Genetics of Bipolar Disorder: an Overview

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Abstract

Bipolar disorder (BPD) is a mood disorder caused by the interaction among a large number of genes and the environment. Recently, with the improvement of genome analysis techniques and the introduction of Genome Wide Association Studies (GWAS), the investigation of the genetic causes of BPD has moved several steps forward, allowing the confirmation of previous results and the identification of new genes involved in the pathogenesis of the disorder. Furthermore, in the last few years, several studies focused on the investigation of rare genetic variants, copy number variants (CNV) and epigenetic modifications, leading to a more complete knowledge of the picture. The aim of the present review is to give to the reader a comprehensive view of the current knowledge about the genetics of BPD, focusing on the most investigated genes and their biological function in the context of the more accepted theories about the pathogenesis of the disorder.
Most confirmed liability genes are involved in the serotoninergic, glutamatergic, GABAergic and circadian systems. In particular, a large amount of evidence was found for glutamatergic NMDA and Kainate receptors and some genes of the glutamate cycle, which are thought to be involved in a possible neurotoxic effect on neurotransmission. Other relevant genes are CLOCK, ARNTL and PER3 which may increase the risk of disease by altering circadian rhythms, through the modulation of the serotonin system.
In conclusion, it is still not possible to determine the exact genetic basis of BPD, because several genes are likely to be involved in the pathogenesis of the disorder, as well as environmental factors. Nonetheless, thanks to recent technological advantages, several steps forward have been made, allowing the identification of the main systems involved in the genesis of BPD. Through further technological improvement and the use of specific endophenotypes, more related to genetic and epigenetic variants compared to BPD itself, in the next few years the identification of the exact genetic basis of BPD might be an achievable aim for psychiatric research.

Key words: bipolar disorder, genetics, epigenetics, endophenotypes

Introduction

Bipolar disorder (BPD), previously called manic-depressive illness, is a chronic mood disorder characterized by the lifetime presence of both episodes of elevated mood (mania or hypomania), and episodes of depression, separated by periods of euthymia ("normal" mood). In some patients mania and depression may rapidly alternate in a form of disorder known as cyclothymia. BPD has a lifetime prevalence of about 1% (1) with no significant difference in worldwide or sex distribution (2). The median age of onset is in the range of 18 and 22 years (1). From the clinical point of view, mania, or hypomania, is a state of elevated mood, physical activity, talkativeness, flow of thoughts, decreased

need of sleep, distractibility; hypomania is an episode less severe than mania. The condition of depression is a state characterized by sadness, guilt, fatigue, apathy or indifference, loss of interest, disturbances in sleep and appetite. Sometimes manic and depressive symptoms may be present at the same time in the so called "mixed state". Both manic and depressive symptoms may lead to an impairment in social and occupational functions (3). BPD is often associated with an increased risk of suicide, as well as with impulse-control and substance use disorders. Furthermore, and of particular interest for general practitioners, there are several medical co-morbidities associated with BPD, such as migraine, heart disease, thyroid disease, and type 2 diabetes (4). Another problem of great interest for the GP concerning BPD patients is their poor compliance with any treatment (including the ones for general medical conditions) that these patients have during both depressive and manic episodes. Taking into account all these aspects of the disorder, the great impact on national health systems is clear. Indeed, the cost of the disorder is estimated as a loss of $14.1 billion salary-equivalent in USA (1). Costs are both direct, consistent with hospitalization and treatment, and also for co-morbidities, and indirect related with the loss of workdays, work performance and through delayed diagnosis (5). Despite the relatively low frequency of BPD in the general population, its heritability is high: the concordance in monozygotic twins is more than 40% (up to 70%) compared with 10% in dizygotic twins. Moreover, adoption studies show that biological parents of bipolar adoptees have a higher risk of being affected by a mood disorder than their adoptive parents (6). Finally, there is strong evidence for a genetic overlap between schizophrenia and BPD (7). All these data provide not only the evidence of the indisputable role of genetics in susceptibility for BPD, but also the proof of an influence of other factors such as environment factors or epigenetic modification in the genesis of the disorder (8, 9). As BPD is a multifactorial and very complex disease where many systems take part in the development and determination of phenotypical traits, the use of the modern technique of genome-wide association study (GWAS) seems to be suitable to reach more consistent results, compared to the candidate gene approach. Indeed, this technique does not require any a priori hypothesis (as opposed to candidate gene studies) and is able to take into consideration about a million SNPs, or copy number variants (CNVs), and duplication or deletion of DNA segments of diverse size. Nonetheless, we have to keep in mind that the picture is even more complicated considering that epigenetic modifications may also alter gene expression; implying that this aspect should also be investigated in order to dissect the exact basis of the disorder. Taking into account all these considerations, the aim of the present paper is to give to the reader a comprehensive view of the current knowledge about the genetics and epigenetics of BPD, focusing on the most investigated genes and their biological function in the context of the more accepted theories about the pathogenesis of the disorder.

Methods

We reviewed all studies published on GWAS, epigenetics, linkage and association studies in BPD in the period comprised from January 2008 and June 2012, updating our previous paper on this issue, which makes an exhaustive review of genetic studies on BPD from 1990 to 2007 (10). For our research we employed both the Medline (http://www.ncbi.nlm.nih.gov/) and PsycINFO® (http://www.apa.org/pubs/databases/psycinfo/) databases, entering the following key words: bipolar disorder, mood disorder, gene, genetics, genome, genome wide association study, GWAS, association, linkage, chromosome. We considered only papers written in English, defining BPD according to DSM (3) or ICD-10 (11) criteria and clearly indicating modifications of genetic or epigenetic expression in patients. No other exclusion criteria were applied. This research was made by two different researchers (R.S. and S.P.) who then compared their results in order to diminish the possibility of rejection of some papers. From a total of 7624 papers, 1056 papers were discarded because they were reviews; the remaining 6568 were screened by reading abstracts and chosen following the criteria specified above: 700 studies were considered for the next step. We read full texts of all 700 papers, but 330 were rejected since they described only particular endophenotypes of BPD or they focused on only pharmacogenetics or neuroimaging aspects. Finally only 370 studies were considered for the present review (data available on request). For each article screened we marked every gene and every SNP investigated. All SNPs not unequivocally associated to a gene were searched in the "SNPper" database (http://snpper.chip.org/bio/snpper-enter-snp). Finally, every gene was put into a specific biological pathway through the "KEGG" database (http://www.genome.jp/kegg/pathway.html).

Since our intent is to summarize the current data in the literature on BPD genetics, the results are discussed in a concise way in order to underline consistent evidence about specific biological pathways.

Results

To provide a background to understand how the biological alterations reported could be implicated in the pathogenesis of BPD, here we briefly synthesize the main pathogenetic hypothesis of BPD (for comprehensive reviews see (12) and (13)). Briefly, although the exact pathogenic mechanism of BPD remains unknown, classical theories have identified main alterations in monoaminergic and chronobiological equilibrium (12), as well as in synaptic plasticity (13). Classical monoaminergic theory postulated that a dysregulation of the serotonin, norepinephrine or dopamine systems could explain the oscillation in mood. Subsequently, with the improvement of neuroimaging studies (14), the role of other neurotransmitters have been hypothesized, such as glutamate and GABA (13, 15), which may be involved in a neurotoxic/neuroprotective mechanisms. Finally, the clinical observation of the sleep-wake rhythm disruption and REM alterations in mood disorder and the efficacy of light therapy in major depressive disorder led us to consider as crucial the sleep disturbances in BPD and, therefore, to hypothesize a role for the genes involved in the modulation of the circadian system (16). In our previous review (10), we identified several genome areas and many genes associated with BPD. Now, with the introduction of GWAS, the study of CNVs, and the examination of large samples, we can extend our previous results. In particular, a large amount of evidence suggested the implication of specific neuronal pathways such as serotoninergic, GABAergic, glutamatergic systems, as well as genes implicated in the regulation of circadian rhythms and genes implicated in signalling transduction or cell maintenance in the pathogenesis of BPD.

Serotonin-related genes

The serotonin (5-HT) system has both inhibitory and facilitatory functions in the brain, where it is possible to find a great density of 5-HT receptors in the thalamus, hypothalamus and dorsal raphe nuclei. 5-HT is an important regulator of circadian rhythms, appetite, pain control and libido. It was an accidental discovery that drugs inhibiting monoamino-oxidase, historically used as anti-tubercular drugs, might lead to a hypomania like condition by increasing serotonin, dopamine and norepinephrine levels. Due to this empirical evidence and to the growing body of evidence of the role of these genes in major depressive disorder (17), in recent years many studies have investigated the possible implication of serotonin genes in the aetiology of BPD (18). Some positive associations were found for HTR1A (19) and HTR5A (20), which have an inhibitory role on neuronal excitability in favour of synaptic plasticity in the serotoninergic synapses. Moreover, in BPD the promoter of HTR1A is found to be hypermethylated, with the consequence of a diminution of gene expression and a decline of receptor function. There is also strong evidence of hypermethylation of the HTR2A (21) promoter region and hypomethylation of its first exon. This receptor, in contrast to HTR1A and HTR5A receptors, is coupled to stimulating G-protein, which activates the transcription of other genes and synaptic plasticity. Consequently, an inhibitory feedback in the presynaptic membrane and its epigenetic alteration may lead to a disruption in serotoninergic biological modulation, particularly in chronic stress conditions.

Table 1. Association studies for serotoninergic system genes.

Gene	Name	N° of association studies (+ positive, - negative)
SLC6A4	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	+++ ---------
TPH1	tryptophan hydroxylase 1	++ -----
TPH2	tryptophan hydroxylase 2	++++++ ---------
HTR1A	5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled	++++ -
HTR1B	5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled	-
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	++++ ---
HTR2C	5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled	++++ ---
HTR5A	5-hydroxytryptamine (serotonin) receptor 5A, G protein-coupled	+
MAOA	monoamine oxidase A	+++ -----

GABA-related genes

GABA is one of the most important inhibitory neurotransmitters, particularly in the mesocortical and mesolimbic pathways, and its receptors are the target of benzodiazepines, as well as of some mood stabilizers. An alteration in its receptors had been implicated in schizophrenia (22), while only marginal associations have been found in BPD. Our research confirms a minor role of the GABAergic system in the pathogenesis of BPD. Indeed among the GABA receptor genes investigated, no metabotropic receptors appear to have any SNP or epigenetic modification of particular interest. On the other hand there are a few positive results for an SNP in the GABRA5 (22) and GABRB2 (23) genes, two subunits of the ionotropic receptor GABAA. This receptor has the function of hyperpolarizing and so decreasing global neuronal excitability, if activated by other neural systems such as the 5-HT or endocannabinoid pathways. Moreover, the biosynthesis of GABA itself has been associated with BPD as well. Particularly, a CNV in GAD1 (24), the enzyme responsible for catalyzing the production of GABA from L-glutamic acid, was associated with the disorder. This CNV leads to a decrease of enzyme activity and consequently to a reduction of GABA level in the synaptic cleft, i.e. a reduction of the main brain inhibitor. All these data suggest a possible role of disequilibrium in GABA inhibiting control in the central nervous system in BPD.

Table 2. Association studies for GABAergic system genes.

Gene	Name	N° of association studies (+ positive, - negative)
GABRA1	gamma-aminobutyric acid (GABA) A receptor, alpha 1	+ --
GABRA3	gamma-aminobutyric acid (GABA) A receptor, alpha 3	+ --
GABRA4	gamma-aminobutyric acid (GABA) A receptor, alpha 4	-
GABRA5	gamma-aminobutyric acid (GABA) A receptor, alpha 5	++ -
GABRB1	gamma-aminobutyric acid (GABA) A receptor, beta 1	-
GABRB2	gamma-aminobutyric acid (GABA) A receptor, beta 2	+
GABRB3	gamma-aminobutyric acid (GABA) A receptor, beta 3	-
GABRR3	gamma-aminobutyric acid (GABA) A receptor, rho 3	-
GAD1	glutamate decarboxylase 1	+++ --
GAD2	glutamate decarboxylase 2	--

Glutamate-related genes

Glutamate is the main excitatory neurotransmitter in the central nervous system and this system has been recently associated with psychosis and schizophrenia (25). When in excess it can exert neurotoxic effects and, in conjunction with high cortisol levels, it has been hypothesized to mediate the deleterious effects of chronic stress on cognition. Consistently, the hippocampus and amygdala, which have a high concentration of glutamate ionotropic receptors, were found to be decreased in volume in BPD (26). Among ionotropic receptors, the mRNA levels of GRIN1 and GRIN3A (27), which encode for NMDA receptors, are increased in BPD post-mortem studies. Moreover, some alterations of DAOA gene products, which degrades an activator of NMDA receptors, has been strongly correlated with BPD (28). Consistently, genetic association studies also found positive associations among both SNPs and CNVs for GRIK4 (29), GRIK5 (30), GRIK2 (24), which encode for kainate receptors, and BPD. Interestingly, NMDA receptors seem to mediate an excitatory activation and neuronal plasticity in postsynaptic cells and preclinical studies provided evidence about the antidepressant-like action of their antagonists (31). On the other hand, kainate receptors have an inhibitory function and loss of their action may be related to maniac behaviour. Among metabotropic receptors, a rare CNV was associated with BPD in the GRM7 gene (32), which encodes for a receptor activating other neuroprotection systems. Therefore, its depletion may lead to disease through losing the functionality of these neuroprotective systems. Finally, in BPD a significantly decreased expression of glutamate transporter SLC1A2 and SLC1A1 (33) and of vesicular glutamate transporter, SLC17A7 (VGLUT1), has been found (34). These alterations lead to a diminished re-uptake and recycling of the neurotransmitter at the presynaptic level, with an easier achievement of toxic neurotransmitter levels. Finally, not only receptors, but also the glutamatergic signal transduction pathway was found to be altered in BPD; particularly, the mRNA expression of the PPP1R1B gene (35), normally associated with synaptic modification due to NMDA stimulation, seems to be modified in BPD patients.

Table 3. Association studies for glutamatergic system genes.

Gene	Name	N° of association studies (+ positive, - negative)
DAOA	D-amino acid oxidase activator	++++++++++ ----------
GRIN1	glutamate receptor, ionotropic, N-methyl D-aspartate 1	++
GRIN2A	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	---
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	+ ----
GRIN2C	glutamate receptor, ionotropic, N-methyl D-aspartate 2C	-
GRIN2D	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	+ -
GRIN3A	glutamate receptor, ionotropic, N-methyl D-aspartate 3A	+
GRIA1	glutamate receptor, ionotropic, AMPA 1	+ -
GRIA2	glutamate receptor, ionotropic, AMPA 2	--
GRIA3	glutamate receptor, ionotropic, AMPA 3	-
GRIA4	glutamate receptor, ionotropic, AMPA 4	--
GRIK1	glutamate receptor, ionotropic, kainate 1	+ -
GRIK2	glutamate receptor, ionotropic, kainate 2	++ -
GRIK3	glutamate receptor, ionotropic, kainate 3	-
GRIK4	glutamate receptor, ionotropic, kainate 4	++
GRIK5	glutamate receptor, ionotropic, kainate 5	++
GRM2	glutamate receptor, metabotropic 2	-
GRM3	glutamate receptor, metabotropic 3	-
GRM7	glutamate receptor, metabotropic 7	++
SLC1A3	solute carrier family 1 (glial high affinity glutamate transporter), member 3	+
SLC1A2	solute carrier family 1 (glial high affinity glutamate transporter), member 2	+
SLC1A1	solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	-
SLC1A6	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	-
SLC17A7	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7	+
SLC17A6	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 6	-
SLC17A8	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 8	-
PPP1R1B	protein phosphatase 1, regulatory (inhibitor) subunit 1B	++ -

CLOCK-related genes

Body temperature, hypothalamic-pituitary-adrenocortical axis function and sleep-wake cycles are examples of circadian rhythms regulated by a primary circadian pacemaker located in hypothalamus, whose zeitgeber is the light which regulates biosynthesis and secretion levels of melatonin by the pineal gland (36). The interest in clock-related genes came from the clinical observation of the disruption of the sleep-wake rhythm in affective disorders. Indeed, in major depressive disorder there is can be insomnia or hypersomnia and early awakening, while in bipolar patients, sleep deprivation may be conducive to a state of hyperactivation. The detail of the specific function of single genes which take part in the modulation of circadian cycles is still not known. Nonetheless, the knowledge about this fundamental system has greatly increased in the last decade. For example, the role of the

CLOCK and ARNTL genes, which are highly correlated with BPD (37), has begun to be clarified. They encode for proteins which form a heterodimer, enhancing the transcription of PER and CRY genes. PER3 and CRY2 genes (37), together with CSNK1D gene (37), are able to activate other pathways involved in preference of diurnal hours for daily activity and sleep hygiene; the aberrant transcription of all these three genes was associated not only with BPD but also with common co-morbidities of BPD, such as alcohol abuse and anxiety disorders (38).

Table 4. Association studies for circadian rhythm genes

Gene	Name	N° of association studies (+ positive, - negative)
AANAT	aralkylamine N-acetyltransferase	--
ARNTL	aryl hydrocarbon receptor nuclear translocator-like	+++
CLOCK	clock homolog (mouse)	++++ --
CRY2	cryptochrome 2 (photolyase-like)	++ -
MTNR1A	melatonin receptor 1A	-
NR1D1	nuclear receptor subfamily 1, group D, member 1	+ --
PER3	period homolog 3 (Drosophila)	+++
PROK2	prokineticin 2	-
CSNK1D	casein kinase 1, delta	+
TIMELESS	timeless homolog (Drosophila)	-

Abbreviations

Gene	Name
AANAT	aralkylamine N-acetyltransferase
ANK3	ankyrin 3, node of Ranvier (ankyrin G)
ARNTL	aryl hydrocarbon receptor nuclear translocator-like
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit
CLOCK	clock homolog (mouse)
CRY2	cryptochrome 2 (photolyase-like)
CSNK1D	casein kinase 1, delta
DAGKH	diacylglycerol kinase, eta
DAOA	D-amino acid oxidase activator
DISC1	disrupted in schizophrenia 1
GABRA1	gamma-aminobutyric acid (GABA) A receptor, alpha 1
GABRA3	gamma-aminobutyric acid (GABA) A receptor, alpha 3
GABRA4	gamma-aminobutyric acid (GABA) A receptor, alpha 4
GABRA5	gamma-aminobutyric acid (GABA) A receptor, alpha 5
GABRB1	gamma-aminobutyric acid (GABA) A receptor, beta 1
GABRB2	gamma-aminobutyric acid (GABA) A receptor, beta 2
GABRB3	gamma-aminobutyric acid (GABA) A receptor, beta 3
GABRR3	gamma-aminobutyric acid (GABA) A receptor, rho 3

GAD1	glutamate decarboxylase 1
GAD2	glutamate decarboxylase 2
GRIA1	glutamate receptor, ionotropic, AMPA 1
GRIA2	glutamate receptor, ionotropic, AMPA 2
GRIA3	glutamate receptor, ionotropic, AMPA 3
GRIA4	glutamate receptor, ionotropic, AMPA 4
GRIK1	glutamate receptor, ionotropic, kainate 1
GRIK2	glutamate receptor, ionotropic, kainate 2
GRIK3	glutamate receptor, ionotropic, kainate 3
GRIK4	glutamate receptor, ionotropic, kainate 4
GRIK5	glutamate receptor, ionotropic, kainate 5
GRIN1	glutamate receptor, ionotropic, N-methyl D-aspartate 1
GRIN2A	glutamate receptor, ionotropic, N-methyl D-aspartate 2A
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2B
GRIN2C	glutamate receptor, ionotropic, N-methyl D-aspartate 2C
GRIN2D	glutamate receptor, ionotropic, N-methyl D-aspartate 2D
GRIN3A	glutamate receptor, ionotropic, N-methyl D-aspartate 3A
GRM2	glutamate receptor, metabotropic 2
GRM3	glutamate receptor, metabotropic 3
GRM7	glutamate receptor, metabotropic 7
HTR1A	5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled
HTR1B	5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled
HTR2C	5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled
HTR5A	5-hydroxytryptamine (serotonin) receptor 5A, G protein-coupled
MAOA	monoamine oxidase A
MTNR1A	melatonin receptor 1A
NR1D1	nuclear receptor subfamily 1, group D, member 1
NRG1	neuregulin 1
ODZ4	odz, odd Oz/ten-m homolog 4 (Drosophila)
PER3	period homolog 3 (Drosophila)
PPP1R1B	protein phosphatase 1, regulatory (inhibitor) subunit 1B
PROK2	prokineticin 2
SLC17A6	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 6
SLC17A7	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7
SLC17A8	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 8
SLC1A1	solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1
SLC1A2	solute carrier family 1 (glial high affinity glutamate transporter), member 2
SLC1A3	solute carrier family 1 (glial high affinity glutamate transporter), member 3
SLC1A6	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6
SLC6A4	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4
TIMELESS	timeless homolog (Drosophila)
TPH1	tryptophan hydroxylase 1
TPH2	tryptophan hydroxylase 2

Other Genes

Among other genes investigated in BPD, genes which encode for proteins involved in signal transduction seem to play a relevant role in the pathogenesis of the disorder. Consistently, the gold

standard of mood stabilizers, lithium, seems to act through the stabilization of the signal transduction cascade, although the exact mechanism of action of this drug is still unknown (39). Main activators of the signal transduction cascade associated with BPD are the CACNA1C (40, 41) and DGKH (42) genes. The first encode for an L-type calcium channel mediating a variety of calcium-dependent processes in neurons. Its variants have also been associated with a severe prolongation of the QT interval in the electrocardiogram, cognitive abnormalities and autism spectrum features. It is involved in serotoninergic, GABAergic and glutamatergic transmission and, together with DGKH, in the modulation of MAPK pathway, which is involved in neural plasticity, proliferation and differentiation. Similar is the action of ANK3 product (41), the function of which is to stabilize the cytoskeleton, to maintain the membrane Na+/K+ channels and to mediate signal in response to cell adhesion. Genes implicated neurodevelopment may also play a role in BDP and alterations in these genes may lead to a disequilibrium in neurotransmission. Among these, are the ODZ4 gene (43), which is involved in transcriptional control of other genes during neurogenesis, the DISC1 gene (28), primarily associated with schizophrenia, which acts by guiding the migration of the cortical interneurons, the NGR1 gene (44), the task of which is to manage myelination, both central and peripheral, by influencing the proliferation of oligodendrocytes and Schwann cells. Finally, also the expression of miRNAs may be modified in BPD during neurodevelopment. Particularly, in BPD these RNA particles, which control gene expression by a post-transcriptional mechanism, are found to be under-expressed (45) and some genes, normally silenced or acting with attenuated transcription by this mechanism, lose their physiological control.

Discussion

BPD is a worldwide public health problem, characterized by fluctuations in mood alternating with periods of normal mood. It is a life-lasting diagnosis which affects patients with both direct symptoms and several co-morbidities, with the consequence of important impairment in both social and economic life. We have endeavoured to provide a comprehensive view of current evidence on the genetic background of BPD, updating our previous paper on this issue (10).

We found an increasing body of evidence supporting the role of multiple neurotransmission and neurodevelopment pathways, which interact differently in the various regions of the central nervous system. The main genetic factors involved in the pathogenesis of BPD seem to be the glutamatergic and the CLOCK-related genes systems, which appear to be the final common effectors of the pathogenetic mechanism, and the GABA and 5-HT systems, which seem to have a modulation role. In particular, the 5-HT system regulates the expression of CLOCK genes in response to light stimuli in the suprachiasmatic nucleus (46) and modulates, in different central nervous system areas, glutamatergic transmission, enhancing or suppressing its transmission directly or through GABA interneurons (47).

Despite this evidence, it is still impossible to detect the specific genetic alterations underlying this disorder. The main problems in achieving this aim are related to the great phenotypical heterogeneity of BPD itself, as well as to the complexity of the genetics of BPD, which is likely to involve several genes and several interactions among them. Finally, epigenetic modifications and environmental effects are also likely to play relevant roles in the pathogenesis of BPD. The improvement of analysis techniques and the analysis of endophenotypes (48) more related to genetic variants, could lead to substantial improvement in the understanding of the basis of this important psychiatric disorder in the next few years. In the future, the exact biological causes of BPD could be revealed, with clear advantages both for determining the prognosis and choosing the correct treatment for this debilitating disorder.

GP Comment

What have I learned from this paper?

Whilst complex genetics are unlikely to be discussed in a primary care consultation, awareness of these issues, and of the neurotransmitter and circadian rhythm consequences, are important as they may explain some of the symptoms (e.g. irritability, insomnia, hypersomnia). Other research may

bring clarity to this area and may have important ramifications for predicting treatment response and perhaps even heritability. A key message is that bipolar disorder has a significant genetic component and a positive (or suggestive) family history should alert the GP to a possible diagnosis of this condition.

Dr Daniel Dietch, Lonsdale Medical Centre

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