorder; animal study of clock genes and bipolar disorder; association studies of clock genes and bipolar disorder; Dbp bipolar disorder; Serotonergic genes and bipolar disorder; serotonergic receptor genes and bipolar disorder; (5-HT)-receptor genes; HTR1; HTR2A and bipolar affective disorder; HTR3 and bipolar affective disorder; HTR3 and mania; 5-HT receptor and bipolar disorder; HTR4 and bipolar disorder; HTR5 and bipolar disorder; HTR6 and bipolar disorder; HTR7 and bipolar

disorder; serotonin transporter and bipolar disorder; serotonin transporter promoter region and bipolar disorder; 5HTTLPR and bipolar disorder; VNTR and bipolar disorder; SERT and bipolar disorder; CACNA1C and bipolar disorder; CACNA1B and bipolar disorder; ion channel genes and bipolar disorder; KCN2 bipolar disorder; heritability twin studies bipolar disorder. Gene environment interactions bipolar disorder; maltreatment and genotype and depression; BDNF and maltreatment and bipolar disorder; serotonin transporter and maltreatment and bipolar disorder; famines and genes and bipolar disorder; infections and bipolar disorder; serotonin transporter gene and stress; serotonin transporter gene and maltreatment; serotonin transporter gene and stress response; 5-HTTPLR polymorphism and environment; 5-HTTLPR maltreatment bipolar disorder; 5-HTTLPR and life events; CRHR1 linkage bipolar disorder 17q12-q22; CRH and bipolar disorder; HPA and bipolar disorder; 8q13 linkage bipolar disorder; Dopamine system and bipolar disorder; DRD1 and bipolar disorder; DRD2 and bipolar disorder; DRD3 and bipolar disorder; DRD4 and bipolar disorder; DRD5 and bipolar disorder; DAT1 and bipolar disorder; overlaps bipolar disorder and schizophrenia; overlaps bipolar disorder and major affective disorder; overlaps manic depressive disease and major depression; COMT and depression; COMT and schizophrenia; COMT and bipolar disorder; all gene locations were searched with the terms bipolar disorder and linkage studies; all genes in the lists were searched together with the term bipolar disorder; All genes in the lists were searched with the term schizophrenia and major depression;

3. Genetics in bipolar disorder

3.1. Heritability of bipolar disorder

Bipolar disorder is a highly heritable disease- this has been proven by many twin and adoption studies for decades. Heritability is as high as 80-85% [Cardno et al. 1999; McGuffin 2003]. Concordance rates between monocygotic twins are 43% and 6% for dicygotic twins. This assumes that the genetic constitution is very important for development of manic depressive disease, but not the only cause. Genetic and environmental factors are the most probable reasons for the pathogenesis of bipolar disorder [Kieseppä et al. 2004].

3.2. Candidate genes at one view

Many candidate genes for bipolar disorder are coding for elements of the serotonergic system. Since the main model of depression has been dominated by a “neurotransmitter imbalance theory”, especially of serotonin, for decades it is not surprising that many possible

susceptibility genes for bipolar disorder are genes of neurotransmitter systems (serotonergic, noradrenergic, dopaminergic, GABAergic and glutamatergic system) and genes involved in biochemical pathways like biogenic amine modulation or lithium signalling. These genes code for monoamine oxidase A (MAOA), catechol-O-methyltransferase (COMT) and the tryptophan hydroxylase 1 (TPH1). Beside circadian rhythms are often disturbed in bipolar disorder and are therefore hot spots of research too. The growth hormones are another promising chapter of bipolar disorder research, as well as top candidate genes coding for ion-channels [Sklar et al. 2008; Craddock et al. 2009].

Table 1: All candidate genes for bipolar disorder and supportive evidence

Genes involved in biogenic amine modulation				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
MAOA	Xp11.23	**CA-repeat microsatellite** in intron 2	-Furlong et al. 1999 (meta-analysis) -Kawada 1995 -Rubinsztein 1996 -Lim et al. 1995 -Preisig[1] 2000	-Parsian,Todd 1997 -Lin 2008 -Serretti 2002 -Craddock 1995 -Muramatsu 1997 - Nöthen 1995
MAOA	Xp11.23	**Fnu4HI RFLP** =Fnu4HI G/T silent polymorphism =MAOA–941T>G = G to T substitution at the third base of codon 941	-Rubinsztein 1996 -Furlong 1999 -Müller 2007	-Craddock 1995 -Muramatsu 1997 -Preisig 2000 -Serretti 2002
MAOA	Xp11.23	**polymorphic promoter VNTR** (variable number of tandem repeats) located approximately 1,200 bp upstream from the translation start site = MAOA gene-linked polymorphic region (**MAOA-LPR**) = uVNTR polymorphism		-Furlong 1999 -Syagailo 2001 -Müller 2007 -Huang 2008 -Kunugi 1999 -Lin 2008 -Serretti 2002
MAOA	Xp11.23	**VNTR polymorphism in intron 1** (variable number of tandem repeats polymorphism in intron		-Craddock 1995 -Serretti 2002 -Muramatsu 1997 -Preisig 2000

		1)		
MAOA	Xp11.23	**EcoRV Polymorphism=** T-to-C substitution at Position–1460		-Huang 2008 -Serretti 2002
MAOB	Xp11.23	Monoamine oxidase B		-Muramatsu 1997 -Parsian,Todd1997
COMT (Val/Met poly-morphism)	22q11.1-q11.2	Catechol-O-methyltransferase	-Lachman 1996 -Kirov 1998 -Shifman 2004 -Funke 2005 -Goghari 2008 -Zhang 2009 (large study and meta-analys on 19studies)	-Gutierrez 1997 -Kunugi 1997 -Kirov 1999 -Geller 2000
TPH1	11p15.3-p14	Tryptophan hydroxylase 1	-Chen 2008 -Bellivier 1998	-Lai 2005
TPH2	12	Tryptophan hydroxylase 2	-Lin 2007	-Mann 2008
TH	11p15	Tyrosine hydroxylase (TH) is responsibe for the first step in synthesis of catechol-amines. TH converts tyrosine into L-dopa. TH is also the rate limiting enzyme of catecholamine synthesis.	Linkage studies: -Malfosse 1997 -Smyth 1997 -Craddock 1999 -Serretti 2000	Linkage studies: -De bruyn 1994 Family based association study: -Muglia 2002 Case control association study: -Furlong 1999 -Souery 1999

Genes of the serotonergic system

Gene	Location	Polymorphism and function	Supported by	Not supported by
HTR1A	5q11.2-q13	5-HT1A receptor gene	no support	-Curtis 1993 -Vincent 1999
HTR2A	13q14–21	5-HT2A receptor gene Almost all polymorphisms showed negative study results, especially the best studied polymorphism C102T. In detail see chapter of serotonin system!	GWAS: -Le Niculescu2008 Association studies: -McAuley 2009 -Ranade 2003 Linkage studies: -Stine 1997	-Arranz 1997 -Gutiérrez 1997 -Mahieu 1997 -Zhang 1997 -Tsai 1999 -Vincent 1999 -Bonnier 2002 -Blairy 2000 -Heiden 2000 -Massat 2000

			-Badenhop 2001	-Tut 2000 -Murphy 2001 -Robertson 2003 -Etain 2004 -Kishi 2009
HTR2C	Xq24	5-HT2C receptor gene	GWAS: Wigg 2009 Linkage studies: -Pekkarinen 1995 -Ekholm 2002 Association studies: -Gutiérrez 2001 -Lerer 2001	-Oruc 1997 -Vincent 1999 -Meyer 2002
HTR3A	11q23	5-HT3A receptor gene	-Niesler 1a 2001	-Niesler 1b 2001
HTR3B	11q23	5-HT3B receptor gene	-Frank 2004 -Yamada 2006	Lack of studies
HTR3C	3q27	5-HT3C receptor gene	Lack of studies	Lack of studies
HTR3D	3q27	5-HT3D receptor gene	Lack of studies	Lack of studies
HTR3E	3q27	5-HT3E receptor gene	Lack of studies	Lack of studies
HTR4	5q32	5-HT4 receptor gene	-Ohtsuki 2002 Genome wide linkage and association approaches: -Lewis 2003 -Hong 2004 -Park 2004 -Wellcome Trust Consortium 2007	Lack of studies
HTR5A	7q36.1	5-HT5A receptor gene	Genome wide linkage: -Etain 2006 -Cassidy 2007 Association studies: -Birkett 2000 -Yosifova 2009	Lack of studies
HTR6	1p35–36	5-HT6 receptor gene	-Vogt 2000	-Hong 1999
HTR7	10q21-q24	5-HT7 receptor gene		-Vincent 1999
SLC6A4: **VNTR** polymorphism in intron 2	17q11.1-q12	5-HTTLPR polymorphism in the serotonin transporter gene (SLC6A4= 5-HTT)	-Collier 1996 -Craddock 1996 -Battersby 1996 -Kunugi 1996 -Rees 1997 -Bellivier 1998 -Furlong 1998	-Stöber 1996 -Hoehe 1998 -Bocchetta 1999 -Vincent 1999 -Olivieira 2000 -Saleem 2000 -Mellerup 2001

			(meta-analysis) -Kirov 1999 -Bellevier 2002	-Dimitrova 2002 -Yen 2003 -Alaerts 2009
SLC6A4: 5-HTT gene= SERT: 5-HTTPLPR insertion/deletion polymorphism (short and long allele)	17q11.1-q12	5-HTTLPR polymorphism in the serotonin transporter gene (SLC6A4= 5-HTT)	-Bellivier 1998 -Rotondo 2002 -Anguelova 2003 (meta-analysis) -Hauser 2003 -Lasky-Su 2005 (meta-analysis) -Meira-Lima 2005	-Kunugi 1996 -Collier 1996 -Rees 1997 -Esterling 1998 -Hoehe 1998 -Mendes de Oliviera 1998 -Geller 1999 -Kirov 1999 -Serretti 1999 -Vincent 1999 -Olivieira 2000 -Ospina-Duque 2000 -Bellivier 2002 -Serretti 2002 -Mendlewicz2004 -Neves 2008 -Vincze 2008 -Alaerts 2009 -Mick 2009
Genes of the noradrenaline neurotransmitter system				
NET (SLC6A2)	16q12.2	Norepinephrine/ noradrenaline transporter	Lack of studies	-Hadley 1995 -Stöber 1996 -Leszczyńska-Rodziewicz 2002 -Chang 2007
Genes of the dopaminergic neurotransmitter system				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
DRD1	5q35.1	dopamine receptor D1	-Ni 2002 -Severino 2005 -Dmitrzak-Weglarz 2006	-Del Zompo 2007 -Szczepankiewic 2007
DRD2	11q23	Dopamine receptor D2	-Perez de Castro 1995 -Arinami 1996 - Li 1999 -Serretti 2000 -Massat 2002	-Souery 1996 -Stöber 1998 -Manki 1996 -Sasaki 1996 -Furlong 1998 -Bocchetta 1999 -Kirov 1999 -Li 1999

				-Heiden 2000 -Leszczyńska-Rodziewicz 2005 -Szczepankiewicz 2007 -Lafuente 2008
DRD3	3q13.3	Dopamine receptor D3	No support	-Shaikh 1993 -Manki 1996 -Souery 1996 -Piccardi 1997 -Kirov 1999 -Heiden 2000 -Elvidge 2001 (meta-analysis and large case control sample) -Leszczyńska-Rodziewicz 2005 -Szczepankiewicz 2007 -Krelling 2008
DRD4	11p15.5	Dopamine D4 receptor (DRD4)	-Manki 1996 -Serretti 1b 1998 -Serretti 1d 1999 -Serretti 2001 -Muglia 2002 -Lopez 2005 -Aguirre 2007	-Perez de Castro 1994 -Oruc 1b 1997 -Bocchetta 1999 -Li 1999 -1c Serretti 1999 -Serretti 2002 -Serretti 2004 -Leszczyńska-Rodziewicz 2005
DRD5	4p16.1	Dopamine D5 receptor	-Asherson 1998 -Ewald 1998	-Kirov 1999
SLC6A3= DAT1	5p15	Dopamine transporter-mediates reuptake of DA.	-Keikhaee 2005 -Ohadi 2007	-Bocchetta 1999 -Souery 1996 -Kirov 1999 -Heiden 2000 -Georgieva 2002
Channelopathies				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
NTNG1	1p13.3	Netrin-G1, a vertebrate specific axon guidance molecule	-Eastwood 2008	Lack of studies
NTNG2	9q34	Netrin-G2, a vertebrate	-Eastwood 2008	Lack of studies

		specific axon guidance molecule		
ANK3	10q21	Ankyrin G	-Segurado 2003 (meta-analysis of genome scans) -Baum 2008 -Ferreira 2008 -Scott 2008 (meta-analysis of GWAS) -Schulze 2009	Lack of studies
CACNA1E	12p13.3	Codes for the alpha 1C subunit of the L-type voltage-gated calcium channel	-Ferreira 2008 (GWAS) -Sklar 2008 (GWAS) -Askland 2009 (GWAS)	Lack of studies
CACNA1E	1q25-q31	Codes for the alpha-1 subunit of a voltage-dependent calcium channel	-Askland 2009	Lack of studies
KCNN3	1q21.3	Neural development; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	-Mahon 2009	-Jin 2001 -Glatt 2003 (meta-analysis)
KCNC2	12q14.1	*KCNC2* encodes the Shaw-related voltage-gated potassium channel.	-The Wellcome Trust Case Control Consortium 2007	Lack of studies
ATP2A2	12q23q24.1	ATP2A2 (the Darier's disease gene) encodes for the SERCA2- a sarcoplasmic/endoplasmic reticulum calcium pump that plays a role in intracellular calcium signalling	Lack of studies	-Jacobsen 2001
P2RX7/4	12q24.31	P2RX7/4 encodes a purinergic ATP-binding calcium channel receptor, which is expressed in the brain and is involved in 2-arachidonoylglycerol production by microglial cells. It regulates also the stromal organization in corneal tissue and influences osteoclasts and macrophages.	-Barden 2006	Lack of studies
SCL39A3		Channel for zink reuptake.	-Baum 2009 (meta-analysis of two GWAS) -Ollila 2009	Lack of studies

TRPM2	21q22.3	transient receptor potential cation channel, subfamily M, member 2	-Xu 2009	-Kostyrko. 2006
Growth hormones, brain development and neuronal growth				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
EGFR	7p12	epidermal growth factor receptor; Receptor of Neuregulin1.	-Sklar 2008 (GWAS)	Lack of studies
BDNF	11p13	• Neuronal migration • Phenotypic differentiation • Serotonergic axon growth • Synapse formation • Neuronal survival and growth • Key regulator of synaptic plasticity • Memory acquisition and consolidation • Antidepressant • Val66Met polymorphism associated with bipolar disorder in Europeans and not associated in Asians	-Sklar 2002 -Neves-Pereira2002 -Geller 2004 -Lohoff 2005 -Fan and Skar 2008 -Le-Niculescu 2008 (GWAS) -Liu 2008 -Vincze. 2008 -Xu 2009 -Xu 2010	-Hong 2003 -Nakata 2003 -Skibinska 1 2004 -Kunugi 2004. -Oswald 2004 -Kanazawa 2007 -Kim 2008 -Mick 2009
NCAM1	11q23.1	Neural cell adhesion molecule 1. Involved in neuronal growth and pathway formation	-Arai 2004 -Atz 2007	
NRG1	8p12	Neuregulin1; glial growth factor	-Segurado 2003 -Green 2005 -Walss-Bass 2006 -Georgieva 2008 -Perlis 2008 -Sklar 2008 -Goes 2009 -Le-Niculescu 2009 -Prata 2009	
Clock genes				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
DBP	19q13.3	„clock gene“	-Niculescu 2000	-Nievergelt 2006

				-Shi 2008
PER1	17p13.1-17p12	„clock gene“	-Kripke 2009	-Mansour 2006 -Nievergelt 2006 -Shi 2008
PER2	2q37.3	„clock gene“	-Kripke 2009	-Mansour 2006 -Nievergelt 2006 -Shi 2008
PER3	1p36.23	“clock gene“	-Nievergelt 2006 -Mansour 2006	-Kripke 2009 -Shi 2008
ARNTL (=BmaL1)	11p15	„clock gene“	-Le-Niculescu 2008 -Mansour 2006 -Nievergelt 2006	-Kripke 2009 -Shi 2008
NPAS2	2q13	„clock gene“	-Kripke 2009	-Nievergelt 2006
CRY1	12q23-q24.1	„clock gene“	-Ewald 2002 -Glaser 2005 -Green 2005 -Cassidy 2007	-Nievergelt 2005 -Mansour 2006 -Shi 2008
CRY2	11p11.2	„clock gene“		-Mansour 2006 -Nievergelt 2006
CSNK1ε		„clock gene“	-Nievergelt 2006 -Shi 2008	
CLOCK	4q12	„clock gene“	-Shi 2008 -Kripke 2009	-Kishi 2009 (Japanese) -Mansour 2006 -Nievergelt 2006
NRIDI (REV-ERBa gene)	17q11.2	„clock gene“	-Kripke 2009 -Severino 2009	-Shi 2008
PPARGCIB		„clock gene“	-Kripke 2009	
BHLHB2	3p26	„clock gene“	-Shi 2008	
THRA	17q11.2	„clock gene“	-Kripke 2009	
CSNKID		„clock gene“	-Kripke 2009	-Shi 2008
TIMELESS	12q12-q13	„clock gene“	-Mansour 2006	-Shi 2008
Genes of the Lithium signal transduction pathway				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
DGKH	13q14.11	Diacylglycerol kinase-η (encodes a key protein in the lithium-sensitive phosphatidyl inositol (PPI) pathway)	-Ollila 2009 (GWAS) -Baum 2007 (GWAS) -Baum 2008	
SORCS2	4p16.1	Sortilin-related VPS10 domain containing receptor 2 is involved in Lithium pathway	-Baum 2008	

DFNB31	9q32-q34	Deafness, autosomal recessive 31. Involved in Lithium pathway	-Baum 2008	
A2BP1	16p13.3	Ataxin 2-binding protein 1. Involved in Lithium pathway	-Baum 2008	
NXN	17p13.3	Nucleoredoxin. Involved in Lithium pathway	-Baum 2008	
VGCNL1 (NALCN)	13q32.3	sodium leak channel, non-selective. Voltage gated ion channel	-Baum 2008 (meta-analysis of GWAS)	
Copy number variations (CNVs)				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
DISC1	1q42.1	Disrupted in schizophrenia 1. This gene was discovered, because it was translocated in some families.	-Rubinsztein 1996 -Furlong 1999 -Blackwood 2001 -Thomson 2005 -Müller 2007 -Palo 2007 -Hennah 2009 -Le-Niculescu 2009 -Schosser 2009	
Genes of the glutamatergic neurotransmitter system				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
GRIN1	9q34.3	GRIN1, on chromosome 9q34.3, codes for the zeta-1 subunit of NMDA receptors. (Lithium and valproate may produce some of their effects by action on N-methyl-D-aspartatereceptors)	-Mundo 2003	
GRIN2B	12p12	Ionotropic glutamate receptor subunit 2B (GRIN2B)	-Fallin 2005 -Avramopoulos 2007 -Szczepankiewicz 2009 -Lorenzi 2010	-McInnis 2003
GRIN2C	17q25	Glutamate receptor. N-methyl-D-aspartate receptor subunit 2C	-Shi 2008	
GRIN2D	19q13.1-qter	N-methyl-D-aspartate receptor subunit 2D	-Shi 2008	
GRIA1	5q31.1	glutamate receptor,	-Herzberg 2006	

		ionotropic, AMPA 1	-Shi 2008 -Kerner 2009	
GRM3	7q21.1-q21.2	glutamate metabotropic receptor 3	-Fallin 2005	-Marti 2002
GRM4	6p21.3	glutamate metabotropic receptor 4	-Fallin 2005	
GRM7	3p26.1-p25.1	GRM7 (glutamate receptor, metabotropic 7)	-Wellcome Trust Consortium 2007	
GRIK4	11q22.3	excitatory amino acid receptor 1; glutamate receptor KA1	-Pickard 2008	
GRIK 5	19q13.2	excitatory amino acid receptor 2; glutamate receptor KA2	-Gratacos 2009	
Genes of the GABAergic neurotransmitter system				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
GABRB1	4p12	The gamma-aminobutyric acid (GABA) A receptor is a multisubunit chloride channel that mediates the fastest inhibitory synaptic transmission in the central nervous system. This gene encodes GABA A receptor, beta 1 subunit.	-Wellcome trust consortium 2007	
GABRB2	5q34	GABRB2 codes for beta(2)-subunit of gamma-aminobutyric acid type A (GABA(A)) receptor	-Crowe 1999	-Ambrosio 2005
GABRA3	Xq28	Gamma-aminobutyric acid (GABA) A receptor, alpha 3	-Baron 1994 -Wigg 2009 -Massat 2002	-Papadimitriou 2001
GABRA5	15q11-q13	Gamma-aminobutyric acid (GABA) A receptor, alpha 5	-Papadimitriou1998 -Otani 2005	
Signaltransduction				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
RGS4	1q23.3	Regulator of G-protein signaling 4	-Cordeiro 2005	-Prata 2006
GPR50	Xq28	G protein-coupled receptor 50		-Alaerts 2006 -Feng 2007
GRK3	22q12.1	G-protein receptor kinase 3 (GRK3).	-Barrett 2007 -Zhou 2008	-Prata 2006
PPARD	1q25-q31	Wnt signaling proteins,	-Zandi 2008	

(CACNA1E)		which activate cell signaling pathways, which regulate cell fate and play an important role in development.		
WNT2B	1p13		-Zandi 2008	
WNT7A	3p25		-Zandi 2008	
PLA2A	12q23-q24.1.	PhospholipaseA2 encoded in the region around Darier's disease.		-Meira-Lima2003
HPA axis and stress				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
CRHR1	17q12-q22	corticotropin releasing hormone receptor 1	Lack of studies	Lack of studies
CRH	8q13	corticotropin releasing hormone	-Marcheco-Teruel 2006	-Stratakis 1997 -Alda 2000
Cell adhesion				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
JAM3	11q25	junctional adhesion molecule 3	-Baum 2008 (meta-analysis of GWAS)	
CUX2	12q23±q24.1	A potential regulator of NCAM (neural cell adhesion molecule) expression. CUX2 s coded in the region of Darier's disease.		Jacobsen 2001-
Others				
Gene	**Location**	**Polymorphism and function**	**Supportive evidence**	**No evidence**
G72/G30 (DAOA)	13q13-q14	**G30/G72** codes for DAOA (D-amino acid oxidase activator)	-Fallin 2005 -Schulze 2005 -Bass 2009 -Maziade 2009	-Shi 2008 -Gomez 2009 -Maheshwari2009
IL2RB	22q13.1	Interleukin 2 receptor, beta	-Fallin 2005	
TUBA8	22q11.1	Alpha tubulin, peroxisome biogenesis factor 26	-Fallin 2005	
MLC1	22q13.33	megalencephalic leukoencephalopathy with subcortical cysts 1	-Verma 2005	Lack of studies
CHMP1.5	18p11.2	chromatin modifying protein 1B	-Detera-Wadleigh 1999	-McNabb 2005

			-Segurado 2003 (meta-analysis of genome scans)	
GCHI	14q22-24	GTP cyclohydrolase 1	-Liu 2003 - Cassidy 2007 (GWAS) -Zhao 2007 (GWAS)	Lack of studies
BCR	22q11	breakpoint cluster region	-Hashimoto 2005	Lack of studies
NAPG	18p11	N-ethylmaleimide-sensitive factor attachment protein	-Weller 2006 -Li 2009	Lack of studies
PDLIM5	4q22	enigma-like LIM domain protein	-Kato 2005 -Shi 2008 -Zhao 2009	Lack of studies
MYO5B	18q21	myosin VB	-Sklar 2008 (GWAS)	Lack of studies
TSPAN8	12q14.1-q21.1	transmembrane 4 superfamily member 3	-Sklar 2008 (GWAS) -Scholz 2010	Lack of studies
SYBL	Xq28	SYBL1 encodes a member of the synaptobrevin family of proteins that is involved in synaptic vesicle docking and membrane transport.	-Saito 2000	Lack of studies
SYN3 synapsinIII	22q12.3	Synaptic function	-Lachman 2006 (for Czech sample) -Wellcome Trust Consortium 2007	Lack of studies
QDPR	4p15.31	quinoid dihydropteridine reductase	-Shi et al. 2008	Lack of studies
DTNBP1	6p22.3	Dysbindin	-Fallin 2005 -Breen 2006 -Pae 2007 -Joo 2007 -Gaysina 2009	-Raybould 2005
SLC22A16	6q21-q22.1	Carnitine transporter	-Fan 2009 (GWAS) -Fan et al. 2010	Lack of studies
BRD1	22q13.33	bromodomain containing 1	-Severinsen 2006 -Nyegaard 2009	Lack of studies
PALB2 = BRCA2	16p12.2	involved in stability of key nuclear structures including chromatin and the nuclear matrix	-Ollila 2009 -Wellcome Trust Consortium GWAS 2007 -Ekholm 2003 (GWAS)	Lack of studies
SORCS2	4p16.1	sortilin-related VPS10 domain containing receptor 2	-Baum 2008 (meta-analysis of GWAS)	Lack of studies

			-Ollila 2009	
MTHFR	1p36.3	5,10-methylenetetrahydro-folate reductase. Amino acid metabolism.	-Kempisty 2007	-Kunugi 1998 -Chen 2009 (meta-analysis) -Jönsson 2008 (meta-analysis)
DCTN5	16p12.2	Dynactin	The Wellcome Trust Case Control Consortium 2007	Lack of studies
NDUFAB1	16p12.2	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1 Encodes a subunit of complex I of the mitochondrial respiratory chain	The Wellcome Trust Case Control Consortium 2007	Lack of studies
NET (SLC6A2)	16q12.2	Norepinephrine/ noradrenaline transporter		-Leszczyńska-Rodziewicz 2002 -Stöber 1996
DFNB31	9q32-q34	deafness, autosomal recessive 31	-Baum 2008 (meta analys of GWAS)	
ITIH1	3p21.2-p21.1	Codes for heavy chain of a serine protease inhibitor.	-Scott 2008 (meta-analysis GWAS)	
ITIH3	3p21.2-p21.1	Belongs to the inter-alpha-trypsin inhibitors (ITI), a family of structurally related plasma serine protease inhibitors involved in extracellular matrix stabilization	-Scott 2008 (meta-analysis GWAS)	
NEK4	3p21.1	Full gene name: NIMA (never in mitosis gene a)-related kinase 4	-Scott 2008 (meta-analysis GWAS)	
GNL3	3p21.1	Full gene name: guanine nucleotide binding protein-like 3	-Scott 2008 (meta-analysis GWAS)	

3.3. Genes of the serotonergic system

The serotonin (5-HT) neurotransmitter system has been proposed as a target for genetic research, because it is involved in all models for pathogenesis of depression and its receptors and transporters (5-HTT) are inhibited by antidepressants, SSRI and tricyclic antidepressants, with great success. Already in the late 1970s reduced levels of 5-hydroxyindoleacetic acid in cerebral fluid of suicide victims were found and lead to the conclusion, that serotonin metabolism might be involved in affective disorders [Cronholm et al. 1977]. Besides

depletion of tryptophan, which is necessary for the synthesis of serotonin, has mood lowering effects. Altogether genes coding for elements of the serotonergic system are top candidates for bipolar and unipolar depression [Robinson et al. 2009].

3.3.1. Serotonin receptor genes

3.3.1.1. 5-HT1 receptor genes

3.3.1.1.1. HTR1A

The serotonergic receptor 1A is coded on the long arm of chromosome 5q11.2-q13 [Kobilka et al. 1987]. It is a G-coupled receptor, which is distributed in the frontal cortex, septum, amygdala, hippocampus and hypothalamus post-synaptically. The 5-HT1A receptor is also the predominant auto-receptor in the raphe nucleii, which slows down the firing rate of the serotonergic neurons and the production of serotonin. Also the presynaptic 5-HT1A receptors reduce serotonergic transmission through the inhibition of tyrosine hydroxylase synthesis [Savitz et al. 2009]. Animal, postmortem, pharmacological, PET and gene expression studies suggested a role of the 5-HT1 receptors in affective disorders [Lopez-Figueroa et al. 2004; Savitz et al. 2009]. HTR1A knock out mice show anxiety like behaviour and avoid stressful situations [Parks et al. 1998; Ramboz et al. 1998; Gross et al. 2002]. PET studies showed higher raphe autoreceptor binding and thus decreased serotonergic neurotransmission in affective disorder [Sullivan et al. 2009].

Promoter polymorphism -1019C/G (rs6295)

The promoter polymorphism -1019C/G (rs6295), which leads to a cytosine to guanine exchange at position -1019, blocks transcriptional repression and leads to increased autoreceptor expression. This results in relatively decreased serotonin signaling in postsynaptic forebrain target sites via increased negative feedback. The G-allele of this SNP was supposed to play a major role in affective disorders, but with distinct results. Lemonde and colleagues showed that the G-allele was significantly overrepresented in depressed and suicidal patients [Lemonde et al. 2003; Wu et al. 2008]. The bigger part of the groups could not replicate any association of this SNP with depression or suicidal behaviour [Wasserman et al. 2006; Serretti et al. 2007; Hettema et al. 2008; Illi et al. 2009; Videtic et al. 2009].

G659T polymorphism

Another rare R219L 5-HT1A receptor variant (rs1800044; G659T) is associated with major depressive disorder [Haenisch et al. 2009].

Dinucleotide polymorphism (CAn/GTn repeats)

A dinucleotide polymorphism of HTR1A consisting of ten CAn/GTn repeats was analysed by Vincent and colleagues, but they did not find a relationship with bipolar disorder [Vincent et al. 1999].

Relevance for therapy

Animal and clinical studies suggested desensitization of 5-HT 1A receptors in the antidepressant therapeutic mechanism of selective serotonin reuptake inhibitors (SSRIs). Thus gene polymorphism might be useful for treatment response and medication decisions, because certain HTR1A polymorphisms show better response to antidepressant therapy [Yu et al. 2006; Kato et al. 2009].

3.3.1.1.2. HTR1B and HTR1D

The G861C polymorphism of HTR1B encoded on 6q13 was associated with major depressive disorder, but does not play a role in bipolar disorder [Huang et al. 2003]. HTR1D is unlikely to be involved in pathogenesis of bipolar disorder too [Mundo et al. 2001].

3.3.1.2. 5-HT2 receptor genes

3.3.1.2.1. HTR2A

HTR2A, the gene for the serotonin 2A receptor located on chromosomal region 13q14–21, was significantly associated with bipolar disorder in a genome wide approach and association studies recently [Ranade et al. 2003; Le-Niculescu et al. 2008; McAuley et al. 2009].

Although those positive findings contradict almost all other negative study results [Arranz et al. 1997; Gutiérrez et al. 1997; Mahieu et al. 1997; Zhang et al. 1997; Tsai et al. 1999; Vincent et al. 1999; Blairy et al. 2000; Heiden et al. 2000; Massat et al. 2000; Tut et al. 2000; Murphy et al. 2001; Etain et al. 2004; Bonnier et al. 2002; Robertson et al. 2003; Etain et al. 2004; Kishi et al. 2009].

T102C

The well studied silent T102C single nucleotide polymorphism of the HTR2A gene, also referred as *Msp1* polymorphism, results of a thymidine to cytosine substitution at position 102 in exon 1, which does not result in an amino acid change. Results within schizophrenia patients showed positive findings in relationship with this polymorphism [Peñas-Lledó et al. 2007]. For association with bipolar affective disorder some early studies at the end of the 20th century did not report evidence [Arranz et al. 1997; Gutiérrez et al. 1997; Mahieu et al. 1997;

Zhang et al. 1997; Tsai et al. 1999; Blairy et al. 2000; Heiden et al. 2000; Massat et al.2000; Tut et al. 2000; Murphy et al. 2001]. Also Kishi's association study in 2009 could not provide any evidence for association of four HTR2A markers (T102C, -A1438G, Rs7997012 and Rs1928040) with bipolar affective disorder [Kishi et al. 2009]. The T102C and –1438A/G polymorphisms were also investigated for their relation with bipolar affective puerperal psychosis, but they were not associated with bipolar disorder [Robertson et al. 2003]. Besides, also suicidal behaviour was examined in relation with this polymorphism, but without positive results [DeLuca et al. 2007]. Even genomic imprinting and parent of origin effect at this locus were excluded [Murphy et al. 2001; DeLuca et al 2006]. Since there was no positive study result at all, this polymorphism is very unlikely to be associated with bipolar disorder.

516-C/T

This silent single nucleotide polymorphism in exon 2 of the HTR2A gene was not associated with bipolar disorder in early studies [Arranz et al. 1997; Gutiérrez et al. 1997]. Only one study by Renade and colleagues suggested association with bipolar affective disorder. Since this polymorphism is not as well investigated as T102C further studies might be useful [Ranade et al. 2003].

1354C/T

Significant linkage and association of bipolar disorder with this 1354C/T single nucleotide polymorphism, as well as haplotypes bearing this SNP, were proven by Ranade and his colleagues. Since almost all study results of other HTR2A polymorphisms are negative, this positive association is worth further investigation [Ranade et al. 2003]. In addition this polymorphism was associated with remission and response following paroxetine therapy [Wilkie et al. 2009].Thus different genotypes might affect treatment response to common antidepressant treatment.

His452Tyr

His452Tyr is a structural polymorphism in exon 3 of the $(5\text{-HT})_2$ receptor gene, which is not associated with manic depressive disease [Arranz et al. 1997; Gutiérrez et al. 1997; Etain et al. 2004].

Thr25Asn

Also Thr25Asn, a structural polymorphism in exon1 of the HTR2A gene, is very unlikely to be associated with bipolar disorder [Arranz et al. 1997; Gutiérrez et al. 1997].

-A1438G genetic polymorphism

Etain et al. could not find any association with the -A1438G single nucleotide polymorphism and bipolar disorder, as well as Kishi and colleagues recently [Etain et al. 2004; Kishi et al. 2009]. Bonnier et al. analysed this 5-HT2A polymorphism in patients with major affective disorder and detected lower suicidality in carriers of this polymorphism [Bonnier et al. 2002]. Besides, this polymorphism was investigated in schizophrenic patients with positive results [Peñas-Lledó et al. 2007].

Table 2: HTR2A gene variants and their association with bipolar disorder

HTR2A polymorphisms	**Association**	**No association**
polymorphic DNA variation **T102C** in exon 1 of HTR2A		-Arranz et al. 1997 -Gutiérrez et al. 1997 -Mahieu et al. 1997 -Zhang et al. 1997 -Tsai et al. 1999 -Vincent et al. 1999 -Blairy et al. 2000 -Heiden et al. 2000 -Massat et al. 2000 -Tut et al. 2000 - Murphy et al. 2001 -Robertson[1] et al. 2003 -Kishi et al. 2009
1354C/T	-Ranade et al. 2003	
-A1438G		-Kishi et al. 2009 -Etain et al. 2004 -Bonnier[2]et al. 2002 -Robertson[1] et al. 2003
His452Tyr polymorphism		-Arranz et al. 1997 -Etain et al. 2004 -Gutiérrez et al. 1997
Thr25Asn		-Arranz et al. 1997 -Gutiérrez et al. 1997
516-C/T	-Ranade et al. 2003	-Arranz et al. 1997 -Gutiérrez et al. 1997
Rs7997012		-Kishi et al. 2009
Rs1928040		-Kishi et al. 2009
Rs2224721	McAuley et al. 2009	

[1] this study investigated bipolar affective puerperal psychosis

[2] study associated lower risk of suicide in bipolar disorder to this allele

Linkage studies

Although association studies of the HTR2A gene, mapped to chromosomal region 13q14–21, were disappointing, linkage studies prove evidence for linkage of 13q14 to bipolar disorder [Stine et al. 1997; Badenhop et al. 2001]. Also closeby regions like 13q32 were linked to manic depressive disease in genome wide linkage studies [Detera-Wadleigh et al. 1999]. The region 13q14–21 was also identified in a very recent genome wide approach by Le-Niculescu in 2008. Although there are isolated positive results, the bigger part of the studies are pretty disappointing up to now. Nevertheless time will tell, whether this locus comprises any connection with affective disorder at all [Le-Niculescu et al. 2008].

3.3.1.2.2. HTR2C gene

The serotonergic receptor 2C (formerly serotonergic receptor 1C) is coded on chromosome Xq24 and belongs to the family of seven transmembrane domain containing G-proteincoupled receptors. It mediates effects like appetite and locomotor regulation, sexual behaviour and anxiety, via signaltransduction by phospholipase C [Roth 1999]. HTR2C knock out mice show hyperphagia and increased locomotor activity, as well as increased susceptibility to epileptic seizures [Tecott et al. 1995; Nonogaki et al. 2003]. Linkage studies suggested involvement of the chromosomal region Xq24 in pathogenesis of bipolar disorder [Pekkarinen et al. 1995; Ekholm et al. 2002]. Also a whole genome scan showed linkage to a large region spanning from Xq24 to Xq28 in a pedigree of childhood onset bipolar disorder recently [Wigg et al. 2009]. Lerer and colleagues showed that ser23 allele carriers of the HT2CR cys23ser polymorphism are at greater risk to develop bipolar disorder [Lerer et al. 2001], while Gutiérrez' group could only find slight overrepresentation of the ser23 allele in a subgroup of bipolar women, but not in men [Gutiérrez et al. 2001]. Other groups could not show any association with this HTR2C polymorphism and bipolar disorder at all [Oruc˘ et al. 1997; Vincent et al.1999]. Also other gene variations, two polymorphic dinucleotide repeats separated by a short spacer in the promoter region of the HTR2C gene, were investigated by Meyer and colleagues. Nevertheless no association between the microsatellites in the promoter region and bipolar disorder was found [Meyer et al. 2002]. The 5-HT 2C gene was also discussed in other psychiatric diseases, like suicidal behaviour, depression and eating disorders. The HTR2C gene was investigated in suicidal patients, but with conflicting results. Serretti and colleagues contradict any involvement of this locus in suicide, while Videtic found a significant association of a functional polymorphism 68G>C (Cys23Ser) in female suicide victims recently [Serretti et al. 2007; Videtic et al. 2009]. Serretti also investigated the connection of

this locus with psychotic features, but again with negative results [Serretti et al. 2000]. HTR2C polymorphisms also influence eating habits and are involved in eating disorders [Pooley et al. 2004].

3.3.1.3. 5-HT3 receptor genes

The HTR3 genes (HTR3A, HTR3B, HTR3C, HTR3D and HTR3E) code for the five subunits of the 5-HT_3 receptor, a ligand gated ion channel for Na^+, K^+ and Ca^{2+}. HTR3A and HTR3B are coded on 11q23 and HTR3C, HTR3D, HTR3E on 3q27 [Bloom et al. 1998; Davies et al. 1999; Niesler et al. 2003]. 5-HT_3 receptors regulate many physiological effects, like drug induced emesis and nociception, and it may play a role in behaviour of anxiety and cognitive disorders [Bloom et al. 1998]. Especially HTR3A and HTR3B may have a role in bipolar affective disorder [Niesler et al. 2008]. A missense mutation at the 5' upstream region of the HTR3A gene (C178T) was associated significantly with bipolar disorder by Niesler and colleagues [Niesler 1a et al. 2001]. Further five rare HTR3A variants were not associated with manic depressive disease [Niesler 1b et al. 2001]. The rare gene variants of the HTR3B locus (IVS6 + 31C > T, IVS6 + 40C > A and 1386T >C) were solely detected in patients with bipolar disorder, while a 3 bp deletion was underrepresented in manic depressive patients. Thus this deletion might be protective [Frank et al. 2004]. Certain HTR3B haplotypes are important in female depressive disorder. The 5-HT3 receptor genes haven't been a major focus of molecular psychiatry yet, but might deserve a closer look [Yamada et al. 2006].

3.3.1.4. 5-HT4 receptor genes

The 5-HT4 receptor is coded in the chromosomal region 5q32, which was linked to bipolar disorder in genome wide approaches [Lewis et al. 2003; Hong et al. 2004; Park et al. 2004; Wellcome Trust Consortium 2007]. This widely spread receptor is connected to adenylyl cyclase and contributes to dopamine secretion [Bonhomme et al. 1995]. Four rare polymorphisms and a special haplotype of this receptor gene are significantly associated with bipolar disorder [Ohtsuki et al. 2002]. Some haplotypes have also been associated with schizophrenia [Suzuki et al. 2003]. Nevertheless clear statements about involvement of this receptor gene in psychiatric diseases cannot be done, because association studies are lacking. Further investigations are necessary to clarify the importance of this receptor gene.

3.3.1.5. 5-HT5 receptor genes

The Serotonin 5-HT-5A receptor is coded on 7q36.1 and is distributed in the central nervous system. It regulates many physiological and pathological reactions like anxiety, sleep

regulation, aggression, feeding and depression [Rees et al. 1994]. Genome wide linkage studies suggested this chromosomal region 7q36 as susceptibility locus for bipolar affective disorder [Etain et al. 2006; Cassidy et al. 2007]. Recently also a Japanese association study showed, that the HTR5 gene might be a promising candidate. They showed a very significant association of the SNP rs1800883 of 5-HT5-receptor gene with bipolar disorder [Yosifova et al. 2009]. The 19G/C SNP was proven to be significantly associated with bipolar disorder too [Birkett et al. 2000]. A recent association study showed no association between a SNP of HTR5A (rs1805054) and major depressive disorder. Since there have been only rare studies about this promising locus, future studies have to be carried out to reach conclusions about involvement [Illi et al. 2009].

3.3.1.6. 5-HT6 receptor genes

The HTR6 gene is located on 1p35–36 and codes for the 5-HT 6 receptor, which belongs to the family of G protein-coupled receptors that positively regulate adenylate cyclase. The receptor is mainly expressed in the brain areas involved in cognitive processes [Kohen et al. 1996]. Especially one SNP, which leads to a cytosine to thymine exchange at position 267, was studied in relationship with many neuropsychiatric diseases, but with inconsistant results. An early association study shows that the C267T variant is not associated with mood disorders [Hong et al. 1999]. In contrast Vogt and colleagues found an overrepresentation of the 267C allele among bipolar patients [Vogt et al. 2000]. The CT genotype of the C267T SNP has better treatment response in depressed patients [Lee et al. 2005]. The C267T SNP was discussed to play a role in schizophrenia, but again with unequal results, either positive [Tsai et al. 1999] or negative [Shinkai et al. 1999; Vogt et al. 2000; Dubertret et al. 2004]. Beside the C267T SNP was associated with Alzheimer's disease in a Japanese association study [Kan et al. 2004]. Alzheimer patients showed a 40% decline of neurons expressing the (5HT)-6 receptor. This shows an enourmous involvement of this reptor in cognitive processes and therefore may play a role in neuropsychiatric disease and may be a new target for cognitive enhancement drugs [Lorke et al. 2006].

3.3.1.7. 5-HT7 receptor genes

The serotonin receptor 7 is encoded on 10q21-q24 and might be involved in the pathogenesis of mood disorders, but its gene has not been investigated properly. One study by Vincent and colleagues showed no association between HTR7 genes and bipolar affective disorders [Vincent et al. 1999].

3.3.2. Serotonin transporter gene (= SLC6A4, SERT, 5HTT)

The Serotonin transporter (5-HTT, SERT) belongs to the superfamily of the large-solute carriers (SLC) and is coded by the SLC6A4 gene on 17q11.1-q12 [Ramamoorthy et al. 1993; Esterling et al. 1998]. The chromosomal region around 17q11.2 reached interest in many genome wide approaches and linkage studies for bipolar disorder [Edenberg et al. 1997; Murphy et al. 2000; Liu et al. 2003; Klei et al. 2005; Ewald et al. 2005; Etain et al. 2006; Thomás et al. 2006]. The 5-HT transporter mediates the active transport of serotonin into neurons, enterochromaffin cells, platelets and other cells. In the central nerve system the transporters are located in perisynaptic membranes of nerve terminals and in dendritic arbors in close proximity to serotonin-containing cell bodies in the midbrain and brain stem raphe nuclei [Murphy et al. 2004]. SERT mediates the quick removal of serotonin in the synaptic gap after neuronal stimulation and is therefore the primary target of serotonin reuptake inhibitors (SSRI), which block the transporter and lead to longer maintenance of serotonin in the gap [Murphy et al. 2004]. Its transcriptional activity is regulated by the 5HTT gene-linked polymorphic region (5HTTLPR), a repetitive element in the 5'flanking region located about 1.4kb upstream of the transcription start point. Especially this region is a hot spot of molecular psyhiatric research [Heils et al. 1995; Murphy et al. 2004].

3.3.2.1. Polymorphism of the 5-HTTLPR and the untranslated region

3.3.2.1.1. The variable-number-tandem-repeat (VNTR) within intron 2

The variable-number-tandem-repeat (VNTR) within intron 2 comprises nine, ten or twelve copies of a sixteen or seventeen basepair repeat. The 5-HTTVNTR acts as a transcriptional regulator, whereas the 12 repeat allele has a stronger transcription inducing ability [MacKenzie et al. 1999]. Some positive findings suggested a relation between this variant and bipolar affective disorder, especially with the 12 repeat allele [Battersby et al. 1996; Collier et al. 1996; Craddock et al. 1996; Kunugi et al. 1996; Rees et al. 1997; Furlong et al. 1998; Bellivier et al 1998; Kirov et al. 1999; Bellivier et al. 2002]. Furlong and colleagues pooled 1400 individuals for a meta-analysis, after they failed to show association between their small sample and this 5-HTTVNTR, and showed a significant association between the VNTR in intron 2 and bipolar and unipolar affective disorder in their meta-analysis [Furlong et al. 1998]. Already 14 years ago the Lancet posted association between the 9 repeat allele and unipolar affective disorder [Ogilvie et al. 1996], although this positive result for major depression was not replicated later [Kunugi et al. 1996; Stöber et al. 1996; Hoehe et al. 1998]. Some studies showed association with bipolar disorder, but could not survive correction for

multiple testing, like a study from Vienna [Heiden et al. 2000]. This VNTR was also investigated for a relationship with age at onset of bipolar disorder with positive results. Patients with 2 short alleles tended to get the disease at younger age, while patients with at least one 12repeat allele were affected later [Bellivier et al. 2002]. Nevertheless many groups failed to replicate those positive results. Even a new Swedish study with almost 600 participants, which included association study, mutation analysis and CNV analysis, showed that the serotonin transporter gene might not be associated with bipolar disorder in the Northern Swedish population at all. Nevertheless conflicting results might be due to different sample sizes and to different ethnicities [Stöber et al. 1996; Hoehe et al. 1998; Bocchetta et al. 1999; Liu et al. 1999; Vincent et al. 1999; Olivieira et al. 2000; Saleem et al. 2000; Mellerup et al. 2001; Dimitrova et al. 2002; Yen et al. 2003; Alaerts et al. 2009].

Table 3: Serotonin transporter gene polymorphisms and their relation with bipolar disorder

	Supportive evidence	**No evidence**
5-HTTVNTR in intron 2	-Collier et al. 1996 -Craddock et al. 1996 -Battersby et al. 1996 -Kunugi et al. 1996 -Rees et al. 1997 -Bellivier et al. 1998 -Furlong et al. 1998 (meta-analysis) -Kirov et al. 1999 -Bellevier et al. 2002	-Stöber et al. 1996 -Hoehe et al. 1998 -Liu et al. 1999 -Bocchetta et al. 1999 -Vincent et al. 1999 -Olivieira et al. 2000 -Saleem et al. 2000 -Mellerup et al. 2001 -Dimitrova et al. 2002 -Yen et al. 2003 -Alaerts et al. 2009
44bp Insertion/deletion in the promoter region of SERT	-Bellivier et al 1998 -Rotondo et al. 2002 -Anguelova et al. 2003 (meta-analysis) -Rousseva et al. 2003 -Hauser et al. 2003 -Lasky-Su et al. 2005 (meta-analysis) -Meira-Lima et al. 2005	-Kunugi et al. 1996 -Collier et al. 1996 -Rees et al. 1997 -Esterling et al. 1998 -Hoehe et al. 1998 -Mendes de Oliviera et al. 1998 -Geller et al. 1999 -Kirov et al. 1999 -Serretti et al. 1999 -Vincent et al. 1999 -Olivieira et al. 2000 -Ospina-Duque et al. 2000 -Bellivier et al. 2002 -Serretti et al. 2002 -Mendlewicz et al.2004 -Neves et al. 2008 -Vincze et al. 2008 -Alaerts et al. 2009 -Mick et al. 2009

3.3.2.1.2. Insertion/deletion in the promoter region of the serotonin transporter

The second extensily investigated VNTR (variable number of tandem repeats) polymorphism comprises of 16 repeat elements. Within those VNTR lies a 44 bp insertion or deletion in the area of repeat element 6-8, which results either in a short allele or a long allele. This polymorphism lies exactly at the 5'-flanking regulatory region of the serotonin transporter gene, which is called 5-HTTLPR. 5HTTLPR, the 5HTT gene linked polymorphig region, is a repetitive element of varying length in the 5' flanking region located around 1,4 kb upstream of the transcription start point. The short (s) allele of this polymorhism is associated with low transcriptional activity, while the long (l) allele leads to a high transcription and thus expression rate of the serotonin transporter [Heils et al. 1995; Hoefgen et al. 2005]. So this polymorphisms lead to different serotonin reuptake from the synaptic cleft. The short allele has been significantly associated with major depressive disorder and poorer response to SSRI [Serretti et al. 2004; Hoefgen et al. 2005]. Of course this variant was also investigated for its involvement in bipolar disorder, but with diverging results. Many studies did not find any association between the deletion/insertion polymorphism in the promoter region and bipolar affective disorder [Kunugi et al. 1996; Collier et al. 1996; Rees et al. 1997; Esterling et al. 1998; Hoehe et al. 1998; Mendes de Oliviera et al. 1998; Geller et al. 1999; Kirov et al. 1999; Serretti et al. 1999; Vincent et al. 1999; Olivieira et al. 2000; Ospina-Duque et al. 2000; Bellivier et al. 2002; Serretti et al. 2002; Mednlewicz et al. 2004; Neves et al. 2008; Vincze et al. 2008; Alaerts et al. 2009]. Others showed overwhelming positive results. Especially the short low activity allele (s allele) should influence bipolar affective disorder significantly [Bellivier et al 1998; Hauser et al. 2003; Lasky-Su et al. 2005; Meira-Lima et al. 2005]. Different results may occur because of lack of statistical power of some studies with small size of participants. But also large studies show inconsistant results. A large European multicentre study (539unipolar and 572 bipolar patients and 821 controls) did not identify any association between affective disorder and the 5-HTTLPR polymorpism [Mendlewicz et al. 2004]. Serretti and colleagues performed a large study to solve the relationship between the 5-HTTLPR polymorphism and major psychosis. They investigated 1820 inpatients (789bipolar, 667unipolar, 66 delusional, 261 schizophrenic and 37 not other specified psychotic patients) and 457 controls, but they did not find any association between 5-HTTLPR variants and the disease. Not even a difference in variant frequency between the disorders [Serretti et al. 2002]. A large meta-analysis of altogether 15studies (2774 bipolar cases and 3652 controls) showed significant association between the short allele of the 44bp deletion/insertion polymorphism and bipolar affective disorder [Lasky-Su et al. 2005]. In contrast a Brazil study

of 266bipolar patients and 306 controls suggested no association between the s allele, but showed higher frequency of the l allele and the ls genotype in bipolar participants [Meira-Lima et al. 2005]. Also a systematic review with meta-analysis, which comprised 1382 bipolar participants and 2085 controls, showed evidence of association with this polymorphism [Anguelova et al. 2003]. Conflicting results might be due to the heterogenity of bipolar disorder thus some groups concentrated on subtypes of bipolar disorder. A large study (435 patients with mood disorders like major depression, bipolar disorder and rapid cycling and 456 controls) by Cusin and colleagues concentrated on recurrant and rapid cycling mood disorders and found an excess of 5-HTTLPR long alleles in patients with rapid cycling [Cusin et al. 2001]. Also Rousseva and colleagues found an association between rapid cycling, but with the short (s) allele [Rousseva et al. 2003]. The insertion/ deletion variant of the serotonin transporter promoter was also investigated for association with age at onset of bipolar disorder, but with negative results [Geller et al. 1999; Bellivier et al. 2002]. Mick and colleagues also investigated the deletion polymorphismen in bipolar I disorder in children in 173 offspring triades, but this time with negative results [Mick et al. 2009]. In contrast an excess of the s allele was seen in younger bipolar patients with psychotic symptoms by another group [Ospina-Duque et al. 2000]. Another possibility is the association of the short allele with suicidality, which is also common bipolar disorder. A study by Neves and colleagues investigated 351 subjects with 77 patients with previous suicide attempts with the conclusion, that the s-allele was not associated with bipolar disorder, but with violent suicide attempts [Neves et al. 2008]. So maybe this polymorphism is not exactly associated with the pathogenesis of bipolar disorder itself, but may lead to some possible symptoms included in bipolar disorder as well as other diseases. It may also cause certain personality traits, which predispose pathogenesis for bipolar disorder. The ss genotype leads for example to enhanced stress reactivity in general. A very recent study tested this 5-HTTLPR variant in relation to stress response in newborns. They tested the relation between genotype and cortisol release (a measurement for stress) after a foot prick, which is an element in a routine check, but still associated with stress for the newborn. SS genotype carriers had much higher cortisol levels than other genotypes. Thus s allele carriers show much higher stress response of the hypothalamus-pituitary-adrenal axis (HPA) than l allele carriers [Müller et al. 2009].

3.4. Genes involved in biogenic amine modulation

3.4.1. MAOA gene (monoamine oxidase A gene)

The antidepressant effect of monoamine oxidase inhibitors and the biochemical reaction of MAO in relationship with the monoaminergic neurotransmitter hypothesis of bipolar disorder, as well as some shared symptoms with Brunner's disease (mild mental retardation, impulsive-aggressive behaviour, hypersexuality and attempted rape or exhibitionism) which affects the chromosomal region of MAO, implicate a role of its genes in bipolar affective disorder [Bach et al. 1988; Brunner et al 1993; Fiedorowicz et al. 2004]. The gene of monoamine oxidase A is located on chromosomal region Xp11.23-p11.4 and is expressed in the outer mitochondrial membrane. Transcription of the MAOA gene is regulated by clock proteins and other enhancers. So many other candidate genes for bipolar disorder can affect pathogenesis finally via monoamine oxidase [Hampp et al 2008; Hampp and Albrecht 2008]. MAOA and MAOB degrade monoaminergic neurotransmitters and dietary amines by oxidative deamination of monoamines [Bach et al. 1988]. Oxygen is used to remove an amine group from a molecule, resulting in the corresponding aldehyde and ammonia. MAOA mainly breaks down 5-hydroxytryptamine (serotonin), norepinephrine (noradrenaline), epinephrine (adrenaline), whereas MAOB prefers phenylethylamine. Both MAOs degrade dopamine [Shih et al. 2004].

3.4.1.1. Animal studies

MAO A/B double knock-out (KO) mice have increased brain levels of serotonin, norepinephrine, dopamine, phenylethylamine and decreased serotonin metabolite 5-hydroxyindoleacetic acid levels [Cases et al. 1995; Chen et al. 2004]. MAO A knockout mice show aggressive behaviour and have increased brain levels of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) [Cases et al. 1995]. Also very rare human MAOA null allele carriers show impulsive-aggressive behaviour [Margit Burgmeister 2008]. MAO B deficient mice do not exhibit aggression, but have increased levels of the MAO B preferred substrate phenylethylamine [Shih et al. 2004].

3.4.1.2. Antidepressants

MAO inhibitors, which are used since the 1950s [López-Muñoz F et al. 2007], have well studied antidepressant effects- this implicate MAO genes as candidate regions for affective disorders [Fiedorowicz et al. 2004].

3.4.1.3. Association studies

Brunner discovered in 1993 a point mutation, a 936C-T transition, in the eighth exon of the monoamine oxidaseA gene on chromosome X, which leads to mental retardation and behavioural problems as aggression, attempted rape, arson, exhibitionism, and voyeurism. These impulsive, aggressive symptoms especially arouse during periods of 1-3 days with lack of sleep and are provoked by anger often out of proportion to the provocation. Since manic depressive illness comprises some elements of Brunner's disease, this locus reached interest for association studies [Brunner et al. 1993].

3.4.1.3.1. CA-repeat microsatellite in intron 2

The CA-repeat microsatellite polymorphism in intron 2, a well studied and promising polymorphism of the MAO-A gene [Black et al. 1991], was associated with bipolar disorder within Japanese and Caucasian population in a meta-analysis, which pooled data from seven studies, namely Furlong et al. 1999; Craddock et al., 1995, Lim et al., 1995, Parsian and Todd, 1997, Nöthen et al., 1995, Muramatsu et al., 1997, Kawada et al., 1995 [Furlong et al. 1999]. Additionally other groups showed that some alleles of the microsatellite repeat polymorphism are significantly connected with bipolar affective disorder [Kawada et al. 1995; Lim et al. 1995; Rubinsztein et al. 1996]. Another meta-analysis, which included four association studies by Lim et al., Rubinsztein et al. Craddock et al., Parsian and Todd, proved association only for females [Preisig et al. 2000]. Nevertheless some studies failed to prove association [Nöthen et al., 1995; Parsian and Todd 1997; Muramatsu et al., 1997; Lin et al. 2008; Serretti et al. 2002].

3.4.1.3.2. *Fnu4H1* RFLP (Fnu4H1 restriction fragment length polymorphism)

The *Fnu4H1* RFLP polymorphism got its name, because a *Fnu4H1* site (a restriction enzyme cutting site) is generated by a G to T substitution at the third base of codon 941 of MAOA. This substitution does not result in a change in amino acid at this position but is associated with increased activity of MAOA [Hotamisligil et al. 1991]. Recently Müller et al. investigated this MAOA polymorphism with a G to T substitution at position 941 and found marginal association for the T allele. Beside he associated significantly a special haplotype, comprising of this and other polymorphisms, with manic depressive illness [Müller et al. 2007]. Already in the late 1990s Rubinsztein and colleagues provided evidence for association of the Fnu4HI RFLP polymorphism with manic depressive illness in a meta-analysis by combinating the results of British studies and their own [Rubinsztein et al. 1996].

Also Furlong et al. proved association in a meta-analysis comprising seven studies [Furlong et al. 1999]. However many studies could not prove any association with alleles of this MAOA sequence variance [Muramatsu et al., 1997; Preisig et al. 2000; Serretti et al. 2002].

3.4.1.3.3. EcoRV polymorphism (T-to-C substitution at position–1460)

The sequence of this MAO-A polymorphism resembles the restriction enzyme cutting site of *EcoRV*, a DNA endonuclease, and is produced by a T-to-C substitution at position –1460 [Hotamisligil et al. 1991]. A recent study by Huang showed that the MAOA sequence variance EcoRV was not associated with BD [Huang et al. 2008].

3.4.1.3.4. T-to-A substitution at position 1077 (Promoter VNTR)

Another functional MAO polymorphism contains the MAOA gene-linked polymorphic region (MAOA-LPR) positioned approximately 1.2 kb upstream of the coding sequence. Five alleles of 2, 3, 3.5, 4, and 5 copies of the 30 bp repetitive sequence, of which alleles 3 and 4 are common, have been described. This polymorphism influences transcription activity of the MAO promoter [Sabol et al. 1998]. Nevertheless there is significant evidence, that this promoter polymorphism is not associated with manic depressive disease, since all studies showed no association with bipolar disorder [Furlong et al. 1999; Kunugi et al. 1999; Syagailo et al. 2001; Serretti et al. 2002; Müller et al. 2007; Huang et al. 2008; Lin et al. 2008].

3.4.1.3.5. Variable number of tandem repeats (VNTR) polymorphism in intron 1

This VNTR (Variable number of tandem repeats) polymorphism in intron 1 of the MAO-A gene is not associated with manic depressive illness [Muramatsu et al. 1997; Preisig et al. 2000; Serretti et al. 2002;].

Table 4: MAO-A gene polymorphisms and their relationship with manic depressive disease

Polymorphism of MAO-A gene	Supporting study	Not supporting study
CA-repeat microsatellite in intron 2	-Furlong et al. 1999 (meta-analysis) -Kawada et al. 1995 -Rubinsztein et al. 1996 -Lim et al. 1995 -Preisig[1] et al. 2000	-Parsian and Todd 1997 -Lin et al. 2008 -Serretti et al. 2002 -Muramatsu et al. 1997 - Nöthen et al.1995
Fnu4HI RFLP =Fnu4HI G/T silent polymorphism =MAOA–941T>G = G to T substitution at the third base of codon 941	-Rubinsztein et al. 1996 -Furlong et al. 1999 -Müller et al. 2007	-Muramatsu et al. 1997 -Preisig et al. 2000 -Serretti et al. 2002
polymorphic promoter VNTR (variable number of tandem repeats) located approximately 1,200 bp upstream from the translation start site = MAOA gene-linked polymorphic region (**MAOA-LPR**) = uVNTR polymorphism		-Furlong et al. 1999 -Syagailo 2001 -Müller et al. 2007 -Huang et al. 2008 -Kunugi et al. 1999 -Lin et al. 2008 -Serretti et al. 2002
VNTR polymorphism in intron 1 (variable number of tandem repeats polymorphism in intron 1)		-Serretti et al. 2002 -Muramatsu et al. 1997 -Preisig et al. 2000
EcoR polymorphism= T-to-C substitution at position–1460		-Huang et al. 2008 -Serretti et al. 2002
T-to-A substitution at position 1077		-Serretti et al. 2002

1 for females

3.4.1.4. Linkage studies

X-linked heredity for bipolar disorder has been assumed for a long time, but linkage analysis with X linked markers like G6PD deficiency, color blindness and factor IX had inconsistant results [Mendlewicz et al. 1973; Baron et al. 1987; Pekkarinen et al. 1995; Wigg et al. 2009]. MAOA and MAOB are closely linked in opposite orientation to the X chromosome at Xp11.23-p11.4 [Derry et al. 1989]. Some linkage studies discovered the chromosomal region of the MAOA gene in genome wide approaches [Zandi et al. 2001; Wigg et al. 2009; Pekkarinen et al. 1995].

3.4.2. MAO-B Gene

MAOB association studies are rare-two investigate the relationship with bipolar disorder, but findings are negative. A dinucleotide repeat in the intron 2 (MAOB-GT) is not associated with bipolar affective disorder [Muramatsu et al. 1997; Parsian and Todd 1997].

3.4.3. COMT (Catechol-O-methyltransferase)

The COMT gene is mapped to chromosomal region 22q11.1-q11.2. Catechol-O-methyltransferase (COMT) is a widely expressed enzyme, which inactivates catecholamines and catechol drugs such as L-DOPA. It catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. This O-methylation results in one of the major degradative pathways of the catecholamine transmitters [Hosak et al. 2007]. COMT polymorphisms confer significant genetic risk for psychiatric diseases, especially schizophrenia [Lewis et al. 2003; Shifman et al. 2004; Funke et al. 2005; Allen et al. 2008; Chien et al. 2009; Brisch et al. 2009; Hoenicka et al. 2010; Wang et al. 2009]. But not only schizophrenia is affected by COMT variants, also bipolar disorder to a minor degree [Lachman 1996; Kirov 1998; Shifman 2004; Funke 2005; Goghari 2008; Zhang 2009]. A copy number variation on chromosome 22 (deletion on 22q11), which leads to velocardiofacial syndrome, an autosomal dominant congenital disorder associated with cleft palate, cardiac defects and learning disabilities, helped to identify this causality. Because of common comorbidity with schizophrenia, bipolar disorder or attention deficit syndromes with the velocardiofacial syndrome, this chromosomal region reached interest for genetic research [Carlson et al. 1997]. A polymorphism in the COMT gene that leads to a valine-methionine substitution at amino acid 158 of the membrane-bound form of the enzyme was found. This low activity polymorphism is associated with bipolar disorders in patients with velocardiofacial syndrome [Lachman et al. 1996]. Homozygosity for the COMT158met allele leads to a 3-4-fold reduction in enzymatic activity, compared to homozygotes for the COMT158val allele. Beside there is a good chance, that the low activity allele is associated with bipolar disorder [Lachman et al. 1996]. In general this COMT polymorphism was often associated with bipolar disorder [Lachman et al. 1996; Kirov et al. 1998; Shifman et al. 2004; Funke et al, 2005; Goghari et al. 2008]. A recent large Chinese study comprising 478 BP patients and 469 healthy subjects showed significant association between the Val/Met polymorphism and bipolar disorder. They also conducted a meta-analysis on 19 studies and reached significant positive results for the Met allele of the polymorphism [Zhang et al. 2009]. Although there

have been many positive results, some other studies suggested no association [Gutierrez et al. 1997, Kirov et al. 1999; Kunugi et al. 1997; Geller et al. 2000]. This polymorphism was also investigated for rapid cycling and ultra-ultra rapid cycling in young patients, with positive [Kirov et al. 1998; Papolos et al. 1998] and negative results [Geller et al. 2000]. Nevertheless Kirov and colleagues associated the Met allele with rapid cycling [Kirov et al. 1998]. Further replication studies are necessary to clarify the role of the COMT gene in pathogenesis of bipolar disorder. Beside gene mutations also epigenetic changes influence COMT expression and the risk of bipolar disorder. Hypomethylation of the COMT promoter leads to increased risk for bipolar disorder and schizophrenia. Thus also epigenetic changes should be considered. Maybe they are the missing part of the puzzle within inconsistant research results [Abdolmaleky et al. 2006].

Table 5: COMT gene variants and association with bipolar disorder

COMT polymorphism	**Supporting study**	**Not supporting study**
Val/Met polymorphism (rs4680): low-activity allele (Met)	-Lachman et al. 1996 -Kirov et al. 1998 -Shifman et al. 2004 -Funke et al. 2005 -Goghari et al. 2008 -Zhang et al. 2009 (large study and meta-analys on 19studies)	-Gutierrez et al. 1997 -Kunugi et al. 1997 -Kirov et al. 1999 -Geller et al. 2000

3.4.4. TPH (tryptophan hydroxylase)

TPH, which codes for Tryptophan hydroxylase, maps to the chromosomal region 11p15.3-p14 [Nielsen et al. 1992]. Tryptophan hydroxylase (TPH) is the rate limiting and first enzyme of serotonin synthesis. TPH initiates serotonin synthesis by hydroxylation of tryptophan, which results in 5-hydroxytryptophan. Then aromatic amino acid decarboxylase produces serotonin. Since TPH is the first and rate limiting enzyme in serotonin synthesis its gene might be involved in affective disorders. TPH1 expressed in peripheral tissues [Walther et al. 2003]. There is no evidence for association of TPH1 with bipolar disorder [Vincent et al. 1999; Lai et al. 2005]. Nevertheless TPH1 might influence suicidality [Galfalvy et al. 2009]. TPH2 is a recently discovered isoform encoded on chromosome 12 that is expressed predominantly in serotonin neurons. TPH2 is preferentially expressed in the brain [Walther et al. 2003; Zhang et al. 2004]. The (-C8347G) promoter SNP (rs4131347), which leads to a cytosine to guanine exchange at position 8347, is not associated with mood disorder in general [Mann et al. 2008].

Significant haplotype association of TPH2 polymorphisms and BPD was identified [Lopez et al. 2007; Lin et al. 2007]. The A218C polymorphism of TPH is not associated with bipolar disorder [Rietschel et al. 2000]. Association of TPH with suicide was observed in suicidal depressed patients, but not in suicidal bipolar patients [Tsai et al. 1999]. In contrast some results suggested no association with suicide [Furlong et al. 1997]. Serretti and colleagues investigated the relationship between major psychosis and TPH in a large pedigree, but did not find significant association with major psychosis, but a trend towards association with bipolar disorder [Serretti et al. 2001]. Polymorphisms of the TPH and serotonin transporter gene also influence the response to SSRI and could be future markers for treatment decisions [Serretti et al. 2001; Serretti et al. 2004].

3.4.5. TH (Tyrosin Hydroxylase)

Tyrosin hydroxylase (TH) is encoded on 11p15 and is responsibe for the first step in the synthesis of catecholamines by converting tyrosine into L-dopa. TH and TPH, the biosynthetic enzymes for norepinephrine and 5-HT, were reduced in the locus coeruleus of bipolar suicide victims, which lead to an imbalance of norepinephrine and serotonine. So TH and TPH seem to be involved in pathogenesis of mood disorders [Wiste et al. 2008]. Also linkage studies supposed a relationship between the tyrosine hydroxylase locus and mood disorders [Malfosse et al. 1997; Smyth et al. 1997; Craddock et al. 1999; Serretti et al. 2000 b]. The microsatellite polymorphism HUMTH01 of TH is charcterised by a TCAT repeated motif. In an analysis and meta-analysis by Furlong this polymorphism was not associated with unipolar or bipolar disorder [Furlong et al.1999]. A large multicenter case-control association study, comprising 401 bipolar patients and 401 controls, investigated the tetranucleotide polymorphism of TH and could not find evidence of association with manic depressive disease [Souery et al. 1999]. But TH was significantly associated in association studies of depressive disorder. Although results of linkage studies are promising, further association studies are necessary to identify the relationship between this gene and bipolar disorder [Serretti et al. 1998].

3.5. Clock genes

Many processes in organism (release of melatonin or cortisone, body temperature, ...) underly circadian rhythm operated by an endogen clock. A specialised and centralised pace maker in CNS as well as in peripheral organs and tissues was found. Seasonal changes of mood, sleep disturbance in affective disorders, as well as antidepressant effects of light therapy and sleep

deprivation indicate a role of the circadian system in the pathogenesis of mood disorders [Lee et al. 2007; McClung 2007]. Also Lithium, a powerful mood stabilizer, modulates circadian rhythms via inhibition of glycogen synthase kinase 3 beta (GSK3B) and thus suggests a role of clock genes in bipolar disorder [Yin et al. 2006]. Because of the obvious involvement of circadian rhythms in bipolar disorder the circadian clock and its genes are reviewed in this chapter.

3.5.1. The circadian oscillator in the suprachiasmatic nucleus (SCN)

Circadian rhythms are generated in the suprachiasmatic nucleus (SCN) and connected peripheral oscillators [Moore 1999]. The SCN is located in the anterior hypothalamus above the optic chiasm and its core is linked to light/dark cycles by a direct retinal innervation, the retinohypothalamic tract [Abrahamson et al. 2001]. So light at dusk or dawn can help the SCN to function in an excact 24 hour rhythm by starting gene expression, although the SCN can also maintain almost circadian rhythms without any cues from environment [Porterfield et al. 2009]. Therefore the SCN can help to adapt physiological and hormonal rhythms to the environmental light-dark cycle. Many physiological processes, like wakefulness, sleep, mood, food intake, metabolisms, hormonal and cardiovascular rhythms are dependent on circadian rhythms. Beside the SCN can also recognise seasonal changes by measuring the lengths of a day. Also food-intake and other information like temperature can synchronise the clock [Mendoza 2006]. The 24-hour rhythms are regulated by an intrinsic circadian oscillator located in the SCN, based on interlinked autoregulatory positive and negative transcriptional/translational feedback loops [Shearman et al. 2000; Cermakian et al. 2003].

Course of action:

1. The cycle begins with heterodimerization of Arntl (Bmal1 or Mop3) and Clock [Gekakis et al. 1998] (or alternatively Npas can bind Arntl (Bmal1) [DeBruyne et al 2007]).
2. The Arntl-Clock heterodimer binds to e-box enhancers (transcription factor binding sites) of several clock genes, including PER (period genes) and CRY (Cryptochrome genes), and activates their transcription [Gekakis et al. 1998; Langmesser et al. 2008].
3. Per and Cry proteins accumulate after 12hours in the cytoplasma and get phophorylated by two casein kinases Csnk1, Csnk1E or glycogen synthase kinase 3b (Gsk3B). The phosphorylation of PER genes modulates the length of the cycle [Etchegaray et al.2009]. Then phosphorylated Per and Cry proteins form heterodimers and enter the nucleus. There the Per and Cry protein complexes suppress their own

transcription by binding the Arntl-Clock heterodimers and therefore creating a negative feedback loop [Langmesser et al. 2008].

In addition Clock/Bmal1 complexes initiate transcription of retinoic acid-related orphan nuclear receptors (REV-ERBa and RORa) genes. The gene products, Rev-erba and RORa, can bind to ROREs (retinoic acid-related orphan receptor response elements) in the promoter of Bmal1 and can therefore regulate the expression of BMAL1. RORs activate, whereas REV-ERBa inhibit the transcription of BMAL1 [Raspé et al 2002].

Table 6: Functions of clock genes

"Clock gene"	**Function**
CLOCK	• A dimer of Clock and Arntl is the main transcriptional activator of many clock genes (including CRY1 and 2 and PER 1-3 genes) • Clock and Arntl activate transcription of REV-ERBa gene (Nr1d1) • Clock activates transcription of Dbp, another clock gene product
ARNTL (also BMAL1 or Mop3)	• Arntl heterodimers with Npas2 bind to promoter eboxes of MAOA. This leads to transcription of MAO-A and finally to inactivation of dopamine and inhibition of the promanic effect of dopamine! • Arntl also activates the transcription of other clock genes (PER1, PER2, PER3, and CRY1, CRY2).
NPAS2	
PER1	• Per proteins associate with Cry1 and Cry2. Phosphorylated Cry and Per protein complexes enter the nucleus and suppress their own transcription by binding Arntl-Npas2 or Arntl-Clock heterodimers (negative feedback loop).
PER2	
PER3	
CRY1	• CRY genes code for chryptochromes, which are mammalian circadian photoreceptors in the retina and pacemaker elements in the SCN
CRY2	
CSNK1d	• Casein kinase 1 delta and Casein kinase 1 epsilon phosphorylate core genes of the circadian oscillator (Per1, Per2, Per3 and Cry1, Cry2, Cry3). • Phosphorylation of PER genes is a speed determining step in the circadian cycle and modulates cycle length.
CSNK1e	
NRIDI (REV-ERBa gene)	• Inhibits transcription of ARNTL(Bmal1) • Inhibits Clock and Npas2. • major regulator of cyclic BMAL1 transcription • Lithium leads to degradation of NRIDI (REV-ERBa gene)
PPARGCIB	• This clock protein may bind to RORE sites of Arntl and Nr1D1 and influences their transcription
THRA	• important thyroid nuclear receptor gene
DBP	• Dbp controls expression of many clock genes

TIMELESS	• "Clock protein", which is regulated by CLOCK and Bmal1
BHLHB2	• Basic helix-loop-helix transcription factor, which represses the Clock/Bmal1-induced transactivation of the Per1 promoter through direct protein-protein interactions with Bmal1 and/or competition for E-box elements.

3.5.2. Role of clock genes in bipolar disorder

3.5.2.1. ARNTL (Bmal1 or Mop3)

Many candidate genes for bipolar disorder code for elements of the previous described intrinsic circadian oscillator. ARNTL (Bmal1 or Mop3), which was a top candidate in a large genome wide association study in 2008, is a key element of the molecular circadian oscillator [Le-Niculescu et al. 2008; Nievergelt et al. 2009; Bunger et al. 2000]. Arntl (BmaL1) is very important for the final effect of the circadian feedback loop, which leads to transcription of clock genes (CRY1 and 2 and PER 1, PER2, PER3) and the dopamine degrading enzyme MAOA. Arntl and Npas2 build heterodimers and bind to promoter eboxes of MAOA. This leads to transcription and proteinsynthesis of MAOA. Thus dopamine gets degraded and the promanic effect of dopamine vanishes [Hampp et al. 2008; Hampp and Albrecht 2008; Kripke et al. 2009]. ARNTL (Bmal1) knock out mice have disrupted circadian rhythms and show decreased activity [McDearmon et al. 2006]. Many association studies already prove a connection between individual SNPs (single nucleotide polymorphisms) of ARNTL and bipolar affective disorder [Mansour et al 2006; Nievergelt et al. 2006; Le-Niculescu et al. 2008; Mansour et al. 2009], while others could not replicate this finding recently [Kripke et al. 2009; Shi et al. 2008]. Also special haplotypes in ARNTL and PER3 are significantly associated with bipolar disorder [Nievergelt et al. 2006]. However ARNTL is a promising candidate for molecular genetics of mood disorders and further investigations are necessary.

3.5.2.2. NPAS2 gene

Npas2 is an important clock protein coded on 2q13, which initiate the transcription of many clock genes together with Arntl (Bmal1). The SNP rs1562313 of NPAS2 has been associated with bipolar disorder recently, as well as the SNPs rs13025524 and rs11123857 [Kripke et al. 2009; Mansour et al. 2009]. Besides NPAS2 has also a role in seasonal affective disorder [Johannson et al. 2003].Though those findings could not be found by Nievergelt and colleagues [Nievergelt et al. 2006].

3.5.2.3. NR1D1 (nuclear receptor REV-ERBa gene)

NR1D1 (nuclear receptor REV-ERBa gene), another candidate gene for bipolar disorder, is located on chromosome 17. Nr1d1 inhibits on one hand the transcription of Arntl by inhibitory binding to Arntl RORE promoter sites and on the other hand the activation of Arntl by Clock and Npas2. This leads to decreased MAO-A effects and higher promanic dopamine levels. Some gene variants of NR1D1 for example rs2314339 and special haplotypes are strongly associated with bipolar disorder [Kripke et al. 2009; Severino et al. 2009]. Nuclear Receptor Rev-erba is also a critical Lithium-sensitive component and supports the pathogenesis of manic depressive disorder [Yin et al. 2006]. So NR1D1 seems to be a promising candidate gene, even though Shi et al. could not prove this association [Shi et al. 2008].

3.5.2.4. Period genes (PER1, PER2, PER3)

Some Period3 SNPs and certain haplotypes have been associated with bipolar disorder in family-based and case-control association studies [Nievergelt et al. 2006; Mansour et al. 2006]. Nievergelt et al. found the strongest association with a certain haplotype, which included a combination of 6 markers of the PER3 gene (four intronic markers rs228729, rs228642, rs228666, and rs2859388, a non-synonymous SNP in exon 17 (rs228697) and the 54-bp length polymorphism in exon 18. Beside this haplotype also other combinations of PER3 gene markers showed modest association. However some haplotypes in PER3 could have a protective effect, for example a haplotype comprised of two intronic SNPs (rs3789327 and rs2278749) [Nievergelt et al. 2006]. Furthermore certain length variants of the PER3 gene with variable-number tandem-repeat (VNTR) polymorphism influence age of onset. Homozygotes of this PER3 length variant progress bipolar disorder at young age [Benedetti et al. 2006]. While many studies support association of PER3 polymorphisms with bipolar disorder, Kripke et al. couldn't replicate these findings in a recent association study [Kripke et al. 2009]. At least polymorphisms of the PER3 gene were observed in delayed sleep-phase syndrome and sleep dysregulation in mood disorders indicating a role in symptoms, which are very common in mood disorders [Pereira et al. 2005; Archer et al. 2003; Ebisawa et al. 2001].
PER2, another clock gene, is a further candidate for bipolar disorder. Kripke et al. showed modest evidence for association of three SNPs (single nucleotide polymorphisms) of the Period 2 gene (rs4663868, rs2304672 and rs2304669) with manic-depressive disease [Kripke et al. 2009]. Per2 might have an impact on mood via transcription of MAOA, because it can regulate transcription of the enzyme, beside Arntl and Npas2. A certain mutation of the PER2

gene in mice leads to decreased expression of MAOA, and thus increased dopamine levels and promanic behaviour. Mice mutants of PER2 also show changed behaviour towards cocaine response, increased alcohol consumption and lack of food anticipation [Hampp et al 2008]. Furthermore PER2 has been associated with advanced sleep syndrome [Toh et al. 2001]. Whereas Shiino et al. observed polymorphisms in the binding site of the clock protein CKIe in the PER2 gene, they could not find any association with bipolar disorder [Shiino et al. 2003]. Nevertheless Period genes might have a strong impact on mood, which must be observed in further larger samples.

3.5.2.5. CRY genes

The CRY1 gene, located on 12q23-q24.1, lies within a hot spot discovered in many linkage studies and even in genome wide approaches for bipolar disorder [Ewald et al. 2002; Glaser et al. 2005; Green et al. 2005; Cassidy et al. 2007]. This region is closely linked to Darier's disease, which shows association with bipolar disorder [Green et al. 2005]. Although this region is strongly linked to bipolar disorder, association studies could not prove a connection of CRY1 to bipolar disorder as well as to the second chryptochrome gene CRY2 on chromosomal region 11p11.2 [Nievergelt et al. 2005; Mansour et al. 2006; Nievergelt et al. 2006; Shi et al. 2008]. While others showed nominal association [Mansour et al. 2009].

3.5.2.6. CLOCK gene

The CLOCK gene is located on chromosomal region 4q12 and codes for a basic helix-loop-helix (bHLH)-PAS transcription factor for several clock genes [King et al. 1997]. Many animal studies and association studies indicated a role in mood disorders. Disruption of the CLOCK gene in mice for example leads to manic-like behaviour [Roybal et al. 2007]. Kripke et al. supported evidence of association for many SNPs (see table) of the CLOCK gene with bipolar disorder in a recent association study [Kripke et al. 2009]. Also Shi et al. found modest evidence for association of several individual SNPs (e.g. rs534654, rs6850524, rs4340844) and haplotypes in the CLOCK gene to manic-depressive disorder. An interaction of 3 SNPs in the CLOCK gene region, the BHLHB2 gene and CSNK1E was significantly associated with bipolar disorder [Shi et al. 2008]. On the other hand Kishi et al. could not find significant association of the clock gene with bipolar disorder in Japanese population, as well as Mansour et al. and Nievergelt et al. in Caucasian pedigree [Kishi et al. 2009; Mansour et al. 2006; Nievergelt et al. 2006]. A CLOCK gene variant (T3111C polymorphism = rs1801260) at the 3' untranslated region of the CLOCK gene is involved in a high recurrence rate of

bipolar disorder [Benedetti et al 2003], as well as in sleep dysregulation in bipolar patients [Serretti et al. 2007]. The T3111C polymorphism was also investigated for association with major depression, but Desan et al. could not find any correlation [Desan et al. 2000]. Nevertheless the CLOCK gene is a very important gene in circadian regulation and therefore a candidate gene for mood disorders.

3.5.2.7. DBP gene

The clock gene Dbp codes for a D-box binding protein and is located on chromosome 19. Animal studies suggested a role of Dbp in bipolar disorder. Total Dbp knock-out mice produce bipolar behaviour [Niculescu et al. 2000; Le-Niculescu et al. 2008]. Nevertheless results of association studies were rather disappointing and could not discover a role in pathogenesis [Nievergelt et al. 2006; Shi et al. 2008].

3.5.2.8. CSNKD gene

The region of the CSNKD gene on chromosome 17 was significantly linked to bipolar disorder in an early genome wide association study [Dick et al. 2003]. Kripke et al. found an association of the CSNK1D SNP rs4510078 with bipolar disorder recently [Kripke et al.2009], which could not be replicated by Shi et al. [Shi et al. 2008].

3.5.2.9 CSNKE gene

Casein kinase 1 delta and Casein kinase 1 epsilon phosphorylate core genes of the circadian oscillator (Per1, Per2, Per3 and Cry1, Cry2, Cry3). Phosphorylation of PER genes is a speed determining step in the circadian cycle and modulates cycle length. Some gene variants for those casein kinases were linked with manic-depressive illness in linkage studies [Nievergelt et al. 2006]. Shi et al. found, that a multi-locus interaction between rs6442925 in the 5′ upstream of BHLHB2, rs1534891 in CSNK1E, and rs534654 near the 3′ end of the CLOCK gene, is significantly associated with manic depressive disorder [Shi et al. 2008].

3.5.2.10. TIMELESS gene:

TIMELESS is located in the chromosomal region 12q12-q13 and its transcription is regulated by Clock and Bmal1. Mansour et al. observed modest association of some TIMELESS single-nucleotide-polymorphisms and manic-depressive-disorder [Mansour et al. 2006].

3.5.2.11. PPARGC1B gene

A PPARGC1B coding SNP, rs7732671 (Pro203Ala), might be associated with unipolar and bipolar affective disorder. This clock protein may bind to RORE sites of Arntl and Nr1D1 and influence their transcription [Kripke et al. 2009].

3.5.2.12. THRA gene

THRA, an important thyroid nuclear receptor gene, may also be associated with bipolar disorder [Kripke et al. 2009].

3.5.2.13. EGR3 gene

This clock gene, coding for EGR3, was recently associated with bipolar disorder [Mansour et al. 2009].

3.5.2.14. RORB gene

SNP rs10491929 showed also nominal association with bipolar disorder [Mansour et al. 2009].

3.5.2.15. Summary of clock genes

Table 7: All clock genes and their association with bipolar disorder

"Clock gene"	**Chromosomal region**	**Support of association of a gene polymorphism with bipolar disorder**	**No support of association of a gene polymorphism with bipolar disorder**
DBP	19q13.3	-Niculescu 2000	-Shi 2008
PER1	17p13.1-17p12	-Kripke 2009	-Mansour 2006 -Nievergelt 2006 -Shi 2008
PER2	2q37.3	-Kripke 2009	-Mansour 2006 -Nievergelt 2006 -Shiino 2003 -Shi 2008
PER3	1p36.23	-Nievergelt 2006 -Benedetti 2008 -Mansour 2006	-Kripke 2009 -Shi 2008
ARNTL (also BmaL1 or Mop3)	11p15	-Le-Niculescu 2008 -Mansour 2006 -Nievergelt 2006	-Kripke 2009 -Shi 2008
ARNTL2			-Shi 2008
NPAS2	2q13	-Kripke 2009	-Nievergelt 2006
CRY1	12q23-q24.1	-Ewald 2002 -Glaser 2005	-Nievergelt 2005 -Mansour 2006

		-Green 2005 -Cassidy 2007	-Shi 2008
CRY2	11p11.2		-Mansour 2006 -Nievergelt 2006
CSNK1D			-Shi 2008
CSNK1E		-Shi 2008 -Nievergelt 2006	
NRIDI (REV-ERBa gene)	17q11.2	-Kripke 2009 -Severino 2009	-Shi 2008
CLOCK	4q12	-Shi 2008 -Kripke 2009	-Kishi 2009 -Mansour 2006 -Nievergelt 2006
PPARGCIB		-Kripke 2009	
THRA	17q11.2	-Kripke 2009	
CSNKID		-Kripke 2009	
TIMELESS	12q12-q13	-Mansour 2006	-Shi 2008
CSNK1ε		-Nievergelt 2006	
BHLHB2	3p26	-Shi 2008	

3.6. Growth hormones, brain development and neuronal growth

3.6.1 Brain-derived neurotrophic factor – BDNF

3.6.1.1. Functions of BDNF

The BDNF gene is a highly controversial, but an important candidate gene in bipolar disorder. It is coded in the chromosomal region 11p13-15 [Egeland et al. 1987; Schumacher et al. 2005]. BDNF is a member of the neurotrophin superfamily and is the most abundant and distributed neurotrophic factor in the brain [Sklar et al. 2002]. It has several important functions like neuronal survival [Kirschenbaum et al. 1995], migration, myelination, phenotypic differentiation, neurogenesis [Zigova et al. 1998; Pencea et al. 2001], axonal and dendritic growth and synapse formation [Keri Martinowich 2008]. Beside it has an important role in neural plasticity and behaviour. BDNF expression is also very important for learning and memory, has antidepressant effects and leads to serotonergic axon growth and sprouting [Binder et al. 2004; Rybakowski 2009; Mamounas et al 1995].

Table 8: Functions of Bdnf (brain derived neurotrophic factor)

Functions of Bdnf	
• Neuronal migration • Neuronal regeneration • Phenotypic differentiation • Serotonergic axon growth • Synapse formation • Myelination	• Neuronal survival and growth • Key regulator of synaptic plasticity • Memory acquisition and consolidation • Antidepressant

3.6.1.2. BDNF signal transduction

The various functions of BDNF are mediated by two receptor systems TrkB and p75NTR. Binding of mature BDNF to TrkB leads to tyrosine phosphorylation in its cytoplasmic domain, which activates finally the MEK–MAPK, phosphatidylinositol-3-kinase (PI-3-K) and phospholipase C-g (PLC-g) signalling pathways. The signaltransduction via TrkB regulates most functions of BDNF. Binding of the proneurotrophin to p75NTR ends in activation of apoptotic signalling and NMDA receptor-dependent synaptic depression in the hippocampus [Martinowich et al. 2008; Binder et al. 2004].

3.6.1.3. BDNF Polymorphism

3.6.1.3.1. Dinucleotide repeat (GT)n (BDNF-LCPR)

An intronic microsatellite (GT)n dinucleotide repeat marker at position -1040 of the BDNF gene might be associatiated with mood disorder [Neves-Pereira et al. 2002; Strauss et al. 2004].

3.6.1.3.2. Val66Met polymorphism

A single nucleotide polymorphism (SNP) of the BDNF gene, which carries an exchange of the 66th amino acid valine into methionine (Val66Met) in the pro-domain of BDNF, leads to problems in trafficking the neurotrophin [Rybakowski et al. 2008]. The amino acid change is based on a G/A substituition at nucleotide 196- for this reason this polymorphism is also called G196A [De Luca et al. 2008]. Val66Met carriers show deficits in short-term episodic memory and show abnormal hippocampal morphology [Pezawas et al. 2004; Rybakowski et al. 2008]. The frequency of Val or Met allele shows ethnic differences [Rybakowski et al. 2008; Petryshen et al. 2009]. This polymorphism seems to affect many psychiatric disease and neurodegenerative disorders, like Parkinson's and Alzheimer's disease. There was even association between BDNF function and epilepsy. It has also impact on pain transduction

[Binder et al.2004]. Lately this polymorphism was often associated with bipolar disorder [Hashimoto et al. 2004]. The rare Met allele (=A-allele) of the Val66Met polymorphism also correlates with lower overall neurotocism scores [Sklar et al. 2009]

3.6.1.3. Association of BDNF variants with bipolar disorder

3.6.1.3.1. Antidepressants, mood stabilizers and animal studies:

Depressive states in rats show a decrement in levels of BDNF in the hippocampus [Nibuya et.al.1995; Smith et al. 1995]. Further evidence for involvement of BDNF in affective disorders is the fact that antidepressants, electroconvulsive therapy and mood stabilizers raise the BDNF expression in the brain [Duman et al. 1998; Chang et al. 2009]. Rat studies also showed that BDNF leads to growth of serotonin neurons in the brain [Mamounas 1999]. Brain-derived neurotrophic factor also has antidepressant effects by itself if admitted directly into the brain of animal models [Rybakowski 2009].

3.6.1.3.2. Serum levels of BDNF

BDNF levels are abnormally reduced in manic and depressed states of bipolar disorder. This is proven by a meta-analysis and several studies [Cunha et al. 2006; Matute et al. 2006; Lin et al. 2009; de Oliveira et al. 2009; Tramontina et al. 2009]. Kauer-Sant'Anna claimed that only late stage bipolar disorder shows decreased BDNF serum levels [Kauer-Sant'Anna et al. 2009]. Monteleone and colleagues discovered that BDNF is even decreased in euthymic phases of bipolar and unipolar disorder independent from treatment [Monteleone et al. 2008]. Thus BDNF may be a marker for bipolar disorder. BDNF levels are also decreased in transformed lymphoblasts of patients treated with Lithium [Tseng et al. 2008], although results are inconsistant whether levels are still decreased after treatment [Tramontina et al. 2009]. Beside BDNF serum levels may be a tool to differ between major depression and depressive epidodes during bipolar disorder- patients with major depression have higher serum levels than depressed bipolar patients [Fernandes et al. 2009]. Although some studies show lowered BDNF in unipolar depression too [Monteleone et al. 2008].

3.6.1.3.3. Linkage studies for chromosome 11

Early linkage studies assumed linkage of bipolar disorder to the chromosomal region 11p15. Egeland and colleagues reported the first evidence for linkage to this region, which codes for BDNF, in Old Order Amish people [Egeland et.al. 1987]. But reanalysis of a larger pedigree of Amish people revoked any linkage of bipolar disorder to chromosome 11 [Pauls et al.

1991]. Genome wide linkage studies found association of the following loci 11p15, 11p13-q13 on the 11th chromosome [Schumacher et al. 2005].

3.6.1.3.4. GWAS- Genome wide association studies

Early GWAS detected the chromosomal region 11p13–p14 as a locus of interest [McInnes et al.1996]. Le-Niculescu and colleagues discovered BDNF as one of the top candidate genes for bipolar disorder. Beside BDNF also other growth factors like Nrg1, Fgf12 and Ptn were associated with bipolar disorder in a large GWAS [Le-Niculescu et al. 2009], while other recent genome wide association studies could not find any association of SNPs with bipolar disorder [Scott et al. 2009].

3.6.1.3.5. Genetic association studies and family based genetic studies

Many studies claim significant association between BDNF gene variants, especially the Val66Met polymorphism, and bipolar disorder [Neves-Pereira et al 2002; Sklar et al. 2002; Geller et al. 2004; Lohoff et al. 2005; Green et al. 2006; Müller et al.2006; Vincze et al. 2008; Xu et al. 2009; Liu et al 2008; DeLuca et al.2008; Fan and Sklar 2008; Xu et al. 2009; Xu et al. 2010], while many others cannot find any association at all [Nakata et al. 2003; Hong et al. 2003; Skibinska 2004; Kunugi et al. 2004; Oswald et al. 2004; Kanazawa et al. 2007; Kim et al. 2008; Mick et al.2009]. Two groups could not find significant association with bipolar disorder in general, but with the subtype rapid cycling [Green et al. 2006; Müller et al.2006]. Besides an interaction between the Val66Met polymorphism and the short allele of the 5HTTLPR polymorphism of the serotonin transporter was reported in animal models of bipolar disorder, but this interaction could not be proven in humans, although both variants confer risk to bipolar disorder in this study [Vincze et al. 2008]. Nevertheless BDNF was identified as a top candidate in large genome wide association studies, so involvement of this gene should be considered in pathogenesis [Le-Niculescu et al. 2009].

3.6.1.3.6. Reasons for controversies

One reason for the contrary study results is that there is considerable diversity of BDNF polymorphisms among worldwide populations [Petryshen et al. 2009]! Most negative findings were done in Asian populations, where allele frequencies differ significantly to Europeans. Limited statistic power is another possibility for diverging results in different studies. Larger sample sizes in thousands are necessary for studies of genes with small effect. Inhomogenity of the study population might be another factor for contrary results. It may not be a good idea

to mix patients with bipolar I, bipolar II and schizoaffective disorders- as they do in some studies [Lohoff et al. 2005].

3.6.1.3.7. BDNF and subtypes of bipolar disorder or related disease

Rapid cycling

Another reason for inconsistent findings might be, that some BDNF gene polymorphisms are only linked to some subtypes of bipolar disorder like rapid cycling- Green et al. carried out a case-control study with over 3000 individuals from UK and could not find evidence for the linkage of the Val66Met polymorphism of BDNF with bipolar disorder, but they found significant association of the common Val allele with rapid cycling [Green et al. 2006]. They used the DSM-IV definition of rapid cycling, which needs 4 or more distinct episodes of major affective disorder within a 12month period such that consecutive distinct episodes are either switches of pole or are separated by at least 2 month of euthymia [Green et al. 2006; Müller et al. 2006]

Early onset bipolar disorder

Bipolar disorder is more severe and more familial with an early onset in childhood. Geller et al. reported significant association of the BDNF Val66 allele to preadolescent bipolar disorder [Geller et al. 2004]. Mick et al. tried to replicate this finding, but failed. They couldn't prove any association to this Val66 allele, which carries an amino acid substitution (valine to methionine) at codon 66 of the BDNF gene [Mick et al. 2009]. Strauss et al. showed association of another BDNF variant, the 168 bp allele of the BDNF (GT)n dinucleotide repeat, with childhood-onset mood disorder [Strauss et al. 2004].

Suicidal behaviour and BDNF

The Val/Met polymorphism of the BDNF gene might also lead to suicidal behaviour. Patients with the Met/Met phenotype of the Val66Met polymorphism of the BDNF gene have an almost 5 times higher rate of suicide attempts. Maybe one day BDNF levels will be biological indicators for risk of suicide [Kim et al. 2008]. But findings are again inconsistent. Some studies claim no association of suicidal behaviour to BDNF Val66Met polymorphism [Hong et al. 2003].

3.6.1.3.8. Summary of association studies for BDNF and bipolar disorder

Table 9: BDNF association studies for bipolar disorder

Studies, which show **association** of BDNF polymorphisms with bipolar disorder or subtypes od bipolar disorder	Association studies, which show **NO** association of BDNF polymorphisms with bipolar disorder
• **Sklar et al. 2002** Val allele of the Val66Met polymorphism of BDNF is associated with BP in 470 parent-proband trios. • **Neves-Pereira et al. 2002** Association of the (GT)n-repeat and the G-allele of theVal66Met polymorphism with bipolar disorder in a sample of 283 caucasian nuclear families. • **Geller et al. 2004** 53 complete, independent trios (bipolar child and parents). Association of the Val allele of Val66Met polymorphism with prepubertal bipolar disorder. • **Lohoff et al. 2005** This study (621 Caucasian bipolar patients and 998 controls) showed association of the Val allele (of the val66met polymorphism) to bipolar disorder. • **Green et al. 2006** British case control sample of 3062 participants. Val allele is associated with rapid cycling. • **Müller et al.2006:** family-association study with 312 nuclear families showed association of BDNF variants with patients with rapid cycling. • **Vincze et al. 2008** association with the val66met polymorphism in a study of 447 Caucasian BD patients and 370 controls. • **Liu et al 2008** 1749 Caucasian probands in 250 multiplex bipolar families. Many SNPs of BDNF are associated • **DeLuca et al.2008** Family-based association study in 312 BD Caucasian nuclear families showed association of BDNF Val66 to BD.	• **Nakata et al. 2003:** matched case-control association design in a Japanese population (with 190 controls and 132 bipolar patients) shows no association with the two polymorphisms (21360C ->T and 196G-> A) and bipolar disorder. • **Hong et al. 2003:** Chinese sample, 192 patients (84 MD and 108 BPD) and 293 healthy controls. No association of Val66Met with bipolar disorder. • **Skibinska 2004** Val66Met of BDNF gene was studied in 336 schizophrenics, 352 patients with bipolar affective disorder and 375 healthy controls. • **Kunugi et al. 2004:** A multi-center study of 519 Japanese patients with bipolar disorder and 588 controls claims that the Val66Met polymorphism is unrelated to bipolar disorder. • **Oswald et al. 2004** Association study with 112 bipolar patients and 163 controls. No association of Val66Met polymorphism and bipolar disorder. • **Kanazawa et al. 2007** meta-analysis of 11 case-control studies (with 3143 patients with bipolar disorder and 6347 controls) showed no association of Val66Met polymorphism and bipolar disorder. • **Kim et al. 2008:** Study with 169 bipolar Korean patients and 251 controls. No association of Val66Met polymorphism with bipolar disorder itself, but with suicidal behaviour in bipolar disorder. • **Mick et al.2009:** Family-based association study of 173 bipolar offspring triads. They could not find association of the Val66 allele in children.

• **Fan and Sklar 2008:** Meta-analysis of all original published association studies up to May 2007. 14studies consisting of 4248cases and 7080controls and 858 nuclear families show modest, but significant evidence for association of Val66Met polymorphism with bipolar disorder. • **Xu et al. 2009** association with Val66Met polymorphism in Han Chinese. • **Xu et al. 2010** Chinese ssociation study of 498 bipolar cases and 501 controls. Association of the Val66Met polymorphism with bipolar disorder.	

3.6.2 Neuregulin1

Neuregulin 1, which is encoded on 8p12, has been identified as a susceptibility factor in schizophrenia and bipolar disorder [Green et al. 2005; Georgieva et al. 2008]. Neuregulin1 is involved in neuronal migration and gliogenesis during brain development. The binding of Neuregulin1 to its receptor erbB is also important for oligodendrocyte development. A loss of NRG1-erbB signalling leads to reduced myelin thickness and slower conduction velocity in CNS axons [Roy et al. 2007]. Nrg1 was identified as potential candidate in several large genome wide association studies recently [Segurado et al. 2003; Le-Niculescu et al. 2009; Sklar et al. 2008]. A large family based association study including 515 bipolar participants found association between several SNPs of Nrg1 and bipolar disorder, especially with psychotic manic-depressive-disease [Goes et al. 2009]. Also other studies prove evidence of association [Green et al. 2005; Perlis et al. 2008]. Green and colleagues prove evidence in a study comprising 529 bipolar and 573 schizophrenic participants, as well as 1011 controls. In contrast there were also negative results regarding bipolar disorder and this gene [Voineskos et al. 2009]. Nevertheless there is good evidence for association between Nrg1 and bipolar disorder, as well as schizophrenia.

3.6.3. NCAM1

NCAM1 (Neural cell adhesion molecule 1) is encoded on locus 11q23.1 and is involved in neuronal growth and maybe in the pathogenesis of bipolar disorder [Arai et al. 2004; Atz et al. 2007]. Already in the 1990s increased levels of neural adhesion molecules were found in the CSF of patients with bipolar disorder [Poltorak et al. 1996].

3.6.4. RELN

The gene RELN codes for a protein, which is important for neurodevelopment. In patient with schizophrenia and bipolar disorder reelin is decreased. Epigenetic changes seem to down regulate reelin gene expression. Hypermethylation in the promoter region of RELN leads to reduced binding of transcription factors and therefore silencing of the gene [Goes et al. 2008].

3.7. Genes of the Lithium signal transduction pathways

3.7.1. DGKH

Diacylglycerol kinase eta (DGKH), a key protein in the lithium-sensitive phosphatidyl inositol pathway, is encoded on 13q14.11. A genome wide association study by Baum and colleagues identified this gene as top candidate for bipolar disorder [Baum et al. 2008]. Also two other genome wide studies showed association between DGKH and bipolar disorder. Since this gene product is involved in lithium pathways it may be likely, that this gene influences susceptibility for manic depressive disease [Baum et al. 2007; Ollila et al. 2009].

3.8. Genes coding for ion channels and axonguidance

3.8.1. ANK3

Genes coding for voltage gated ion channels are hot spots for bipolar disorder research, because they were identified with high significance in many genome wide association studies recently [Askland et al. 2009]. Ferreira and colleagues found in their 4387 bipolar cases and 6209 controls comprising whole genome scan a region of very strong association with the ANK3 gene (rs10994336, $P = 9.1 \times 10\text{-}9$) very recently. The gene ANK3 codes for Ankyrin G an adaptor protein, which regulates the assembly of voltage-gated sodium channels at axon initial segments [Ferreira et al. 2008]. In addition a meta-analysis of genome scans found significant linkage to chromosomal region 10q11.21-22.1, which overlaps with the location of the ANK3 gene on 10q21 [Segurado et al. 2003].

3.8.2. CACNA1C

This top candidate gene codes for the alpha1C subunit of the L-type voltage-gated calcium channel. A polymorphism of this gene showed very strong association with bipolar affective disorder in a whole genome scan by Sklar, which included 1461 bipolar participants and 2008 controls, as well as in a whole genome scan by Ferreira, which included 4387 cases and 6209 controls [Sklar et al. 2008; Ferreira et al. 2008]. This proves that ion channelopathies play an

important role in the pathogenesis of bipolar disorder [Ferreira et al. 2008; Askland et al. 2009]. Beside it is also involved in schizophrenia and major depression [Casamassima et al. 2010; Green et al. 2009; Moskvina et al. 2009;] CACNA1C also influences verbal fluency [Krug et al. 2010].

3.8.3. NTNG1 and NTNG2

NTNG1 and NTNG2 are vertebrate specific axon guidance molecules and their expression is reduced in bipolar disorder and schizophrenia. NTNG plays a role in synaptic formation and maintenance [Eastwood et al. 2008].

3.8.4. KCNC2

KCNC2 encodes the Shaw-related voltage-gated potassium channel [The Wellcome trust consortium 2007].

3.8.5. P2RX7/4

P2RX7 is mapped to 12q24.31 and codes for a purinergic ATP-binding calcium channel receptor, which is expressed in the brain. It is involved in 2-arachidonoylglycerol production by microglial cells. Beside it influences several cells, like osteoclasts and macrophages [Kapoor et al. 2009]. Significant association exists between the promising Gln460Arg polymorphism of the P2RX7 gene (rs2230912, P2RX7-E13A) and bipolar disorder. This SNP, which leads to a change of the amino acid glutamine to arginine at position 460, is also associated with unipolar disorder [Lucae et al. 2006; Barden et al. 2006; McQuillin et al. 2009; Hejjas et al. 2009]. Other groups tried to replicate this finding recently, but failed [Green et al. 2009; Grigoroiu-Serbanescu et al. 2009]. Beside also the microsatellite marker NBG6, was related to bipolar disorder [Shink et al. 2005; Barden et al. 2006; McQuillin et al. 2009]. This gene is a promising candidate since its coding region on chromosome 12q24, which lies closeby the chromosomal region of Darier's disease (an autosomal dominant skin disease, which cosegregates with affective disorders) has been implicated in several linkage studies of bipolar disorder [Dawson et al. 1995; Ewald et al.1998; Morissette et al.1999; Degn et al. 2001; Maziade et al. 2001; Ewald et al. 2002; Ekholm et al.2003; Green et al. 2005; Shink et al. 2005; Cassidy et al. 2007] and unipolar mood disorder [Abkevich et al., 2003; Zubenko et al. 2003; McGuffin et al. 2005; Lucae et al. 2006].

3.8.6. ATP2A2

ATP2A2, a gene encoding SERCA2-a sarcoplasmic/endoplasmic reticulum calcium pump that plays a role in intracellular calcium signalling, is coded in the susceptibility region for Darier's disease 12q23-q24.1 [Craddock et al. 1993]. Darier's disease is an autosomal dominant skin disease (keratosis follicularis), which cosegregates with affective disorders. This made this region a hot spot for bipolar disorder research. Some groups showed no evidence for the involvement of ATP2A2 in producing susceptibility to bipolar disorder [Jacobsen et al. 2001; Ruiz-Perez 1999].

3.8.7. SLC24A3

SLC24A3 codes for a potassium dependant sodium/calcium exchanger that plays a critical role in neuronal calcium homeostasis. It was identified in large genome wide linkage study for bipolar disorder with comorbid migraine [Oedegaard et al. 2009].

3.8.8. SLC39A3

SLC39A3 (ZIP3) codes for a channel, which is responsible for zink reuptake. This gene was associated with bipolar disorder in several large genome wide association studies and might be worth for further investigation [Baum et al. 2009; Olila et al. 2009].

3.9. HPA axis, cortisol and stress

Chronic distress can lead to mood disorders and burnout. Nevertheless some people can cope better with the same amount of stress than others. Bipolar patients have disturbed cortisol release after stressful events [Watson et al. 2004]. Depressive reaction to stress may be due to special genetic constitution. Certain genotypes lead to enhanced stress response. The ss genotype (patients carrying a pair of short alleles) of the 5-HTTLPR polymorphism in the serotonin transporter promoter region leads for example to enhanced stress reactivity. A very recent study tested this 5-HTTLPR variant in relation to stress response in newborns. They testet the relation between genotype and cortisol release (a measurement for stress) after a foot prick, which is an element in a routine check, but still associated with stress for the newborn. SS genotype carriers had much higher cortisol levels than other genotypes. Thus s allele carriers show much higher stress response of the hypothalamus-pituitary-adrenal axis (HPA) than l allele carriers [Müller et al. 2009]. Since chronic stress and stressful events often influence pathogenesis of bipolar disorder, genes involved in the hypothalamic-pituitary-

adrenal axis (HPA) are possible suceptibility genes for manic depressive disease. The HPA is strongly associated with stress response and modulation. The hypothalamus releases CHR, which binds to CRH receptors in the anterior pituitary gland. In consequence adrenocorticotrophic hormone (ACTH) is released, which leads to release of cortisol from the adrenal cortex [Gillespie et al. 2009]. This can be followed by anxiety-related behavior and influences arousal, attention, executive functions, emotions and learning and memory consolidation related to these emotions. So the CRHR1 gene (corticotropinreleasing hormone receptor 1 gene) encoded on 17q12-q22 might be candidate gene for bipolar disorder, although not extensively investigated yet. CRHR1 is a G protein-coupled receptor localized in frontal cortical areas, forebrain, brainstem, amygdala, cerebellum, and the anterior pituitary [Refojo et al. 2009]. CRH gene encoded on 8q13 could be another susceptibility gene, but the rare genetic studies did not show evidence [Alda et al. 2000]. Also linkage studies showed negative results [Stratakis et al. 1997]. Nevertheless some genome wide linkage and association studies showed association between the area of 8q13 and bipolar disorder [Liu et al. 2003; Marcheco-Teruel et al. 2006]. Although those genes in HPA might be candidate genes for bipolar disorder no evidence of association is possible, because of great lack of performed studies. But it may be possible that the HPA system genes are only influenced by other susceptibility genes, but are not the underlying cause of pathogenesis. Nevertheless the HPA system and stress response is for sure disturbed in bipolar disorder [Watson et al. 2004].

3.10. Genes of the dopaminergic neurotransmitter system

The dopamine system has received increased attention in bipolar disorder research recently. Dopamine was suggested to be involved in pathogenesis of bipolar disorder, because dopamine agonists and precursor can induce mania in high dose, whereas dopamine antagonists have antimanic effects and are used for treatment in manic episodes. Those promanic effects of high-dosed dopamine precursors can be seen in treated patients with Parkinson's disease. Beside there have been case reports of Parkinson patients with switching mood. This may implicate a role of dopamine in manic depressive disease. Dopaminergic hyperactivity is suggested to produce mania, while hypoactivity of the dopaminergic system may lead to depression [Murphy et al. 1971; Cannas et al. 2002].

3.10.1. DAT1 (dopamine transporter)

The dopamine transporter is encoded by the gene SLC6A3 (=DAT1) on 5p15, which was linked to bipolar disorder by linkage studies [Waldman et al. 1997]. Recently there have been

identified a lot of new SNPs in the DAT1 gene and many SNPs and haplotypes are associated with bipolar disorder [Grünhage et al. 2000]. One of the well studied -67A/T DAT1 SNP was studied in 136 Iranian bipolar patients and 163 controls. The T allele was associated with bipolar disorder [Keikhaee et al. 2005; Ohadi et al. 2007]. Nevertheless many studies denied an association between DAT1 polymorphisms and bipolar disorder [Souery et al. 1996; Bocchetta et al. 1999]. Another 40bp VNTR in the 3'UTR of DAT1 was also investigated by some studies, but with negative results [Souery et al. 1996; Bocchetta et al. 1999; Kirov et al. 1999; Heiden et al. 2000; Georgieva et al. 2002].

Table 10: Dopamine transporter gene (DAT1) and bipolar disorder

DAT1 polymorphism	**Supporting study**	**Not supporting study**
40-bp nucleotide repeat polymorphism (VNTR), located in 3'UTR (= 3' untranslated region)		**-Bocchetta et al. 1999** Family-based association study from Sardinia with 53 bipolar probands and parents. **-Souery et al. 1996** 69 bipolar patients and 69 controls from Belgium. **-Kirov et al. 1999** British family association study with 122 bipolar offspring trios. -**Heiden et al. 2000** 102 Austrian bipolar patients and 79 healthy controls. **-Georgieva et al. 2002** Family based association study from Bulgaria with schizophrenia (178 trios), bipolar disorder I (77 trios) and schizo affective disorder (29 trios).
-67A/T polymorphism	**-Keikhaee et al. 2005** 136 Iranian patients and 163 controls **-Ohadi et al. 2007** 240 Iranian cases and 213 controls. Association of T-allele with male bipolar patients, but not with females	

3.10.2. DRD1 (dopamine receptor)

Dopamine receptors belong to the superfamily of the G-protein-coupled-receptors and can be divided in two major parts, the D1 like receptors,comprising of D1 and D5, and the D2 like

receptors,comprising of D2, D3 and D4 receptors [Emilien et al. 1999]. DRD1 codes for the dopamine 1 receptor and maps to the region 5q35.1. Linkage studies about this region and bipolar affective disorder showed controversial results. While some showed positive results [Garner et al. 2001; Ni et al. 2002; Shink et al. 2002; Sklar et al. 2004], others rejected any linkage [De Bruyn et al. 1994]. A study comprising of 315 bipolar patients, 40 of them with comorbid alcoholism, and 350 controls investigated the relation between the dopamine receptor genes (DRD1-4) and bipolar disorder with and without comorbid alcoholism. Neither bipolar disorder alone nor with comorbid alcoholism was associated with DRD genes [Szczepankiewicz et al. 2007]. A Canadian and Sardinian haplotype analysis showed only trends of association [Del Zompo et al. 2007]. A -48 A/G polymorphism of DRD1, which leads to an A to G exchange at position -48, was associated with bipolar disorder in Sardinian, as well as Polish population [Severino et al. 2005; Dmitrzak-Weglarz et al. 2006]. The -48 A/G polymorphism is also associated with outcome of prophylactic lithium treatment. The G/G genotype leads to poorer response [Rybakowski et al. 2009].

Table 11: DRD1 gene polymorphisms and their relation with bipolar disorder

Gene polymorphism	**Supporting study**	**Not supporting study**
-48 A/G polymorphism	**-Severino et al. 2005** 107bipolar I patientsand 129 healthy control subjects of ex-clusively Sardinian descent. **-Dmitrzak-Weglarz et al 2006** 407 patients with schizophrenia or 380 bipolar affective disorder and 399 healthy controls.	**-Del Zompo et al. 2007** Sardinian sample:170 bipolar patients and 129 controls. Canadian sample: 229 trios **-Szczepankiewicz et al. 2007** 317 Polish patients with bipolar disorder (42 patients with comorbid alcohol abuse) and 350 controls.
-800T/C polymorphism		**-Del Zompo et al. 2007** Sardinian sample:170 bipolar patients and 129 controls. Canadian sample: 229 trios
1403T/C polymorphism		**-Del Zompo et al. 2007** Sardinian sample:170 bipolar patients and 129 controls. Canadian sample: 229 trios

3.10.3. DRD2 (dopamine receptor)

DRD2 maps to 11q23, a region identified in some linkage studies for schizophrenia and bipolar disorder [Craddock et al. 1999; Serretti et al.1b 2000; Gurling et al. 2001]. Significant

positive association between bipolar disorder and allele 5 of the microsatellite polymorphism DRD2 was detected in a large multi-center study [Massat et al. 2002]. Also smaller studies detected association with (CA)n repeat in first intron of DRD2 [Pérez de Castro et al. 1995]. A Chinese study (118 bipolar Han Chinese and 196 controls and for replication 157 English and 143 controls) found significant association with the promoter variant and the taq1A polymorphism of DRD2 in Chinese population, but not in English population [Li et al.1999]. Further negative results were also shown by other studies [Sasaki et al. 1996; Souery et al. 1996; Bocchetta et al. 1999; Kirov et al. 1999; Leszczyńska-Rodziewicz et al. 2005; Szczepankiewicz et al. 2007]. The insertion/deletion variant (-141C Ins/Del) in the 5' regulatory region of the dopamine D2 receptor gene is not associated in Caucasians [Stöber et al.1998]. The Ser311Cys polymorphism of DRD2 was significantly associated with mood incongruent psychotic disorder in Japanese and with the symptoms of delusion and disorganisation in Italians [Arinami et al. 1996; Serretti et al. 2000]. But this Ser311Cys SNP was not associated in Japanese and Caucasian studies [Manki et al. 1996; Sasaki et al. 1996; Heiden et al. 2000].

Table 12: DRD2 gene variants and association with bipolar disorder

Gene polymorphism of DRD2	**Supporting study**	**Not supporting study**
TaqA1 polymorphism	- **Li et al. 1999:** case-control analysis in 118 bipolar Han Chinese and 196 controls.	- **Li et al. 1999:** case-control replication study 157 bipola English cases and 143 controls.
Promoter variant	- **Li et al. 1999:** case-control analysis in 118 bipolar Han Chinese and 196 controls.	- **Li et al. 1999:** case-control replication study 157 bipolar English cases and 143 controls.
Microsatellite polymorphism (allele 5)	-**Massat et al. 2002** Multi-center study of 358 bipolar cases and 358 controls.	**-Souery et al. 1996** We studied 69 bipolar patients and 69 matched controls.
(CA)n repeat in first intron	**-Perez de Castro et al. 1995:** Spanish 51bipolar cases and 46 controls.	
-141C Ins/Del polymorphism		**-Stöber et al. 1998:** A total of 620 unrelated German individuals (260schizophrenics, 70bipolars and 290controls) **-Kirov et al. 1999** British family association study with 122 bipolar offspring trios. **-Leszczyńska-Rodziewicz et al. 2005**

		339 Polish patients with bipolar disorder (143 males, 196 females) and 366 controls. -**Szczepankiewicz et al. 2007:** 317 Polish patients with bipolar disorder (42 patients with comorbid alcohol abuse) and 350 controls.
Ser311Cys polymorphism	**-Arinami et al.1996:** Japanese Case-control study in 291 schizophrenics, 78 patients with affective disorders, and 579 controls. Significant association with mood incongruent psychotic affective disorder ($P < 0.0001$) **-Serretti et a. 2000** 1182 inpatients (480 bipolar disorders, 269 major depressive disorder, 366 schizophrenias, 44 delusional disorder, 23 psychotic disorder not otherwise specified) and 267 healthy controls. Significant association with delusion and disorganisation!	**-Manki et al. 1996** 101 Japanes patients (52 bipolar and 49 unipolar) and 100 controls. **-Sasaki et al.1996** 273 Caucasian patients with schizophrenia, 621 with delusional disorder, 63 with bipolar I affective disorder and 255 controls. **-Heiden et al. 2000** 102 Austrian bipolar patients and 79 healthy controls.
TG dinucleotide polymorphism in first intron		**-Bocchetta et al. 1999** Family-based association study from Sardinia with 53 bipolar probands and parents.

3.10.4. DRD3

The D3 receptor is of special interest, because it is especially expressed in the limbic area. It is encoded on 3q13.3, an area suggested to be linked to schizophrenia and bipolar disorder [Serretti et al. 2000; Maziade et al. 2001]. BalI RFLP, a DRD3 polymorphism leading to a serine-to-glycine substitution in the first exon, is not asssociated with bipolar disorder. This claims at least an analysis of 454 bipolar patients and a meta-analysis of previous association studies by Elvidge and colleagues [Elvidge et al. 2001]. Also other association studies pointed out, that the DRD3 Ser9Gly polymorphism is not associated with psychosis and bipolar disorder [Shaikh et al. 1993; Manki et al. 1996; Souery et al. 1996; Piccardi et al. 1997; Kirov et al. 1999; Heiden et al. 2000; Elvidge et al. 2001; Leszczyńska-Rodziewicz et al. 2005; Szczepankiewicz et al. 2007; Krelling et al. 2008].

Table 13: DRD3 and bipolar disorder

Polymorphism of DRD3	Supporting studies	Not supporting studies
Ser9Gly polymorphism (=BalI polymorphism, Allele 1 and 2)		**-Shaikh et al. 1993** 75 bipolar patients and controls. **-Manki et al. 1996** 101 Japanes patients (52 bipolar and 49 unipolar) and 100 controls. **-Souery et al. 1996** We studied 69 bipolar patients and 69 controls **-Piccardi et al. 1997** Family based study of 44 bipolar probands from Sardinia with both parents. **-Kirov et al. 1999** British family association study with 122 bipolar offspring trios. **-Heiden et al. 2000** 102 Austrian bipolar patients and 79 healthy controls. **-Elvidge et al. 2001** Large English bipolar case control sample (n= 454) showed negative results. Additional meta-analysis of 980 bipolar patients and 1100 controls showed no evidence of association between the Ser9Gly polymorphism of DRD3 and bipolar disorder! **-Leszczyńska-Rodziewicz et al. 2005** 339 Polish patients with bipolar disorder (143 males, 196 females) and 366 controls. -**Szczepankiewicz et al. 2007:** 317 Polish patients with bipolar disorder (42 patients with comorbid alcohol abuse) and 350 controls. **-Krelling et al. 2008** 105 Brazilian women (58 schizophrenic patients and 47 bipolar patients) and 62 gender-matched controls. No association with functional psychosis.

3.10.5. DRD4

DRD4 is located on 11p15.5 and is a highly polymorphic gene. It contains a functional variable number tandem repeat (VNTR) polymorphism in the third exon, which consists of 2–10 imperfect tandem repeats of 48 bp, each repeat encoding for 16 amino acids [Van Tol et al. 1992]. The different length polymorphisms reflect different response to clozapine [Van Tol et al. 1991]. This VNTR polymorphism of DRD4 was significantly associated with bipolar disorder [Manki et al. 1996; Muglia et al. 2002], while many other studies could not show this association [Perez de Castro et al. 1994; Oruc 1b et al. 1997; Bocchetta et al. 1999; Li et al. 1999; 1c Serretti et al. 1999; Serretti et al. 2002; Serretti et al. 2004]. Also a SNP, which leads to an C to T exchange at position 521, might not be associated, at least in Polish population [Leszczyńska-Rodziewicz et al. 2005; Szczepankiewicz et al. 2007]. DRD4 was also investigated for delusional symptoms in major psychosis in 2011 inpatients with positive results. The DRD4 exon 3 VNTR polymorphism was significantly associated with delusions [Serretti et al. 1b 1998; Serretti et al. 1d 1999; Serretti et al. 2001]. Also a Mexican association investigation showed evidence of association between the exon 3 and exon1 polymorphism of DRD4 and psychosis [Aguirre et al. 2007]. The long allele of the exon 3 polymorphism was also associated with certain personality traits like low harm avoidance [Serretti et al. 2006]. Altogether this is a promising candidate gene for mood disorders, because a meta-analysis (917 patients with bipolar and unipolar patients and 1164 controls) showed significant association between the 48-base-pair- repeat polymorphism and mood disorders in general. Although the association between bipolar disorder and the DRD4.2 allele dropped to insigificance after correction for multiple testing. Nevertheless association between unipolar depression, as well as the combined group (unipolar and bipolar patients together), stayed significant even after Bonferroni correction [Lopez et al. 2005].

Table 14: DRD4 polymorphisms and their association with bipolar disorder

Polymorphism of DRD4	**Supportive evidence for association with bipolar disorder**	**No evidence of association with bipolar disorder**
48-bp-repeat polymorphism in the third exon of DRD4 (VNTR polymorphism)	**-Manki et al. 1996** 101 Japanese patients (52 bipolar and 49 unipolar) and 100 controls. **-Serretti et al. 1d 1999** 461 Italian inpatients affected by major psychoses (criterias: mania, depression, delusion and disorg-anization) were genotyped for DRD4 variants. Exon3 long alleles	**-Perez de Castro et al. 1994** 64 Spanish patients with bipolar affective disorder (25 males and 39 females) and 46controls. **-Oruc et al. 1997** 83Croatian bipolars or unipolars and 71 healthy controls. **-Bocchetta et al. 1999**

	associated with high delusional score! **-Serretti et al. 2001** A total of 2011 Italian inpatients! (811 bipolars, 635depressed, 419 schizophrenics, 104 delusionals and 42 psychotics not otherwise specified and 601healthy controls). Long allele is associated with delusion! **-Muglia et al. 2002** 145 Canadian nuclear families (bipolar patients and their biological parents). **-Lopez et al. 2005** Meta-analysis comprising of 917 patients with unipolar or bipolar affective disorder and 1164 controls from 12 samples. Significant association even after correction for multiple testing between mood disorders (unipolars + bipolars) and DRD4.2 allele, as well as major depression alone. **-Aguirre et al. 2007** 149 unrelated Mexican subjects different kinds of psychosis and 169 individuals free of psychiatric illnesses.	Family-based association study from Sardinia with 53 bipolar probands and parents. **-Li et al. 1999** 118 Han Chinese bipolar patients and 196 controls, and replication analysis in 157 English cases and 143 controls. **-Serretti et al. 1c 1999** Total of 651 Italian inpatients (229 schizophrenis, 86delusionals, 210 bipolars and 126 unipolars and 471 controls). Association between exon3 variants and bipolar disorder, but not significant after multiple testing correction. **-Serretti et al. 2002** Italian family-based association study of 134 nuclear families (103bipolar patients and 58patients with major depressive disorder).
12 bp-VNTR (at exon 1)		**-Serretti et al. 1c 1999** Total of 651 Italian inpatients (229 schizophrenis, 86delusionals, 210 bipolars and 126 unipolars and 471 controls) **-Aguirre et al. 2007** 149 unrelated Mexican subjects different kinds of psychosis and 169 individuals free of psychiatric illnesses.
-521 C/T SNP		**-Leszczyńska-Rodziewicz et al. 2005** 339 Polish patients with bipolar disorder (143 males, 196 females) and 366 controls. -**Szczepankiewicz et al. 2007:** 317 Polish patients with bipolar disorder (42 patients with comorbid alcohol abuse) and 350 controls.

3.10.6. DRD5

DRD5 is encoded on 4p16.1, a region implicated in bipolar disorder by linkage studies recently [Asherson et al. 1998; Ewald et al. 1998]. Microsatellite markers close to DRD5 show association with schizophrenia, but not with manic depressive disorder [Muir et al. 2001]. Concording with this an association by Kirov and colleagues did not find evidence for association. Further studies are necessary since investigation of this gene has been rare [Kirov et al. 1999].

3.11. Genes of the noradrenergic neurotransmitter system

3.11.1. Norepinephrine transporter (NET= SLC6A2)

The silent mutation 1287 A/G in exon 9 of the norepinephrine transporter gene is neither associated with bipolar disorder, nor with schizophrenia [Leszczyńska-Rodziewicz et al. 2002]. Stöber and colleagues identified 5 missense substitutions Val69Ile, Thr99Ile, Val245Ile, Val449Ile and Gly478Ser, but association in case control studies for bipolar disorder was lacking [Stöber et al. 1996]. Only F528C NET (norepinephrine transporter) might be associated with depressive disorder. NET mediates rapid re-uptake of released NE into noradrenergic neurons and is one of the main target of antidepressants, which involve NA reuptake inhibition e.g. reboxetin. The F528C polymorphism leads to increased transporter expression and enhanced NA reuptake [Haenisch et al. 2009].

3.12. Genes of the GABAergic neurotransmitter system

Gamma-Aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters in the CNS. GABAergic receptors consist of two main types GABA-A, a ligand-gated inhibitory chloride channel, and GABA-B receptors. GABA-A receptors have 5subunits and mediate fast synaptic inhibition in the human brain. GABA binds to the beta subunit, while benzodiazepines bind to the alpha subunit, which inhances GABA binding. Some genes have been suggested in genome wide approaches, but studies are lacking. Here I review the rare results.

3.12.1. GABRBI

GABRBI, which codes for a ligand gated ion channel of the GABA system, is encoded on 4p12. The polymorphism rs7680321 was associated with bipolar disorder in the GWAS of the Wellcome Trust Consortium 2007. This may implicate a role of the GABA system in mood disorders [Wellcome Trust Consortium 2007].

3.12.2. GABRB2

GABRB2 on 5q34 codes for beta2-subunit of the gamma-aminobutyric acid type A receptor. Linkage studies show inconsistant results [Crowe et al. 1999; Ambrosio et al. 2005]. Also alternative splicing at exon -10 and the resulting different isoforms also influence risk for psychotic disorders [Zhao et al. 2009].

3.12.3. GABRB3

GABRB3 is coded on Xq28, which was suggested to be linked with bipolar disorder in many genome wide approaches and smaller linkage studies [Baron et al. 1994; Wigg et al. 2009]. A European multicenter study with 185 bipolar participants and 370 controls showed association between the dinucleotide polymorphism and female bipolar patients [Massat et al. 1b 2002]. The CA repeat polymorphism was not associated with bipolar disorder in a small Greek sample [Papadimitriou et al. 2001].

3.12.4. GABRA5

GABRB5 on 15q11-q13 codes for the alpha5 subunit of the GABA A receptor and might influence pathogenesis of bipolar disorder. Polymorphism IVS1-21G>A and some haplotypes are associated with manic depressive disease, at least in Japanese population [Otani et al. 2005]. The 282-bp allele of a dinucleotide (CA) repeat was significantly associated with dominance of manic episodes [Papadimitriou et al. 1998].

3.13. Genes of the glutamatergic neurotransmitter system

3.13.1. GRIN genes

GRIN1, on chromosome 9q34.3, codes for the zeta-1 subunit of NMDA receptors. Mundo and colleagues showed association between GRIN1 and bipolar disorder in a family association study comprising 288 patients with their parents [Mundo et al. 2003]. GRIN2B is located on 12p12 and was associated in some linkage and association studies for bipolar disorder [Fallin et al. 2005; Martucci et al. 2006; Avramopoulos et al 2007; Lorenzi et al. 2009; Lorenzi et al. 2010]. Nevertheless a very recent study comprising of 419 bipolar patients and 487 controls could not show association [Szczepankiewicz et al. 2009]. GRIN2C is encoded on 17q25 and GRIN2D on 19q13.1-qter was only associated in one family-based association study comprising of 101 trios and 203 quads from bipolar Caucasian families. Because of a lack of further studies association has to be seen with caution [Shi et al. 2008].

3.13.2. GRIA1

GRIA1 located on 5q31.1 codes for the ionotropic glutamate receptor AMPA1, which has been associated with cognitive functions like memories. This locus was significantly linked to bipolar disorder in a Latin-American linkage study [Herzberg et al. 2006]. GRIA1 was also associated with manic depressive disorder in Shi's family based association study [Shi et al. 2008]. Beside GRIA1 was associated with psychotic bipolar disorder recently [Kerner et al. 2009].

3.13.3. GRM3

GRM3, a metabotropic glutamate receptor gene, located on 7q21.1-q21.2, was associated with bipolar disorder in a Jewish study by Fallin, while Marti and colleagues could not find any association in a German sample [Marti et al. 2002; Fallin et al. 2005]. One genome wide linkage approaches also showed linkage to 7q21, nevertheless replication studies are absolutely necessary, since studies are lacking [Minnis et al. 2003].

3.13.4. GRM4

GRM4 on 6p21.3 codes for the metabotropic glutamate receptor 7. Fallin and colleagues found association between GRM4 and bipolar disorder, but further association studies are lacking [Fallin et al. 2005].

3.13.5. GRM7

Glutamate neurotransmission was implicated to play a role in bipolar disorder by the GWAS of the Wellcome Trust Consortium 2007. Polymorphism rs1485171 in the GRM7 (metabotropic glutamate receptor 7) gene encoded on 3p26.1-p25.1 showed high association with this disease in a large GWAS. Nevertheless evidence of association is not given because of lacking replication studies [Wellcome Trust Consortium 2007].

3.13.6. GRIK genes

GRIK4 on 11q22.3 codes for a glutamate receptor KA1, which was associated with bipolar disorder recently [Pickard et al. 2008]. The glutamate receptor KA2 is coded on the GRIK5 gene on 19q13.2 and was associated with bipolar disorder in a large study about substance-abuse, anxiety, eating, psychotic and mood disorders comprising 3214 samples. Further studies are absolutely necessary, because of a lack of them [Gratacos et al. 2009].

3.14. Copy number variations (CNVs)

Structural variations in DNA from one kilobase (kb) to several megabases (Mb), which are called copy number variations, are responsible for the bigger part of interindividual heterogenity of the genome and are still underestimated. CNVs are quantitative variations in the genome, including tandem arrays of repeats as well as submicroscopic deletions and duplications. They are created by retrotransposition, which duplicates and inserts some coding and non-coding DNA segments randomly around the genome. Some CNVs interrupt genes and can thus disturb their functions, but the bigger part do not affect physiology at all [Redon et al. 2006; Lachman et al. 2008; Conrad et al. 2009]. Single nucleotide polymorphisms often reside next to copy number variations and may be a hint for finding new SNPs responsible for bipolar disorder. CNVs can be responsible for pathogenesis by themselves of course, but are not overinvestigated yet. Nevertheless even top candidates of large genome wide association studies (DGKH, SORCS2, DFNB31, A2BP1, and NXN) are affected by polymorphic copy number variations [Baum et al. 2008; Lachman et al. 2008]. DGKH, DFNB31, A2BP1, and NXN influence the Wnt/GSK3I3 signaling pathway, a lithium inhibited pathway. GSK3β itself is affected by several copy gain and copy loss variants [Lachman et al. 2007]. A complex CNV at 15q13–14 containing a polymorphic inversion involving CHRNA7 and its fusion variant CHRFAM7A was also associated with bipolar disorder [Flomen et al. 2008]. Another study by Wilson detected copy number variations in genes involved in glutamate signaling [Wilson et al. 2006]. A recent study by Zhang and colleagues examined singleton CNVs in bipolar disorder, copy number variations occurring once in a dataset, with the following gene discoveries: GRM7, DLG2, SOX5, LARGE [Zhang et al. 2009]. There are also many disease based on deletions, insertions or transversions in genes or chromosomal areas (CNVs), which cosegretate with bipolar disorder. Those disorders can be a possibility to find new susceptibility genes for mood disorders. The 3-megabase microdeletion on 22q11 in VCFS (velocardio facial syndrome), a congenital disorder associated with heart disease, cleft palate and very often schizophrenic or bipolar symptoms, helped to identify the COMT gene predisposing for mood disorder and schizophrenia [Craddock et al. 2009]. A 1:11(q42.1; q14.3) translocation, which disrupts the DISC1 gene, is another major cytogenetic mutation that influences bipolar disorder, as well as schizophrenia [Murphy et al. 1999; Millar et al. 2000; Blackwood et al. 2001; Kas et al. 2009].

Table 15: Candidate genes for bipolar disorder affected by copy number variation

Susceptibility gene for bipolar disorder affected by CNVs (copy number variation)	**Gene function**	**Supportive evidence**
COMT	Catechol-O-Methyl-Transferase	-Lachman et al. 2008
ARVCF	ARVCF (armadillo repeat gene deletes in velocardiofacial syndrome) codes for a member of catenin family which play an important role in the formation of adherens junction complexes	-Lachman et al. 2008
PRODH	PRODH (proline dehydro-genase 1 gene) codes for a mitochondrial proline de-hydrogenase that catalyzes the first step in proline degradation. The gene is located on 22q11.21	-Lachman et al. 2008
DISC1	The gene product of DISC1 on 1q42.1 is involved in neurite outgrowth and cortical development through its interaction with other proteins. It was discovered by a translocation within this gene, which cosegregate with psychiatric disease in a Scottish family.	-Blackwood et al. 2001 -Palo et al. 2007 -Lachman et al. 2008 -Schosser et al. 2009
PDE4B	Disc1 binding proteins	-Lachman et al. 2008
FEZ1		-Lachman et al. 2008
NDEL1		-Lachman et al. 2008
MFAP1		-Lachman et al. 2008
ATF5		-Lachman et al. 2008
DGKH	Involved in Lithium pathway!	-Baum et al. 2008
SORCS2		-Baum et al. 2008
DFNB31		-Baum et al. 2008
A2BP1		-Baum et al. 2008
NXN		-Baum et al. 2008
GSK3β		-Lachman et al. 2007
DPP10	codes for a protein that binds to potassium channels	-Wellcome trust consortium 2007
RNPEPL1	arginyl aminopeptidase family member	-Wellcome trust consortium 2007
GABRB1	gamma-aminobutyric acid (GABA) A receptor	-Wellcome trust consortium 2007
GRM7	Metabotropic glutamate	-Wellcome trust consortium

	receptor 7	2007 -Zhang et al. 2009
CHRFAM7A	a hybrid gene formed from a partial duplication involving the nicotinic receptor subunit gene	-Flomen et al. 2006
EFNA5	EFNA5 codes for ephrin-A5, which is plays a role in neurodevelopment.	-Wilson et al. 2006
GLUR7	glutamate signaling; kainate receptor-subunit gene	-Wilson et al. 2006
CACNG2	glutamate signaling	-Wilson et al. 2006
AKAP5	glutamate signaling	-Wilson et al. 2006
DLG2	channel-associated protein of synapses	-Zhang et al. 2009
SOX5	SRY (sex determining region Y)-box 5 encodes for a transcription factor involved in the regulation of embryonic development and in the determination of the cell fate.	-Zhang et al. 2009
DIBD1	mannosyltransferase gene	-Baysal et al. 2002

3.15. Others

3.15.1. GCHI

GCHI codes for a GTP cyclohydrolase and is located on 14q22-24, a region which was identified as bipolar disorder susceptibility locus in several GWAS and meta-analysis of genome scans [Segurado et al. 2003; Liu et al. 2003; Cassidy et al. 2007; Zhao et al. 2007]

3.15.2. CHMP1.5

CHMP1.5 on 18p11.2 encodes for a chromatin modifying protein and its chromosomal region lies within GWAS identified regions associated with bipolar disorder [Detera-Wadleigh SD et al. 1999; Segurado et al. 2003].

4. Genetic overlaps between bipolar disorder, schizophrenia and major depression

4.1. Introduction

Since Kraepelin divided affective disorders and schizophrenia in two distinct categories nobody has ever questioned the Kraepelinian dichotomy, although both diseases share at least psychosis. But nowadays genetic discoverments argue that bipolar affective disorder and schizophrenia are more related than we thought. To determine whether boundaries between schizophrenia and bipolar disorder are blurred one must elucidate the genes, which are shared by both diseases [Lin et al. 2008].

4.2. Overlaps between mood disorders and schizophrenia

4.2.1. Schizophrenia

Kraepelin described schizophrenia as „dementia praecox“already over 150 years ago [Peters et al. 2006]. Then Eugen Bleuler (1857-1939) coined the term schizophrenia. Kurt Schneider, a German psychiatrist and a pupil of Karl Jaspers, divided then the symptoms into first and second rank. First rank symptoms comprised of audible thoughts, arguing voices, commenting voices, experience of influences playing on the body, thought withdrawal, thought insertion, thought diffusion (also called thought broadcast) and delusional perception. Modern classifications include fundamental symptoms of Bleuler and Schneider. Since some decades the symptomatology distinguishes between positive and negative symptoms. Positive ones are delusions and hallucinations, negative ones are flattening of affect, poor planning, more generally expressed lowering of energetic potential [Tölle 2008]. The etiology and pathophysiology of schizophrenia is not exactly known, but it is for sure multifactorial. A combination of neurobiochemical, neuroanatomic and genetic alterations lead to disease. The classical „dopamin hypothesis“states that schizophrenia is based on a „dopaminergic hyperactivity“. But there are also imbalances in the serotonin-, glutamate- and GABA-systems [Kapfhammer et al. 2008]. Beside biological factors one might not forget psychosocial and environmental factors. Those factors lead to disease outbreak if there is an underlying genetic susceptibility for schizophrenia. Schizophrenia has a very strong genetic predisposition. Heritability is even around 80% [Norton et al. 2006; Burmeister 2008]. The genetic endowments of schizophrenia are proven by many twin, adoption and family studies. The concordance rate for monozygotic twins is around 50%, while it’s only 10% for fraternal twins, whereas the average person has only a risk of 0,5-1,6% to fall ill with schizophrenia

[Rothenhäusler 2007]. Although not all genes leading to schizophrenia are discovered yet, some are already known. The following genes showed nominal evidence of association with schizophrenia in a meta-analysis recently: APOE, COMT, DAO, DRD1, DRD2, DRD4, DTNBP1, GABRB2, GRIN2B, HP, IL1B, MTHFR, PLXNA2, SLC6A4, TP53 and TPH1 [Allen et al. 2008]. DRD2 (11q23.1), GABRB2 (5q34), DTNBP1 (6p22.3), IL1B (2q13) and COMT (22q11.21) were also proven to be associated in a meta-analysis of genome scans [Lewis et al. 2003].

4.3. Overlaps between mood disorders and schizophrenia

4.3.1. Symptomatic overlaps between mood disorders and schizophrenia

The most overlapping feature between schizophrenia and bipolar affective disorder is psychosis. Over 50% of patients classified with bipolar affective disorder experience at least one psychotic episode during their lifetime [Coryell et al. 2001]. Affective symptoms are another overlap. Schizophrenic patients have affective symptoms similar to those in mood disorders. All the negative symptoms, for example anhedonia, are similar to depressive ones. Beside schizophrenic patients may exhibit reduced emotional responses or experience hyperactive and exultant feelings like manic patients. There are also overlaps in medication. Atypical antipsychotics that target the dopamine 2 (D2) - and serotonin 5-HT2A-receptors can be used in schizophrenics, but have recently been used in bipolar patients too. Since those drugs are effective in both disorders, this implicates that the dopaminergic and serotonic pathways may be involved in the pathogenesis of both disorders [McIntyre et al. 2007; Rothenhäusler 2007; Bishara et al. 2009; McFadden et al. 2009; Tohen et al. 2009; Fountoulakis et al. 2010]. Bipolar and unipolar disorder share symptoms too. Depressive symptoms can occur in major depression, as well as in bipolar disorder during depressive states. Another common feature is suicidality. Both patients, unipolar and bipolar, experience suicidal ideation at some point of the disease or even try to commit suicide. So there is a great possibility, that both disease are genetically related [Rothenhäusler 2007].

4.3.2. Genetic overlaps between mood disorders and schizophrenia

4.3.2.1. COMT

The COMT gene is located at 22q11, which lies in the deleted region of the congenital velocardiofacial syndrome (VCFS). This syndrome includes cleft palate, heart disease, cognitive and learning impairments, as well as high risk for schizophrenia and bipolar

disorder. The VCFS microdeletion increases the risk for schizophrenia by the 30 to 50-fold! VCFS and the 22q11 deletion represent the highest known risk factor for schizophrenia aside from having either parents or a monozygotic twin with the disease [Murphy et al. 1999]. Patients with velocardiofacial syndrome show a schizophrenia rate of 24%, which made the gene in this region to a top target for schizophrenia research [Hamilton et al. 2008]. Many asssociation studies supported the relationship between COMT gene variants and schizophrenia, especially the Val158Met polymorphism [Lewis et al. 2003; Shifman et al. 2004; Fan et al. 2005; Funke et al. 2005; Allen et al. 2008; Chien et al. 2009; Brisch et al. 2009; Wang et al. 2009; Hoenicka et al. 2020]. Even a large meta-analysis comprising 2628 schizophrenic participants and 7340 controls prove association between COMT gene variants and schizophrenia [Allen et al. 2008]. In contrast there have been also negative results, even a recent Japanese meta-analysis denied association [Okochi et al. 2009]. COMT is not only a promising susceptibility gene for schizophrenia, but also for bipolar disorder. Goghari and colleagues showed that the well investigated Val158Met polymorphism is associated with psychotic symptoms in bipolar disorder and schizophrenia [Goghari et al. 2008]. Also further association studies prove evidence of COMT involvement in bipolar affective disorder [Lachman 1996; Kirov 1998; Shifman 2004; Funke 2005; Burdick et al. 2007; Goghari 2008; Zhang 2009]. Altogether COMT is a very important risk gene for schizophrenia and bipolar disorder, but could not be matched in major depressive disorder [Kunugi et al. 1997; Frisch et al. 1999; Baekken et al. 2008; Waray et al. 2008]. Although Massat and colleagues found that the Val/Val genotye of the Val158Met polymorphism is associated with early onset depressive disorder [Massat et al. 2005].

4.3.2.2. Serotonintransporter polymorphisms

4.3.2.2.1. SERT (=5HTT = serotonin transporter gene)

The gene coding for the serotonin transporter (5-HTT) has been a hot spot of mood disorder research for several decades, since this transporter is the main target of the effective and widely used SSRI. Decreased synaptic serotonin during depressive episodes is a central element of the monoamine hypothesis of depression. Therefore the serotonin transporter, which reuptakes the serotonin from the synaptic gap, is the most attractive candidate gene. Efficiency of 5-HTT-mediated inward and outward transport is enhanced in depressed patients [Willeit et al.2008].

4.3.2.2.2. VNTR in intron 2 of the serotonin transporter gene

Already 14 years ago this variable number tandem repeat polymorphism was the center of interest in renowned scientific magazines like the Lancet. The 9 repeat allele of this 5-HTTVNTR was associated with major affective disorder by Ogilvie and colleagues [Ogilvie et al. 1996], which was confuted in the same year by a Japanese group [Kunugi et al. 1996]. Haplotype analyses recognised certain haplotypes, which comprise a special VNTR in intron2 and a deletion in the promoter region, to be associated with depression [Gutierrez et al. 1998]. Nevertheless there are results which negate any association of this VNTR in intron 2 and depression in Chinese people [Yen et al. 2003]. Results in bipolar disorder research are also conflicting. Many association studies claim involvement of the intron 2 VNTR polymorphism in manic depressive disease [Collier et al. 1996; Craddock et al. 1996; Battersby et al. 1996; Kunugi et al. 1996; Rees 1997; Bellivier 1998; Furlong 1998; Kirov 1999; Bellevier 2002]. Almost the same amount showed negative results in bipolar disorder [Stöber et al. 1996; Hoehe et al. 1998; Bocchetta et al. 1999; Vincent et al. 1999; Olivieira et al. 2000; Saleem et al. 2000; Mellerup et al. 2001; Dimitrova et al. 2002; Yen et al. 2003; Alaerts et al. 2009]. Also schizophrenia has a good chance to be associated with this polymorphism. A meta-analysis comprising of 12 population-based association studies consisting of 2177 cases and 2369 control subjects showed, that the 12repeat allele is highly significantly associated with schizophrenia [Fan et al. 2005]. Also another meta-analysis for schizophrenia showed association with this polymorphism. Conflicting results may be due to small study sizes and different ethnic populations [Allen et al. 2008].

4.3.2.2.3. Deletion/insertion in the promoter region of SERT

A 44base pair insertion/deletion polymorphism in the 5'regulatory region of the serotonin transporter gene (5-HTTLPR) has been centre of research for decades. Association between the polymorphism and depression was observed in many studies. A large German study, which comprised 466 patients and 836 controls, prove that the short allele of the 5-HTTPLR polymorphism is significantly associated with major depressive disorder. The short allele, which contains the deletion, leads to reduced transcriptional activity of the promoter, which consequently reduces the rate of expression by 30–40% [Heils et al. 1995; Hoefgen et al. 2005]. Also subtypes of depression were investigated. Melancholic depression was associated with the 5-HTTLPR s-allele and atypical depression with the l allele [Willeit et al. 2003]. In addition seasonal affective disorder was also associated with the s-allele [Rosenthal et al. 1998; Sher et al. 1999]. Altogether there are many studies which favour an association

between depression and the s-allele or haplotypes [Gutierrez et al. 1998; Hauser et al. 2000]. Nevertheless there are also studies which deny any association, even a large meta-analysis [Frisch et al. 1999; Serretti et al. 1999; Lasky-Su et al. 2005]. Beside there is a possibility, that the short allele is associated with suicidal behaviour, which can be part of many diseases [Neves et al. 2008]. Schizophrenia was also investigated for this polymorphism, but the 5-HTTLPR insertion/ deletion polymorphism is not likely to be involved in pathogenesis. This claims at least a large meta-analysis [Fan et al. 2005]. Bipolar depression is again a controversial candidate. The bigger part of the studies shows no evidence of association [Kunugi et al. 1996; Collier et al. 1996; Rees et al. 1997; Esterling et al. 1998; Hoehe et al. 1998; Mendes de Oliviera et al. 1998; Geller et al. 1999; Kirov et al. 1999; Serretti et al. 1999, Vincent et al. 1999; Olivieira et al. 2000; Ospina-Duque et al. 2000; Bellivier et al. 2002; Serretti et al. 2002; Mendlewicz et al. 2004; Neves et al. 2008; Vincze et al. 2008; Alaerts et al. 2009; Mick et al. 2009]. Although some studies, also two meta-analysis, show a possible factor in pathogenesis of bipolar disorder [Bellivier et al. 1998; Rotondo et al. 2002; Anguelova et al. 2003; Hauser et al. 2003; Lasky-Su et al. 2005; Meira-Lima et al. 2005].

4.3.2.3. G72/G30 gene (DAOA)

DAOA is located at the locus in 13q13-q14 and codes for the D-amino acid oxidase activator. Although many studies suggest evidence of association with bipolar disorder [Bass et al. 2009; Fallin et al. 2005; Schulze et al. 2005; Maziade et al. 2009], some do not [Shi et al. 2008; Gomez et al. 2009; Maheshwari et al. 2009]. Furthermore this gene may confer risk to schizophrenia [Zou et al. 2005; Allen et al. 2008; Bass et al. 2009; Maziade et al. 2009; Shi et al. 2008; Shi et al. 2009]. A large Japanese multi center study with 1774 patients with schizophrenia and 2092 healthy controls found association with several SNPs, which did not survive correction for multiple testing [Ohi et al. 2009]. Moreover other association studies neglected association with schizophrenia [Jönsson et al. 2009]. DAOA may also confer risk to major depressive disorder, but studies are lacking. Nevertheless G72 was associated with major depression and neuroticism [Rietschel et al. 2008].

4.3.2.4. DAO

DAO might confer susceptibility to schizophrenia, bipolar disorder and unipolar disorder [Fallin et al. 2005; McGuffin et al. 2005; Schulze et al. 2005; Allen et al. 2008; Rietschel et al. 2008; Shi et al. 2008; Wirgenes et al. 2009]. But some association studies neglected

association of DAO with schizophrenia and bipolar disorder [Bass et al. 2009; Jönsson et al. 2009].

4.3.2.5. CACNA1C

CACNA1C codes for the alpha1C subunit of the L-type voltage-gated calcium channel. CACNAIC is significantly associated with bipolar disorder. This was proven by several large genome wide association studies and even their meta-analysis [Ferreira et al. 2008; Sklar et al. 2008; Moskvina et al. 2009; Askland 2009]. CACNA1C might also be associated with major depression and schizophrenia [Green et al. 2009; Moskvina et al. 2009; Casamassima et al. 2010].

4.3.2.6. DTNBP1

DTNBP1 on chromosome 6p22.3 is coding for the protein dysbindin or dystrobrevin binding protein1 and is one of the most important susceptibility gene for schizophrenia [Lewis et al. 2003;Breen 2006; Duan et al. 2007; Allen et al. 2008; Réthelyi et al. 2009; Wessman et al. 2009; Wirgenes et al. 2009]. Dysbindin is part of the dystrophin complex and has functions in synaptic plasticity and signaltransduction. This complex regulates for example nicotinic receptor clustering and recruits specific signaling molecules, such as neuronal nitric oxide synthase, and also interacts with postsynaptic density proteins involved in *N*-methyl-D-aspartate (NMDA) receptor clustering. Defects in this gene product could lead to problems in synaptic transmission and postsynaptic receptor regulation [Miyamoto et al. 2003]. Only some studies for schizophrenia showed negative results for this gene [Jönsson et al. 2009]. This susceptibility gene might be another overlap with bipolar disorder [Fallin et al. 2005; Breen 2006; Pae et al. 2007; Gaysina et al. 2009]. Nevertheless it is not likely to play a role in major depressive disorder [Zill et al. 2004].

4.3.2.7. Neuregulin1

Neuregulin1, which is encoded on 18p12, is strongly associated with susceptibility for schizophrenia [Green et al. 2005; Lachman et al. 2006; Georgieva et al. 2008; Réthelyi et al. 2009]. Although there are association studies with negative results [Jönsson et al. 2009]. Manic depressive disease shares this susceptibility gene with schizophrenia [Segurado et al. 2003; Green et al. 2005; Georgieva et al. 2008; Perlis et al. 2008; Sklar et al. 2008; Goes et al. 2009; Le-Niculescu 2009]. In contrast major depressive disorder was not associated in a large scale study with almost 1400 depressed participants and 1300 controls [Schosser et al. 2010]. Neuregulin1 functions in neuronal migration and brain development. It is also associated with

several neurotransmitter systems like the NMDA-, glutamat- and GABA-system [Miyamoto et al. 2003].

4.3.2.8. DISC 1

The DISC-1 and DISC-2 (Disrupted in schizophrenia1 and 2) are risk genes for schizophrenia. Both genes are disrupted by a balanced 1:11 translocation and they reside at 1q42.1 [Miyamoto et al. 2003]. The mutation leads to altered neuronal structure and cognition [Kvajo et al. 2008]. DISC1 is involved in cytoskeletal, synaptogenic and neurodevelopmental functions [Duan et al. 1b 2007; Hennah et al. 2009]. The translocation leads to a truncated DISC protein in which the carboxy-terminal end is deleted. DISC1 protein seems to play a role in cortical development. This may happen through interactions with NUDEL and LIS1 proteins, which are important in neuronal migration [Kamiya et al. 2006]. DISC1 regulates proliferation and differentiation of neuronal progenitor cells via GSK3beta/beta-catenin signaling. A suppression of DISC1 leads to reduced neuronal proliferation [Mao et al. 2009]. DISC1 locus was identified in a genome wide linkage scan for schizoaffective disorder, as well as bipolar disorder [Macgregor et al. 2004; Hamshere et al. 2006]. Many studies supported evidence of association between schizophrenia and DISC1, also a recent meta-analysis [Hodgkinson et al. 2004; Saetre et al. 2008; Schumacher et al. 2009; Tomppo et al. 2009]. Nevertheless many studies doubt this association [1b Kim et al. 2008]. Also bipolar disorder is associated with DISC1 variants. Thus DISC1 might be another overlap between both diseases [Hodgkinson et al. 2004; Macgregor et al. 2004; Maeda et al. 2006; Palo et al. 2007; Le-Niculescu 2009; Schosser et al. 2009].

4.3.2.9. BDNF

BDNF is a promising well studied candidate gene for bipolar disorder [Sklar et al. 2002; Neves-Pereira et al 2002; Geller et al. 2004; Lohoff et al. 2005; Green et al. 2006; Vincze et al. 2008; Xu et al. 2009; Liu et al 2008; DeLuca et al.2008; Fan and Sklar 2008; Le-Niculescu 2009] and might also be associated with schizophrenia and major depressive disorder [Watanabe et al. 2007; Schumacher et al. 2005]. A meta-analysis showed evidence of association between the BDNF C270T polymorphism and schizophrenia [Watanabe et al. 2007]. In contrast a Japanese meta-analysis rejected association of the two most important BDNF variants with schizophrenia recently [Kawashima et al. 2009] as well as a meta-analysis for major depression denied association with BDNF [Chen et al. 2008].

4.3.2.10. MAOA gene

MAOA gene variants seem to be associated at some degree with all three psychiatric disease.Yu and colleagues showed significantly increased frequency of the 4-repeat allele of the promoter VNTR polymorphism of MAOA in major depressed patients [Yu et al. 2005]. The more active longer allele of the MAO-A VNTR was significantly associated with complicated grief in the female subgroup of patients [Kersting et al. 2007]. Some association studies supposed a connection of MAO variants and schizophrenia [Jönsson et al. 2003; Qiu et al. 2009]. But a meta-analysis stated that there is no association between variable number tandem repeat (VNTR) and T941G polymorphisms and schizophrenia [Norton et al. 2002; Li et al. 2008]. Syagailo and colleagues showed no association between the MAOA-LPR variant and susceptibility to recurrent major depression, bipolar disorder and schizophrenia in our population [Syagailo et al. 2001]. The CA-repeat microsatellite polymorphism of intron2 and the -941T->G SNP are suggested to be associated with bipolar disorder [Furlong et al. 1999; Kawada et al. 1995; Rubinsztein et al. 1996; Lim et al. 1995; Preisig et al. 2000]. Although those two polymorphism had also negative study results for bipolar disorder [Parsian and Todd 1997; Preisig et al.2000; Lin et al. 2008; Serretti 2002; Craddock 1995; Muramatsu 1997; Nöthen 1995].

4.3.2.11. Dopamine receptor genes

4.3.2.11.1. DRD1

DRD1 was associated with schizophrenia in a meta-analysis recently [Allen et al. 2008]. But there are also association studies, which show negative results in schizophrenic patients [Kojima et al. 1999]. DRD1 has also a conflicting role in bipolar disorder, as well as unipolar disorder. Some association studies show positive results for bipolar disorder [Severino et al. 2005; Dmitrzak-Weglarz 2006]. But some presented negative results. Further studies are necessary to find the role of DRD1 in mood disorders, since studies are lacking [Savoye et al. 1998; Del Zompo 2007; Szczepankiewicz 2007].

4.3.2.11.2. DRD2

DRD2 might be a susceptibility gene for schizophrenia and bipolar disorder, although results are inconsistant. There are some positive results for bipolar disorder [Perez de Castro 1995; Arinami 1996; Li 1999; Serretti 2000; Massat 2002; Serretti et al. 2000], but there are also many results which lead to a doubt of association with manic depressive disease [Souery 1996; Stöber 1998; Manki 1996; Sasaki 1996; Furlong et al. 1998; Savoye et al. 1998;

Bocchetta 1999; Kirov 1999; Li et al. 1999; Heiden 2000; Leszczyńska-Rodziewicz 2005; Szczepankiewicz 2007]. DRD2 seems not to play a major role in major depressive disorder, but subsequent studies are also lacking [Furlong et al. 1998]. Evidence for mood disorder is inconsistant, while some meta-analysis showed evidence of association for the DRD2 gene with schizophrenia [Gurling et al. 2001; Lewis et al. 2003; Allen et al. 2008; Serretti et al. 2000].

4.3.2.11.3. DRD3

There is overwhelming evidence that DRD3 polymorphism are not important for development of bipolar disorder [Savoye et al. 1998; Shaikh 1993; Manki . 1996; Souery 1996; Piccardi 1997; Kirov 1999; Heiden 2000; Elvidge 2001; Leszczyńska; Rodziewicz 2005; Szczepankiewicz 2007; Krelling 2008] and additionally the rare studies for unipolar disorder show negative results [Manki et al. 1996]. Existing studies suggested association of DRD3 with schizophrenia [Talkowski et al. 2006; Dominguez et al. 2007], but the bigger part of the studies neglected a relation. Concording with this large case control studies and even Japanese and Chinese meta-analysis could not find a relation between schizophrenia and D3 dopamine receptor gene variants, especially the Ser9Gly polymorphism [Lorenzo et al. 2007; Fathalli et al. 2008; Ma et al. 2008; Utsunomiya et al. 2008; Nunokawa et al. 2010]. So maybe all three diseases have in common, that they are not associated with DRD3.

4.3.2.11.4. DRD4

DRD4 seems to play a major role in schizophrenia and bipolar disorder, but not in major depression [Oruc et al. 1997; Firsch et al. 1999]. There are much more supporting studies for bipolar disorder than unipolar disorder [Manki 1996; Serretti 1b 1998; Serretti 1d 1999; Serretti 2001; Muglia 2002; Lopez 2005; Aguirre 2007]. Nevertheless there are even more negative results in association studies for bipolar disorder [Perez de Castro et al. 1994; Oruc et al. 1b 1997; Bocchetta et al. 1999; Li et al. 1999; 1c Serretti et al. 1999; Serretti et al. 2002; Serretti et al. 2004; Leszczyńska-Rodziewicz et al. 2005]. Schizophrenia was even associated with DRD4 variants in a meta-analysis recently [Allen et al. 2008]. Nevertheless there are also negative results for schizophrenia and bipolar disorder [Oruc et al. 1997].

4.3.2.11.5. DRD5

Schizophrenia and manic depressive disorder show evidence of association with the dopamine recptor D5 gene. But further studies are lacking [Asherson et al. 1998; Ewald et al. 1998; Muir et al. 2001; Pal et al. 2009].

4.4. Summary of the overlaps

Table 16: Supportive evidence of association for overlapping candidate genes of schizophrenia, bipolar disorder and unipolar depression

	Supportive evidence schizophrenia	**Supportive evidence bipolar disorder**	**Supportive evidence unipolar depression**
COMT:	-Lewis et al. 2003 (meta-analysis) -Shifman et al. 2004 -Fan et al. 2005 (meta-analysis) -Funke et al. 2005 -Allen et al. 2008 (meta-analysis) -Chien et al. 2009 -Brisch et al. 2009 -Hoenicka et al. 2010 (in Spanish males) -Wang et al. 2009	-Lachman 1996 -Kirov 1998 -Shifman 2004 -Funke 2005 -Burdick 2007 -Goghari 2008 -Zhang 2009 (large study and meta-analys on 19studies)	-Ohara et al. 1998 -Massat et al. 2005
MAOA	-Jönsson et al. 2003 -Qiu et al. 2009 (only in men)	-Furlong et al. 1999 (meta-analysis) -Kawada et al. 1995 -Rubinsztein et al. 1996 -Lim et al. 1995 -Preisig et al. 2000 -Fan et al. 2010 (meta-analysis)	-Yu et al. 2005 -Fan et al. 2010 (meta-analysis)
DISC1 on 1q42	-Hodgkinson et al. 2004 -Hamsgire et al. 2005 -Saetre et al. 2008 -Schumacher et al. 2009 (association study and meta-analysis) -Tomppo et al. 2009	-Rubinsztein et al. 1996 -Furlong et al. 1999 -Blackwood et al. 2001 -Hamshere et al. 2005 -Maeda et al. 2006 -Müller et al. 2007 -Palo et al. 2007 -Schosser et al. 2009	-Hashimoto et al. 2006
DRD1	-Allen et al. 2008 (meta-analysis)	-Severino 2005 -Dmitrzak-Weglarz 2006	-Cannon et al. 2009
DRD2	-Gurling et al. 2001 -Lewis et al. 2003 (meta-analysis)	-Perez de Castro 1995 -Arinami 1996 - Li 1999	No association detected

	-Allen et al. 2008 (meta-analysis) -Serretti et al. 2000	-Serretti 2000 -Massat 2002 -Serretti et al. 2000	
DRD4	-Allen et al. 2008 (meta-analysis) -Shi et al. 2008	-Manki 1996 -Serretti 1b 1998 -Serretti 1d 1999 -Serretti 2001 -Muglia 2002 -Lopez 2005 -Aguirre 2007	-Manki et al. 1996 -Xiang et al. 2008
DRD5	-Muir et al. 2001 -Pal et al. 2009	-Asherson 1998 -Ewald et al. 1998	Lack of studies
GABRB2	-Lewis et al. 2003 (meta-analysis) -Allen et al. 2008 (meta-analysis) -Shi et al. 2008	-Crowe 1999	Lack of studies
GRIN2B	-Allen et al. 2008 (meta-analysis)	-Fallin et al. 2005 - Avramopoulos -Szczepankiewicz et al. 2009	Lack of studies
NRG1 Neuregulin on 18p12 Wichtig	-Green et al. 2005 -Lachman et al. 2006 -Georgieva et al. 2008 -Réthelyi et al. 2009	-Segurado et al. 2003 -Green et al. 2005 -Walss-Bass et al. 2006 -Georgieva et al. 2008 -Perlis et al. 2008 -Sklar et al. 2008 -Goes et al. 2009 -Le-Niculescu 2009 -Prata et al. 2009	No association detected
MTHFR	-Arinami et al. 1997 -Kempisty et al. 2007 -Allen et al. 2008 (meta-analysis) -Shi et al. 2008	-Kempisty et al. 2007	-Arinami et al. 1997 -McGuffin et al. 2005
CACNA1C	-Green et al. 2009 -Moskvina et al. 2009	-Ferreira et al. 2008 (GWAS) -Sklar et al. 2008 (GWAS) -Moskvina et al. 2009 (GWAS) -Askland 2009 (GWAS)	-Green et al. 2009 -Casamassima et al. 2010
APOE	-Digney et al. 2005	-Bellivier et al. 1997	No association detected

	-Allen et al. 2008 (meta-analysis) -Dean et al. 2008	-Digney et al. 2005 -Dean et al. 2008	
BDNF:	-Watanabe et al. 2007 (meta-analysis) -Neves-Pereira et al.2005 -Rosa et al. 2006	-Le-Niculescu 2009 -Sklar et al. 2002 -Neves-Pereira et al 2002 -Geller et al. 2004 -Lohoff et al. 2005 -Green et al. 2006 -Vincze et al. 2008 -Xu et al. 2009 -Liu et al 2008 -DeLuca et al.2008 -Fan and Sklar 2008 (Meta-analysis of 14studies) -Xu et al. 2009 -Xu et al. 2010	-Schumacher et al. 2005 -Hilt et al. 2007
SERT/5HTT	-Chotai et al. 2005 -Fan et al. 2005 (meta-analysis) -Allen et al. 2008 (meta-analysis) -Shi et al. 2008	-Battersby et al. 1996 -Collier et al. 1996 -Craddock et al. 1996 -Rees et al. 1997 -Furlong et al. 1998 (meta-analysis) -Bellivier et al 1998 -Rotondo et al. 2002 -Anguelova et al. 2003 (meta-analysis) -Hauser et al. 2003 -Lasky-Su et al. 2005 (meta-analysis) -Meira-Lima et al. 2005	-Battersby et al 1996 -Ogilvie et al. 1996 -Hauser et al. 2000 -Willeit et al. 2003 -Hoefgen et al. 2005 -Dong et al. 2009 -Rucci et al. 2009
TPH	-Chotai et al. 2005 -Zaboli et al. 2006 -Allen et al. 2008 (meta-analysis)	-Chen et al. 2008 -Bellivier et al. 1998	-Gizatullin et al. 2006
DTNBP1 Dystrobrevin-binding protein WICHTIG On 6p	-Lewis et al. 2003 (meta-analysis) -Breen 2006 -Duan et al. 2007 -Allen et al. 2008 (meta-analysis) -Réthelyi et al. 2009 -Wessman et al. 2009 -Wirgenes et al. 2009	-Fallin et al. 2005 -Breen 2006 -Joo et al. 2007 -Pae et al. 2007 -Gaysina et al. 2009	No association detected
DAO D-amino acid oxidase	-Allen et al. 2008 (meta-analysis) -Shi et al. 2008 -Wirgenes et al. 2009	-Fallin et al. 2005 -Schulze et al. 2005	-McGuffin et al. 2005 (GWAS)

DAOA= G30/G72 On 13q13-q14 Coding for: DAOA D-amino acid oxidase activator	-Zou et al. 2005 -Allen et al. 2008 (meta-analys) -Bass et al. 2009 -Maziade et al. 2009 -Shi et al. 2008 -Shi et al. 2009	-Fallin et al. 2005 -Schulze et al. 2005 -Bass et al. 2009 -Maziade et al. 2009	-Rietschel et al. 2008

5. Gene-environment-interactions and prevention

5.1. Epigenetics

Lifestyle and environmental factors, like diet, drugs, alcohol and hormones, can influence inherited features without changing DNA sequence, but with epigenetic changes, like methylation, acetylation, ubiquitination and phosphorylation of DNA or histones. Thus environment has an impact on inheritibility and gene regulation with chemical modification of DNA segments important for gene expression, for example promoters. Especially cytosine in so called CpG islands, which are located especially in regulatory elements, gets methylated. The methyl group is provided by S-adenosyl methionine. Hypermethylation of promoters lead to silencing of the gene or reduced transcription, irreversible if very dense methylated [Bogdanovic et al. 2009]. Potentially all genes of our genome could be expressed in every cell, because every cell carries the whole genome inside. But since cells are specialised and adaption to environment is important, not all genes are necessary and some must be silenced. This happens along with other mechanisms by epigenetic modification. Those chemical changes are performed by many host enzymes. DNA methyltransferases are responsible for DNA methylation and histones are modified by histone acetyltransferases (HATs) and histone deacetylases (HDACs) as well as methyl-transferases and demethylases [Abdolmaleky et al. 2004; Connor et al. 2008]. Many neurodevelopmental and neuropsychiatric diseases, like Prader Willi und Angelman syndrome, are influenced by epigenetic changes and genomic imprinting [Horstthemke et al. 2008]. Epigenetic changes, like pathological increased CpG methylation and repressive chromatin remodeling at 5' regulatory sequences, might also be a cause for heritable susceptibility to bipolar disorder. [Connor et al. 2008; Mill et al.2008]. Methylation of the promoter regions of BDNF, DRD2, REELN, HTR2A and other genes lead to predisposition for bipolar disorder. Also genes of the glutamatergic and GABAergic system with epigenetic modification lead to vulnerability for psychiatric diseases [McGowan et al. 2008; Mill et al. 2008]. Hypomethylation of the COMT promoter, which leads to enhanced

expression of the enzyme, leads to increased predisposition for bipolar disorder and schizophrenia [Abdolmaleky et al. 2006; Connor et al. 2008]. Although this is also in doubt [Dempster et al. 2006].Epigenetic changes of REELN confer suceptibility for bipolar disorder and schizophrenia. Hypermethylation of the REELN promoter leads to decreased expression of Reelin, which is important for neuronal migration and synaptogenesis [Abdolmaleky et al. 2004; Abdolmaleky et al. 2005]. Aberrant methylation status was also identified in twins disconcordant for bipolar disorder. Especially the X-chromosome showed different patterns of methylation [Rosa et al. 2008].

5.2. Sleep deprivation

Sleep deprivation has antidepressant effects and can lead to a switch of mood in bipolar patients. It leads to better brightening of mood in long allele carriers of the SERT promoter deletion/insertion polymorphism [Benedetti 1999].

5.3. Nutrition and famines

Famines lead to reduced proteinsynthesis and in consequence to oligodendrocyte cell loss and hypomyelination. Many proteins involved in nerve growth are coded by genes disturbed in bipolar affective disorder. So hunger might affect especially bipolar patients with certain genetic predisposition [Carter 2007]. Acute tryptophan depletion leads to reduced transient serotonergic neurotransmission and negative mood [Nugent et al. 2008; Robinson et al. 2009]. Special variants of the serotonin transporter gene lead to different response to this depletion of tryptophan. The short allele of 5-HTTLPR, a 44bp insertion/deletion polymorphism in the 5' regulatory region of the serotonin transporter gene (SLC6A4), leads especially in relationship with tryptophan depletion and positive family history to depression. While the ss genotype leads more frequently to depression during tryptophan depletion, the ll genotype is protective [Neumeister et al. 2002; Firk et al. 2009]. Totally opposing results show another small study. They suggest the ll genotype to lead to depressive response during tryptophan depletion [Moreno et al. 2002].

5.4. Infections and risk of bipolar disorder

Infections might increase the risk of mood disorders. Already in the late 1970s the Borna virus, which cause a rare meningoencephalitis, was highly discussed to play a role in mood disorders and many studies showed borna virus antibodies and antigenes in patients with affective disorder [Pini et al. 1996; Salvatore et al. 1997; Ferszt et al. 1999; Bode et al. 2001;

Terayama et al. 2003]. Amantadine treatment reduces mania in bipolar patients infected with borna virus [Ohlmeier et al. 2008]. Also HSV-1 could be considered. HSV-1 infection and COMT Val158Met polymorphism affect cognitive functioning in individuals with bipolar disorder [Dickerson et al. 2006].

5.5. Season of birth

The season of birth is a well replicated environmental factor for development of bipolar disorder, maybe because infections occur more often in winter and spring [Torrey et al. 1996; Mino et al. 2000]. Chotai and colleagues investigated the connection between season of birth and gene variants of tryptophan hydroxylase (TPH), serotonin transporter (5-HTTLPR) and dopamine receptor (DRD4) with positive results [Chotai et al. 2003].

5.6. Urban/rural residency and genotype

A study by Jokela claims, that urban residency is associated with low depressive symptoms in Finnish individuals carrying the T/T or T/C genotype of the T102C polymorphism of HTR2A, but not in those carrying the C/C genotype. The T allele was associated with high depressive symptoms in remote rural areas, but with low depressive symptoms in urban or suburban areas [Jokela et al. 2007].

5.7. Antidepressant induced mania and relation to genotype

Antidepressants can lead to a switch to manic symptoms, especially with a predisposing genotype. Carriers of the short allele of 5-HTTLPR are prone to get antidepressant induced mania [Mundo et al. 2001; Ferreira et al. 2009]. But no association was found in a study of 305 bipolar patients between the 44bp insertion/deletion polymorphism in the 5-HTTLPR of the serotonin transporter with antidepressant-induced-mania [Rousseva et al. 2003]. Also children and youth with bipolar disorder do not show any association between the serotonin transporter promoter polymorphism and antidepressant induced mania. Nevertheless especially young people, irrespective of genotype, are at risk and should be observed when given antidepressants [Baumer et al. 2007].

5.9. Stress, gene expression and bipolar disorder

Chronic stress or stressful events can lead to mood disorders and burnout, but not in everybody. People cope differently with distress. While some people put away stress easily,

others react exaggeratedly. This may all be due to genetic predisposition and personality traits. Certain genotypes of serotonergic system related genes lead to greater susceptibility for depressive disorder after stress exposure, because they modulate the acute serotonergic reaction to the stressor [Holmes 2009]. The ss genotype of 5-HTTLPR, a regulatory region of the serotonin transporter gene, leads to depressive reaction after stress exposure, while ll allele carriers are protected against depression [Eley et al. 2004; Kendler et al. 2005; Firk et al. 2009]. The ss genotype of the 5-HTTLPR polymorphism also leads to enhanced stress reactivity in general. A very recent study tested the 5-HTTLPR variant in relation to stress response in newborns. They testet the relation between genotype and cortisol release after a foot prick, which is an element in a routine check, but is still associated with stress for the newborn. SS genotype carriers had much higher cortisol levels than other genotypes. Thus s allele carriers show much higher stress response than l allele carriers [Müller et al. 2009].
Stress and glucocorticosteroids lead to decreased expression of BDNF in the brain, especially the hippocampus [Smith et al. 1995]. Beside chronic unpredictable stress leads to reduced serotonergic firing and desensitization of 5-HT1A autoreceptors. Altogether it is proven that chronic stress induces mood instabilities and especially genetically predisposed people should try to reduce stress and find good coping strategies [Bambico et al. 2009].

5.10. Mood changes after delivery- association with genes

The so called “baby blues” is a widespread depressive episode in the postpartum period, which may be influenced by certain gene variants. Not only depressive episodes can occur, also psychosis is an issue in postpartum period. Especially women with bipolar disorder are at special risk for psychosis after delivery. Almost half of bipolar women get puerperal psychosis some days after delivery [Coyle et al. 2000]. After childbirth there is a sharp reduction in tryptophan availability in the brain, thus polymorphic variations in 5-HTT may play a role in the post-partum psychosis. High expression 5-HTT genotypes (ll genotype) might be a risk factor under certain environmental conditions such as tryptophan depletion after childbirth [Sanjuan et al. 2008]. Also other groups show that certain 5-HTTLPR polymorphism of the serotonin transporter influence the susceptibility to puerperal psychosis [Coyle et al. 2000]. A genome wide linkage study for postpartum mood disorder identified the regions 1q21.3-q32.1 with KCNN3 and 9p24.3-p22.3 as hot spots. Within the finemapping study the gene HMCN1 at 1q25.3-q31.1 reached the best results [Mahon et al. 2009].

5.11. Maltreatment and negative life events

Maltreatment in childhood is a severe trauma, which leads very often to psychological problems in adulthood. Nevertheless some victims can cope better than others with similar childhood experience. Therefore there might be some protective genotypes, which help to prevent outbreak of depression or other psychiatric disease [Caspi et al. 2002].

5.11.1. MAOA polymorphism

Maltreated children sometimes grow up and develop antisocial behaviour and victimize others, while others do not. Caspi and colleagues found, that the functional promoter polymorphism of the MAOA gene moderates the effect of maltreatment. Polymorphisms, which lead to high levels of monoamine oxidase, were protective against antisocial behaviour, while carriers of polymorphisms, which produce low activity MAOA were likely to invent violent behaviour in their adulthood after maltreatment experience in their childhood. So genotypes seem to moderate children's sensitivity to environmental insults [Caspi et al. 2002]. Also other goups showed that low activity MAO is associated with anti social behaviour after traumatic life events, which do not only include maltreatment, but also a parent's death, parent's marital problems or other emotional difficult events [Frazzetto et al. 2007].

5.11.2. Genes involved in hypothalamic-pituitary-adrenal (HPA) axis

The hypothalamic-pituitary-adrenal-axis (HPA) is strongly associated with stress response and modulation. The hypothalamus releases CHR, which binds to CRH receptors in the anterior pituitary gland. In consequence adrenocorticotrophic hormone (ACTH) is released, which leads to release of cortisol from the adrenal cortex [Gillespie et al. 2009]. Specific CRHR1 polymorphisms appear to moderate the effect of child abuse on the risk for adult depressive symptoms [Bradley et al. 2008; Bet et al. 2009; Tyrka et al. 2009]. Polanczyk and colleagues reported, that the TAT haplotype, comprising of 3 CRHR1 SNPs, is protective against developing depression after childhood maltreatment [Polanczyk et al. 2009].

5.11.3. FKBP5

FKBP5 polymorphism are associated significantly with childhood abuse followed by post traumatic stress disorder in adulthood. Beside certain FKBP5 genotypes influence glucocorticoid receptor sensitivity [Binder et al. 2008].

5.11.4. Serotonin transporter 5-HTTLPR polymorphism

The short (s) less active allele of the serotonin transporter 5-HTTLPR polymorphism was associated with a greater risk of adult depression in the presence of a history of either childhood maltreatment or multiple life events in a 5-year period before onset [Brown et al. 2008]. Also a large prospective-longitudinal study published in Science showed the same results. More depressive results occurred in ss genotype carriers after recent life traumas than in carriers with a set of two "long alleles" of the 5HTTLPR polymorphism. Therefore homocygosity of long alleles are protective against depressive reaction after traumatic life events [Caspi et al. 2003]. Also Kendler, as well as Kaufman and colleagues showed enhanced depressive reaction to life events in ss genotype carriers [Kaufman et al. 2004; Kendler et al. 2005]. A Swedish cohort of 1482 students at the age of 17-18years was investigated for the relationship between depression, maltreatment and genotype. The association between maltreatment and depression alone was significant in both genders, while the association with the ss genotype was only significantly associated in girls [Aslund et al. 2009]. Totally opposite results reached a study over 247 young adult femal twins. The results showed significantly more depressive reactions to life traumata in long allele carriers [Chorbov et al. 2007]. Also a recent Chinese study showed that 5-HTTLPR polymorphisms influence the reaction to negative life events in the same way [Zhang et al. 2009]. So genetic predisposition might be an explanation why stressful experiences lead to major depression in some people, but not in others. But although special genotypes confer high risk to depression after maltreatment, special social support can help ss genotype carriers to reach very low depression scores. Positive social environment can recover negative experiences in childhood, even with ss genotype [Kaufman et al. 2004].

5.11.5. BDNF

Also BDNF variants lead to more depressive reaction after maltreatment or other life events. The met allele of the BDNF Val66Met variant leads especially in combination with two short alleles of the 5-HTTLPR deletion polymorphism to very high depression scores after maltreatment. Nevertheless social support lowered the risk very much, even in ss genotype carriers [Kaufman et al. 2004; Kaufman et al. 2006].

5.11.6. COMT

COMT polymorphisms were investigated for a relation between high emotionality in children following maternal postpartum depressive symptoms and adverse life events for children in a

large English longitudinal study comprising of 8511 children recently. Maternal postpartum depression and traumatic life events increases the risk of high emotionalty of children, but this does not correlate with any COMT genotype [Evans et al. 2009].

5.12. Implications for clinical practice- therapy and prevention

5.12.1. Treatment and genotype

5.12.1.1. Antidepressant treatment and genotype

Different genotypes of certain gene variants involved in molecular pathogenesis of affective disorders lead to different treatment results. The ss genotype of the serotonin transporter promoter polymorphic region leads to poor response to SSRI [Serretti et al. 2004]. Also other gene variants influence antidepressant efficacy. The A218C TPH polymorphism was associated with slower response to fluvoxamin in the AA carrier [Serretti et al. 2001]. COMT polymorphisms also influence antidepressant response. The Val/Val genotype of the COMT val158met polymorphism leads to worse effects of antidepressant treatment [Baune et al. 2008]. Since genotypes influence efficacy of therapy, genotyping could be a means for planning therapy in the future. This would personalize treatment decisions and would help to give the right effective medication even to non responders. The results of genetic research may help to construct guidelines for antidepressant or antimanic chronic treatment. Of course this is still far from clinical practice, but maybe dreams of the future [Luddington et al. 2009].

5.12.1.2. Antimanic treatment and genotype

Response to lithium is associated with certain genotypes of susceptibility genes. Also the -48 A/G polymorphism of the dopamine receptor D1 gene is associated with outcome of prophylactic lithium treatment. The G/G genotype leads to poorer response [Rybakowski et al. 2009]. Serotonin transporter gene polymorphisms, like the the s allele of the 5-HTTLPR, influence Lithium treatment outcome too. Non responders had significantly more ss genotypes [Rybakowski et al. 2005]. While the ls genotype shows better response [Serretti et al. 2004]. BDNF polymorphisms, like the Val66Met polymorphisms, are also associated with Lithium response [Rybakowski et al. 2005]. A combination of s-alleles of the 5-HTTLPR and Val/Val genotype of the BDNF Val66Met polymorphism leads for example to non response during Lithium treatment [Rybakowski et al. 2007].

5.12.2. Psychotherapy may help to lead to better gene expression

Body and mind are not independent entities. The brain creates our mind and our mind influences our body. Emotions can influence gene expression via hormonal response, signaltransduction and epigenetic changes and thus stressful life events can influence mental health. For example fear leads to arousal of the sympathetic nervous system, which leads to enhanced gene expression of ACTH and cortisol, which influences in consequence several reactions of our body. Thus our way of life leads to epigenetic changes, which can be enherited, because of methylation or acetylation of DNA or histones. Already Engel pleaded in 1977 for the bio-psycho-social paradigma, which includes all 3 dimensions of human life, the biological, psychological and sociological interacting aspects [Engel 1978]. Since our way of life, our feelings and emotions can change gene expression of susceptibility genes, psychotherapy might be an important preventive weapon against bipolar disorder, especially with a genetic predisposition. It might be a helpful tool to resolve stress and childhood traumatas and might help to influence gene expression and epigenetic changes in a positive way. Therefore not only genes can influence our susceptibility toward depression or mania, but also our way of life and our emotions can influence how often and how fast certain genes are transcribed and expressed [Abdolmaleky et al. 2004; Connor et al. 2008; Bogdanovic et al. 2009].

5.12.3. Lifestyle changes

Lifestyle changes may help a little bit to prevent manic or depressive episodes. Extreme sleep deprivation, which can trigger manic episodes, especially with genetic predisposition to bipolar disorder, should be avoided if possible. So shift work, excessive going out or staying up extremely late is contraproductive. A well regulated sleep-wake-cycle will help to prevent manic episodes triggered by extreme sleep deprivation and will reset the molecular clock, which is often disturbed in patients with mood disorders. Another way to influence our dayly rhythms is light therapy. This might be of additional benefit especially in winter time. Clock genes expression is also disturbed by obesity [Kaneko et al 2009]. So loosing weight might help to reorganize the clock gene system. Especially sport would help here, because sport is not only helpful for loosing weight, but also influences BDNF (brain derived neurotrophic factor) in a positive way, which increases neurogenesis and antidepressant effects [Sylvia et al. 2009]. Healthy nutrition with a balanced protein, carbohydrate and vegetable intake might help to loose weight and to prevent depressive episodes. Tryptophan depletion and glucose depletion leads especially in some allele carriers to depressive reactions. So a well balanced

diet might be partly beneficial. Even to eat at regular times would help as a time keeper for the circadian system [Mendoza et al. 2006]. Chronic stress is another point, which should be considered. Extreme dystress over long periods can trigger depressive episodes especially with a predisposing genotype. So everything resolving stress might be useful: autogenic training, sports or better time management.

Table 17: Gene environment interactions leading to mood disorders and possibility of treatment and prevention

Gene-environment-interaction leading to affective disorders	Supporting studies	Prevention + treatment
Obesity	-Kaneko et al. 2009	-Loosing weight: -Healthy and balanced diet -Sport
Stress	-Eley et al. 2004 -Kendler et al. 2005 -Firk et al. 2009 -Holmes et al. 2009 -Müller et al. 2009 -Bambico et al. 2009	-Sport -Coping strategies -Mental training -Psychotherapy -Social support -Time management
Maltreatment	-Caspi et al. 2003 -Kendler et al. 2005 -Kaufman et al. 2006 -Chorbov et al. 2007 -Brown et al. 2008 -Aslund et al. 2009	Prevention if possible! Careful look on depressed children. Early interaction. Social support and psycho-therapy helps to moderate risk of affective disorders after childhood maltreatment! Special trauma therapy. Antidepressant treatment or mood stabilizers.
Winter/Summer	-Christensen et al. 2008 -Volpe et al. 2006 -Volpe et al. 2008 -Volpe et al. 2009	-Light therapy -SSRI
Season of birth	-Torrey et al. 1996 -Mino et al. 2000 -Chotai et al. 2003	-Difficult to influence
Urban/ rural residency	-Jokela et al. 2007	-Moving to more relaxing spot
Rauchen inhibits MAO		-Stopping smoking
Famines (Hungerzeiten) and nutrition	-Carter 2007	-Balanced healthy diet -Enough proteins, carbo-hydrates and vitamines
Tryptophan depletion	-Neumeister 2002	
Sleep deprivation/ shift work		-Sleep hygiene -Avoiding excessive going out -Avoiding shiftwork
Delivery	-Sanjuan 2008	-Professional support after delivery if necessary

6. Conclusion

Bipolar disorder is a highly heritable diasease- this has been proven by many family, twin and adoption studies, as well as by modern genetic approaches. A long list of possible susceptibility genes have been discovered yet (see page 21). Interestingly top candidates belong to the ion channel group- especially ANK3 and CACNA1C are favourite predisposing genes. CACNA1C codes for the alpha1C subunit of the L-type voltage-gated calcium channel and influences verbal fluency aside from other important functions. ANK3 codes for an adaptor protein, which regulates the assembly of voltage-gated sodium channels at axon initial segments. Until now both genes show significant evidence of association with bipolar disorder. Another promising chapter of bipolar disorder research are genes encoding for growth hormones. BDNF seems to be associated with bipolar disorder in Caucasians, but not in Asians. BDNF could even be a laboratory marker for bipolar disorder, because serum levels are decreased in manic, depressed and euthymic states of manic depressive disease. Since BDNF codes for the brain derived neurotrophic factor, which is responsible for neuronal development, synapse formation, serotonergic axon growth, memory acquisition and consolidation, as well as antidepressant effects, a role in pathogenesis of bipolar disorder is not unlikely. A further candidate gene group includes the “clock genes”, like ARNTL, CRY1 and 2, PER1-3 and others. Changes in circadian rhythms are typical features in mood disorder. This goes along with the positive study results for many “clock gene” polymorphisms. Although everybody would expect the serotonin system to play a major role, the serotonin receptor genes are not very likely to influence bipolar disorder a lot. The very well examined serotonin transporter polymorphisms are more likely to be involved in pathogenesis of manic depressive disease. Also other neurotransmitter systems, like the dopamine and noradrenaline systems, do not show overwhelming results. The genes of the GABA and glutamate systems have not been highly investigated yet, but show some positive results. Beside those well examined gene groups a huge list of new detected genes exists. Some might have been found just by chance, so further investigation is necessary to clarify the role of the candidate genes. Nevertheless the benefits of molecular psychiatry research are beyond question. Many gene variants are related with bad treatment response or depressive reaction after maltreatment in childhood, for example the short allele of the 5-HTTLPR deletion polymorphism. Those detected gene-environment-interactions can help to tailor individual therapy plans in the future. Genetic knowledge also helps to clarify nosology. Boundaries between psychiatric diseases are blurred. Schizophrenia, bipolar and unipolar disorders share a huge amount of susceptibility genes (see chapter 5). Although hundreds of

genes have been discussed yet one must not be too enthusiastic. We are still far from elucidation of the underlying mechanism of bipolar disorder. Even though bipolar disorder has a strong genetic background and although association studies, as well as linkage studies, have been carried out for decades, findings are still totally inconsistent. It may be due to too small study sizes. Larger studies are needed to finally elucidate the true susceptibility genes. It could be also due to population stratification. There have been totally diverging results in Asian and Caucasian studies. Future studies have to account for different allele frequencies in different populations and even for gender differences. Another reason for conflicting results might be, that bipolar disorder by itself could be an inhomogenous disease with several subtypes and maybe different susceptibility genes. Maybe even every single individual patient has a unique constellation of susceptibility genes and this could lead to converging study results. It may also just not be possible to find evidence for association for exactly one susceptibility gene. Maybe a group of genes must be investigated for its risk to lead to bipolar disorder. Much more combinations have to be tested. Isn't it a possibility that we have to say goodbye to strict boundaries of psychiatric disease, which existed for centuries? Maybe borders are even more fluent than we think at the moment. As we could see there are strong genetic overlaps between bipolar affective disorder, schizophrenia and unipolar depression. Maybe Kraepelin's dichotomy of psychosis in schizophrenia and bipolar disorder is not valid anymore [Craddock et al. 2005]. Finally we must admit that psychiatric genetics is still in its infancies and we have to overcome teething troubles.

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