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1. ABSTRACT

Bipolar disorder (BD) is a severe chronic multifactorial disease that requires maintenance therapy with mood stabilizers (MS). Even with medications, the rate of response among patients with BD is low and the risk of relapse is high. Therefore, in this context of the urgent need for reliable and reproducible predictors of individual responses to MS, pharmacogenetics research is expected to provide helpful progress. Most pharmacogenetic studies of MS have focused on the response to lithium with several good putative candidate genes but informative results are sparse. There have been few studies on valproate, lamotrigine or atypical antipsychotics. Overall, the results of pharmacogenomics studies have not provided sufficient data to change daily practices in BD significantly and further investigation is warranted to identify highly relevant genetic predictors of response their roles. Although progress still remains to be made, the clinical assessment of a subject including the identification of specific individual phenotypic and pharmacogenetic characteristics is likely to become a powerful instrument for the development of personalized therapies.

2. INTRODUCTION

Bipolar disorder (BD) is a chronic multifactorial psychiatric disorder that is characterized by recurrent alternating episodes of mania/hypomania and depression interspaced with euthymic periods variably affected by residual symptoms and dysfunction (1). BD causes impairment in functioning and health-related quality of life, and BD patients require maintenance therapy (2). The lifetime prevalence of BD is about 1% for the traditional BD I subtype and up to 6.5% if all BD spectrum subtypes are included; thus, it is evidence that BD is a major public health problem (3,4). Indeed, BD is seventh most major cause of disability-adjusted life-years according to the World Health Organization (WHO) (5).

The etiological determinants of BD remain poorly understood; similarly, the mechanisms of action of psychotropic drugs have not been described in detail, and indeed the exact targets are still to be definitively identified. Current guidelines

advocate the use one of a group of variably similar treatment algorithms for all patients, such that the clinical, pathophysiological, and lifetime heterogeneity of BD is not taken into accounts, because of the lack of evidence (2). Thus, personalized therapeutic strategies with targeted interventions —taking into account both individual characteristics and the characteristics of the clinical expression of the disorder in a given individual— are clearly required to improve prognosis. Pharmacogenomics can be exploited to identify key biomarkers and therefore drive innovation in this field of personalized medicine.

Numerous studies have attempted to identify genetic markers that could be used to predict drug efficacy and safety in several fields of medicine. Pharmacogenetics is "the study of variability in drug response due to heredity", and may thus be contribute to the development of 'personalized' treatment strategies in medicine, and including BD. However to date, there is only one US FDA-approved commercial pharmacogenetic test available (Roche Diagnostic, AmpliChip CYP450) which allows genotyping for the two cytochrome P450 genes (CYP2D6 and CYP2C19). Using this chip, patients can be genotyped to help predict the metabolizer status of patients, which may influence choice and dose of antipsychotic or antidepressant medication (6). No clear genetic biomarker for use in routine clinical care in BD has been described.

This is particularly unfortunate because BD patients show a low rate of response, a high risk of relapse and several side effects to MS that are unfortunately not predictable. Indeed, survival analysis of BD patients indicates a 5-year risk of relapse into mania or depression of 73% despite continual and adequate MS medication (7). Even for those who do not relapse, considerable affective morbidity is observed (7). The large EMBLEM prospective study with BD I patients shows that 64% achieved remission and 34% achieved functional recovery at 2 years (8). A naturalistic observation study of the response to MS described very low rates of full response to individual MS: lithium 30%, carbamazepine 0%, valproate 13%, lamotrigine 11%, and olanzapine 25% (9). The predictors were few and uncertain: lithium responders were more likely to be bipolar II with earlier onset of illness, and responders to valproate presented higher rates of psychosis (9). Various evidence indicates that the response to long-term lithium treatment is a familial trait and clusters in families (10). Also, the mode of inheritance of BD responsive to lithium appears to conform to a recessive model with sex-specific penetrance of transmission (11). Evidence for such heritability is consistent with the relevant genes exerting a high-magnitude effect on the response to long-term lithium treatment. Thus, the response to long-term prophylactic treatment with mood stabilizers (MS) has been suggested to be a clinical trait that could be exploited to identify homogeneous subgroups of BD and to map genes relevant to both treatment response and BD itself (12–15). Therefore, informative and helpful results are expected from pharmacogenomics research in this context of the urgent need to find reliable and reproducible predictors of individual responses to MS and MS safety (14,16–18).

We review the current state of, and perspectives for, pharmacogenetic research on MS treatments in BD. First, we consider issues pertaining to the diagnosis of BD patients, sample selection and definitions of treatment response phenotypes used in various pharmacogenetic studies. Then, we review existing evidence for genetic predictors of the response of BD patients to MS treatment. Finally, we discuss the possible challenges and future directions for pharmacogenetics in BD.

3. METHODS

We conducted in March 2013 an extensive review on the pharmacogenomics studies exploring MS treatment in BD. The publications were obtained from the PubMed electronic database. The literature search was performed using the Mesh heading: "Bipolar Disorder" AND ("genetics" OR "gene" OR "pharmacogenomics" OR "pharmacogenetics") AND ("mood stabilizer" OR "lithium" OR "valproate" OR "valproic acid" OR "lamotrigine" OR "carbamazepine" OR "oxcarbazepine" OR "topiramate" OR "gabapentin" OR "antipsychotic"). We also used the related articles function of the PubMed database, the reference list of retained studies and searched Google Scholar to identify additional articles. We included only published data written in English.

4. PHENOTYPIC FEATURES AND DEFINITIONS

A research in pharmacogenetics is confronted by a methodological question: should the response to MS treatment in all BD subjects be studied, or should phenotypically defined subgroups of subjects with BD be studied?

The genetic and phenotypic heterogeneity of BD clearly cloud the identification of its biological determinants (19). The use of valid and consensual definitions for all steps of studies is essential for reliable and comparable results to be obtained. Rigorous definitions of the probands and clear criteria for the definition of treatment are needed to detect causative determinants of differences in response to medication.

4.1. Which phenotype should be assessed for subjects with BD?

Investigations of drug responders (20) and the comparison of patients responsive to different drugs (21) have led to promising results. Responsive patients that differ with respect to course of the disease, comorbidity and family history, may represent distinct subtypes of BD. There is now evidence to suggest that lithium-responsive BD is a core bipolar phenotype (20): responders to lithium show a family history of BD and a familial response to lithium consistent with genetic factors having a prominent role (20). Also, family histories and some clinical characteristics differ between responders to lithium and responders to other MS (20).

BD is a broad-large spectrum with wide range of symptoms. Defining intermediate phenotypes, or homogeneous subgroups within the BD population may be useful. Indeed, the early genetic research with the whole BD spectrum, or even with the traditional BD I subgroup, failed to obtain significant and relevant results (19). Consequently, recent studies focus on more homogeneous subgroups, and there has been substantial effort directed towards phenotypic refinement. The purpose of phenotypic refinement is to select subgroups that differ from the whole BD population as concerns clinical presentation, course of the disease, family history, comorbidities and/or possibly long-term response to treatment (22). Alda proposed a classification based on three main subtypes of BD: (1) classical, (2) psychosis spectrum and (3) 'characterological' which includes cases with distinct clinical characteristics and specific patterns of drug treatment response that might lead to more targeted treatment (23).

Such phenotype selection of BD populations aims to increase the probability of identifying genes of interest. They highlight the importance of careful diagnostic assessment of BD cases, with attention to specific clinical features, family history, comorbidities and clinical course as these factors may be closely linked to the treatment response phenotype.

4.2. How should treatment response phenotypes be assessed?
Assessment of treatment response phenotypes is central to identifying the role of genetic factors in determining a subject's response to a drug or the onset of adverse drug reactions (ADR). The definitions of treatment response used in the literature are often not clear and divergent between pharmacogenetic studies. Defining treatment response phenotypes is expected to be highly complex, largely because the clinical quantification of the response to treatment is complex.

The simplest phenotype is dichotomous (responders/non-responders) and has been used in most pharmacogenetic studies of MS (14). Nevertheless, a binary trait of this type does not allow correct measurement of the response to a drug, which is, constitutively, a quantitative trait. Indeed, such binary measurement does not reflect the clinical reality because most patients show partial responses and very few of presented a full response to MS (9). If a categorical approach is used, partial responses to a drug can be usefully assessed in addition to the classical traits of responders/non-responders. Applying a dimensional approach, the response to MS is studied as a quantitative trait, and this may facilitate the identification of genetic variants and their expression associated with a wide range of intermediate phenotypes. The dimensional approach allows the degree of variation in the treatment response phenotype to be studied, and this contrasts with the dichotomous approach that only the two extreme points of the dimensional gradient into account. Moreover, combining assessment of the response to treatment as measured from the improvement of BD symptoms, with assessment of treatment side effects, as with the Clinical Global Impressions Scale (CGI), might be useful to separate out the two effects (24). The method of "extreme discordant phenotype" (EDP) may increase the statistical power and consequently the probability of detecting gene variants associated with drug efficacy or toxicity (25). Alternatively, individual trait values, for example treatment response, can be used as indices for phenotype selection, and selective genotyping has been proven to be effective for mapping quantitative trait loci (QTL) (26).

The definition of treatment response is complex, especially in BD: several factors have to be considered, including the long-term response to MS, the severity and the duration of episodes before and after the introduction of the MS, the presence of possible confounders, for example multiple pharmacotherapy, and the degree of compliance. Thus, stringent definitions are tricky to establish, and several tools have been proposed. The average Affective Morbidity Index and the Illness Severity Index are both analytical tools (27) (28). They each provide a quantitative evaluation of the improvement under MS and take into account both severity and duration of episodes before and after the introduction of MS treatment. However, they suffer limitations because they do not take the presence of confounders into account, such as compliance or poly-pharmacotherapy. Grof *et al.* recently compared response to long-term lithium treatment in bipolar relatives of BD lithium responders and BD controls, and proposed a more complete rating scale referred to as the "Alda scale" (10). It is a quantitative scale for measuring the degree of improvement under MS taking the presence of confounders into account. As well as allowing improvement due to MS only to be observed, it also permits both an intermediate phenotype approach (partial response to MS) and an EDP approach (10). This approach involves rating the degree of response on a 10-point scale ("A" criteria) and the number of episodes off the treatment, the frequency of episodes off the treatment, the duration of treatment, the compliance during period (s) of stability, and the use of additional medications during the periods of stability ("B" criteria); a total score from 0 to 10 is then obtained by subtracting B from A criteria (10).

However, irrespective of the definition used, we observed that the rate of response to various MS treatments in monotherapy is always close to 50% (and about 30% for placebo), with an incremental benefit of about 20% when adding a second MS agent (29). Thus, treatment refractoriness in BD remains a substantial medical challenge. We believe therefore that it is very important to identify markers that are predictive of the response to MS treatments; this may involve the identification of genetic variant patterns that can be used to help choose between different molecules available as treatment in routine practice.

5. PHARMACOGENOMICS OF MOOD STABILIZERS

5.1. Lithium

Lithium salts are the best studied MS and remain a cornerstone of treatment in BD. Pharmacogenetic studies have for the most part focused on the response to lithium prophylaxis as a way to define a more homogeneous population (Table 1).

5.1.1. Linkage studies on the response to lithium

Linkage studies on the response to lithium were the first to generate relevant and informative results. Analysis of the Faroese population with eight lithium-responsive BD probands provided evidence of increased haplotype sharing on the distal part of chromosome 18q23, confirming the preliminary findings for this region by Freimer *et al.* (30). A linkage study focused on this region of chromosome 18: in the sample of lithium-responsive BD probands including only unilineal families, two chromosomal regions with modestly positive LOD scores were found at D18S53 and at D18S61 for maternal and paternal pedigrees, respectively (31). Further linkage studies using a temperament-based measure (cyclothymic temperament) as a quantitative intermediate phenotype found the highest linkage on chromosome 18p11 and weaker linkage for chromosomes 3 and 7 (32). Consequently, chromosome 18 is a potential region of interest and quantitative measures may lead to the detection of loci for BD and maybe for the response to lithium. Work with a very large pedigree derived from a homogeneous population in Quebec from Saguenay-Lac-St-Jean area found the chromosome 12q23-q24 region to be linked with the response to lithium in a BD population (33). Linkage to chromosome 12q24 was confirmed later in a larger study in the same population, and other regions of lower interest were found on chromosomes 2, 5, 7, 9, 10, 17 and 20 (34). Evidence for linkage was found in 31 BD families identified as excellent lithium responders with loci on chromosomes 15q14 and 7q11.2 (35); considering response phenotype, this study also suggests that chromosome 7q11.2 may be more involved in the response to lithium than chromosome 15q14, which was implicated in the etiology of BD (35). These observations highlight how it is important to pay attention to the interpretation of studies of this type. Indeed, comparing responders to non-responders allows treatment response genes to be identified, whereas studying BD responders alone only allows conclusions about genes associated with the disease. A very relevant recent linkage study considered 36 families recruited through responsive probands to long-term lithium treatment; it involved an initial linkage study followed by fine mapping and gene expression analysis. Exploiting these two complementary strategies, the authors found evidence of linkage to lithium-responsive BD in 3p25, 3p14 and 14q11 regions; they also found significantly deregulated synaptic and mitochondrial genes in these regions (36).

These linkage studies on the response to lithium generated enthusiastic results and should also be performed in the future on the "non-response" phenotype. Moreover, some methodological issues, such as spontaneous remission of the illness, will have to be addressed.

5.1.2. The candidate gene approach
5.1.2.1. The inositol pathway

Selecting candidate genes for pharmacogenetic investigation is difficult because the exact mechanism of action of lithium remains unclear (37). Lithium inhibits the activity of several enzymes including those involved in the phosphatidylinositol cycle and in phospholipase C signal transduction that may be responsible for mood stabilization. Williams RS *et al.* reported that the effects of MS (including valproate and carbamazepine as well as lithium) are mediated through action on inositol depletion (38). They demonstrate that all three drugs inhibit the collapse of sensory neuron growth cones and increase growth cone area, and that this action is reversed by inositol (38). Consequently, numerous candidate gene studies on the response to lithium prophylaxis have addressed inositol-related genes.

The hypothesis that inositol polyphosphate 1-phosphatase (INPP1) in the phospholipase C signaling pathway is a putative target of lithium has been investigated: several pharmacogenetic studies have tested for associations between polymorphisms in the *INPP1* gene and the response to lithium of BD patients. An association between the C973A variant of the *INPP1* gene and good efficacy of lithium in BD has been reported (39), but not subsequently confirmed by Michelon *et al.* (40).

Candidate genes studies have drawn attention to the myo-inositol monophosphatase 2 (*IMPA2*) that encodes an enzyme of the phosphatidylinositol signaling system and is inhibited by lithium (41). One study compared good responders to lithium treatment with the poor responders among 237 parent-offspring trios, 174 cases and 170 controls: this study reported a trend for significant associations in predicting the response to lithium treatment for two polymorphisms (41). The two polymorphisms of *IMPA2* on chromosome 18p11.2 were confirmed in a supplementary study (42). Two studies found no association between the polymorphisms of myo-inositol monophosphatase 1 (*IMPA1*) on chromosome 8q21.13-21.3 with variation in the response to lithium treatment in cases of BD (42,43). Generally, preliminary studies implicate several enzymes related to inositol phosphate metabolism and therefore the genes of this pathway may be suitable targets for studies of the action of lithium.

Diacylglycerol kinase eta (DGKH) is a key protein in the lithium-sensitive phosphatidyl inositol pathway responsible for the recycling and degradation of diacylglycerol (DAG). A recent genome-wide association study implicates the diacylglycerol kinase eta gene (*DGKH*), and found the strongest association signal at a marker within the first intron of *DGKH* (44). However, study of a sample of 199 Sardinian BD patients characterized for the response to lithium therapy did not replicate the association with *DGKH* polymorphisms (45), and an additional study in 91 subjects characterized for lithium response did not find an association but the sample was too small to detect anything other than large, strong effects (46).

Several studies have tested the phospholipase C-gamma 1 (*PLCG1*) gene that codes for a gamma-1 isozyme of phospholipase (PLC), an enzyme of the inositol pathway second messenger system. One study reported a positive association for one *PLCG1* polymorphism in 136 excellent lithium responders compared to 163 controls (47). The same authors screened the *PLCG1* gene for functional polymorphisms and identified three polymorphic sites in three different exons (exons 9, 26, 31); however, none of the markers was found to be associated with BD in a sample of 133 excellent responders to lithium and 99 healthy controls (48). Because of the absence of a comparison non-responder group, these two studies only show that the *PLCG1* gene is associated with BD. A recent study tried to confirm the findings that bipolar patients with an excellent response to lithium treatment have a higher frequency of a specific dinucleotide repeat allele in the *PLCG1* genomic region; however, this was not replicated in a sample of Norwegian lithium-treated bipolar patients sub-classified as lithium responders, non-responders, or partial-responders/unclassified (49). Only a *PLCG1-8* repeat was more frequent among lithium responders than controls when analysing according to presence or absence of different dinucleotide alleles (49). Although further studies are needed to explain these contradictory results, work in the inositol pathway shows promise and generates helpful findings.

5.1.2.2. The circadian signaling system

There is interest in variants of genes associated with the molecular clock, as some of these genes encode enzymes that are inhibited by lithium, for example glycogen synthase kinase 3 alpha and beta (GSK3α and GSK3β). Lithium acts on these enzymes either by direct inhibition or indirectly by regulating other mechanisms like the formation of a signaling complex comprised of beta-arrestin 2 (βArr2) and Akt. (50). Benedetti *et al.* studied the association of *GSK3β* (-50 T/C) polymorphism with the therapeutic response to lithium among 88 bipolar type I patients: the recurrence index for homozygotes for the wild variant (C/C) did not change under treatment, whereas carriers of the mutant allele showed improvement. This thus suggests that the long-term response to lithium in bipolar illness is influenced by the *GSK3β* -50 T/C polymorphism (51). However, contradictory results have been reported: one study concluded that this polymorphism is not related to the response to prophylactic lithium (52) and another found no association (40). GSK3β also phosphorylates and stabilizes the orphan nuclear receptor REV-ERBα, one of the principal components of the circadian rhythm system that is involved in the cyclic regulation of Brain and Muscle Arnt-like protein-1 (BMAL1). Lithium induces degradation of REV-ERBα and *BMAL1* gene expression, implicating REV-ERBα as a target of lithium in its mechanism of action (53). The association of the gene encoding for REV-ERBα (*NR1D1*) and the response to lithium prophylaxis in BD patients has been investigated in a sample of 199 Sardinian BD patients characterized for the response to lithium therapy; the interaction analysis did not show any significant effect of any *NR1D1* polymorphisms (45). However, more recently, Campos-de-Sousa *et al.* observed a significant association between the variant rs2314339 in *NR1D1* and the response to lithium (54). Further evidence of a role for REV-ERBα in the therapeutic mechanism of lithium has recently been described. McCarthy *et al.* conducted a candidate gene association study for 16 variants in seven circadian clock genes and the response to lithium of 282 Caucasian patients with BD (55). They found that a variant in the promoter of *NR1D1* (rs2071427) and a variant in cryptochrome-1 (*CRY1;* rs8192440) were nominally associated with the response to lithium (55). Also, *GSK3β* and *NR1D1* genotypes considered together predicted the response to lithium robustly and additively; the response was proportional to the number of response-associated alleles (55).

Glucocorticoid receptors are regulators of the circadian rhythm. A polymorphism of the glucocorticoid receptor gene (*NR3C1*) on chromosome 5q31-32 is associated with lithium responder status (56). Although the mechanism of action of lithium is not understood, it clearly interferes with the expression of circadian genes and this is involved in its mood stabilizing effect (53). These first results from pharmacogenetic studies with the circadian system are promising but still preliminary and further replications are required.

5.1.2.3. The neurotransmitter system: serotonin, dopamine and GABA pathways

Serretti *et al.* explored the dopamine, GABA and serotonin pathways and did not find any association between the efficacy of lithium and polymorphisms at the genes of any of the following: the D2 receptor (57), the D3 receptor (58), the D4 receptor (57), the γ-aminobutyric acid (GABA) type A receptor α-1 subunit (57), and the 5-HT2A, 2C and 1A receptors (59). The same authors found an association between a functional polymorphism in the upstream regulatory region of the serotonin transporter gene (*5-HTTLPR*) and the prophylactic efficacy of lithium: *5-HTTLPR* s/s variants were associated with a worse response to lithium than either l/s and l/l variants (60). These *5-HTTLPR* s/s and l/s variants showed a significant epistatic interaction with the Val/Val genotype of brain-derived neurotrophic factor (*BDNF*) and response to lithium prophylaxis in a sample of 107 BD patients (61). In the study by Michelon *et al.*, the *5-HTTLPR* gene and *BDNF* gene variants were not predictive factors for the response to lithium prophylaxis (40). Manchia *et al.* investigated several polymorphisms of genes of the neurotransmitter system, including the *DRD1, DRD2, DRD3, DAT1, 5-HTTLPR* and *HTR2A* genes, for association with response to lithium prophylaxis in a sample of 155 Sardinian BD probands (62). No association was found between the polymorphisms of these genes and the response to lithium treatment (62). A recent association study involving *DRD1* showed an association between allele G at −48 A/G and a worse response to lithium (63). An additive association analysis of *5-HT2A* and *5-HT2C* serotonin receptor gene polymorphisms and the response of BD patients to lithium prophylaxis found no association (64). To summarize, four studies have reported associations between genotypes carrying the *5-HTTLPR* s allele and a worse response to lithium (60,61,65,66). An association and linkage study confirmed the absence of association between the response to lithium and GABRA3, GABRA5 and GABRB3 subunits of the GABAA receptor (67).

Enzymes involved in the synthesis/catabolism of amines, including neurotransmitters, may be of relevance. Serretti *et al.* did not find any association between the prophylactic efficacy of lithium in mood disorders and the following variants of enzymes in the corresponding pathways: catechol-O-methyltransferase (*COMT*) G158A, monoamine oxidase A (*MAO-A*) 30-bp repeat, and G-protein beta 3-subunit (*Gβ3*) C825T (68). A further association and linkage study found no association between *MAO-A* and the response to lithium (69). The prophylactic efficacy of lithium may depend in part on variants of the tryptophan hydroxylase (*TPH*) gene, which is a serotonin-related gene. Subjects with the *TPH* A/A variant showed a trend toward a worse response to lithium than subjects with either *TPH* A/C or *TPH* C/C variants (70). An association study focused on the gene encoding tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis: it revealed no association in 54 patients with the long-term response to lithium monotherapy (71).

To conclude, the serotonin-related genes of the neurotransmitter system, and in particular the serotonin transporter gene, show the strongest evidence of interactions with the response to lithium prophylaxis.

5.1.2.4. The BDNF/TrkB signaling pathway

BDNF-related genes have been implicated in the pathogenesis of BD and in the mechanism of action of lithium. Rybakowski *et al.* showed extreme differences in response to lithium prophylaxis between subjects according to their *BDNF* polymorphisms (61). Subsequent studies tended to validate this result and the Val/Met *BDNF* genotype at the Val66Met functional polymorphism showed a positive association with better response to lithium in a sample of 88 BD patients (72). The same authors provided a supplementary study investigating the association in the *BDNF* gene and polymorphisms in the gene encoding the neurotrophic tyrosine kinase receptor type 2 (NTRK2) (73). Among the four *BDNF* polymorphisms tested, two (C/G (rs988748) and G/A (rs6265)) showed an association with the response to lithium prophylaxis (73). No association was found between the response to lithium and either the interaction of *BDNF* and *NTRK2* genes or polymorphism of the *NTRK2* gene alone (73). The Michelon *et al* and Masui *et al* studies did not find such results for *BNDF* (40,74).

Lithium inhibits glutamatergic transmission via NMDA receptors, and the src-family tyrosine kinases (FYN) belong to the protein kinase family that phosphorylates NMDA receptor subunits, participating in the BDNF/TrkB signal transduction pathway. A marginal association between *FYN* polymorphisms and a worse response to lithium in 101 BD patients has been reported (75). The same authors investigated the association between three polymorphisms in the NMDA receptor 2B subunit (GRIN2B) gene and the response to lithium but did not find a significant association (76).

These various findings suggest that the BDNF/TrkB signal transduction pathway may play a key role in the response to lithium prophylaxis.

5.1.2.5. Other signaling pathways

Lithium may affect the cyclic adenosine monophosphate (cAMP) pathway of signal transduction. The first relevant genetic study of BD found significant associations with the *CREB1, CREB2* and *CREB3* genes of this pathway (77). In a BD sample of 180 lithium responders and 69 non-responders, and 127 controls, the same authors found that two *CREB1* polymorphisms may be associated with BD and/or the response to lithium (77). In the same sample, there was no association between the propyl endopeptidase (*PREP*) gene l and the response to lithium (78).

The endoplasmic reticulum (ER)-stress response, a potential pathophysiological mechanism of BD, involves various molecules including the X-box-binding protein 1 (*XBP1*). An association between the response to lithium and -116C/G polymorphism of XBP1 has been reported in Japanese BD patients (79). In the same BD Japanese population, this association was further confirmed, with -116C allele carriers showing a better response than -116G homozygotes to lithium (80). The same authors found a significant association between the breakpoint cluster region (*BCR*) gene and the response to lithium, observing that the allele frequency of the Asn796Ser single-nucleotide polymorphism was significantly higher in non-responders than in responders (81).

The protein kinase C (PKC) pathway is an important mediator of several intracellular responses to neurotransmitter signaling. It has therefore been the subject of investigation, but a recent study failed to show any positive association between the response to lithium and PDLIM5 (PDZ and LIM domain 5), an adaptor protein that selectively binds the isozyme PKC (epsilon) to N-type Ca (2+) channels in neurons (82). Silberberg *et al.* investigated the calcium channel gamma-2 subunit (*CACNG2*, Stargazin) gene on 22q13.1 and found that three single nucleotide polymorphisms (rs2284017, rs2284018, rs5750285) were significantly associated with the response to lithium (83).

These preliminary results need to be replicated before any conclusions can be drawn. Polymorphisms of the genes for activating enhancer-binding protein 2 beta 3 (*AP2-B*), the myristoylated alanine-rich C-kinase substrate (*MARKS*) and the beta-adrenergic receptor kinase 2 (*GRK3, BARK2*) have been found not be to associated with the response to lithium (40,84). Rybakowski *et al.*, who had previously reported an association between BD and a functional polymorphism of matrix metalloproteinase-9 (*MMP-9)* gene, tested for its involvement in the response to lithium and were unable to find any such association (85).

Recently, Rybakowski *et al.* aimed to replicate some of these earlier findings and tested the association of 14 gene polymorphisms with the quality of the response to lithium prophylaxis (86). The authors confirmed an association between the response to lithium and the polymorphisms of *5HTTLPR, DRD1, COMT, BDNF* and *FYN* genes, but not those of *5HT2A, 5HT2C, DRD2, DRD3, DRD4, GSK-3, NTRK2, GRIN2B* and *MMP-9*. A list of these pharmacogenetic studies is provided in Table 1.

5.1.3. Genome Wide Association Studies (GWAS) on the response to lithium

An international consortium on lithium genetics (ConLiGen, www.conligen.org) is currently driving an international effort to elucidate the genetic underpinnings of the response of BD patient to lithium. The consortium aims to establish the largest ever sample of cases of BD characterized for their response to lithium treatment suitable for genome-wide studies (87). In particular, there is a particular effort to develop stringent definitions for the response phenotypes. This consortium has not yet published or made available any results, but the scientific community is awaiting the findings with high hopes.

An early report described a sample of 359 BD patients characterized for the response to lithium and who were participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort (88). The associations identified did not reach genome-wide significance, but the findings for two regions, on chromosome 10p15 (rs10795189) and chromosome 4q32 including a gene coding for the glutamate/alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionate (AMPA) receptor GRIA2, indicate that they deserve further examination (88). Squassina *et al.* performed a GWAS in a sample of 204 Sardinian patients with BD characterized for response to lithium and found an association, supported by quantitative trait analysis, for a single nucleotide polymorphism (SNP) in intron 1 of the amiloride-sensitive cation channel 1 neuronal (*ACCN1*) gene (89). This cation channel has high affinity for sodium and is permeable to lithium and consequently is a putative genetic marker of lithium efficacy for patients with BD (89). However, this possibility needs to be confirmed. McCarthy *et al.* used a multi-level approach focusing on associations between circadian clock genes and BD compared to controls, and also considered the response to lithium (90). They reconciled discordant results from earlier GWAS and candidate gene studies by identifying recognized and previously unrecognized associations between clock genes and BD-spectrum illnesses (90).

The results of these various approaches and the findings generated argue for continued GWAS of the response to lithium in BD patients.

5.2. Pharmacogenomics of other mood stabilizers

Almost all pharmacogenetic studies of MS have focused on the response to lithium but informative results are sparse. The situation for other MS is similarly, in addition to fewer reported studies. Thus, there is little evidence available for valproate and even less for lamotrigine. Lastly, we will review current evidence about atypical antipsychotics' pharmacogenetics.

5.2.1. Valproate (VPA)

The mechanism of action of valproate (VPA) is poorly understood and several hypotheses exist. The X-box-binding protein 1 (XBP1) is involved in the endoplasmic reticulum (ER)-stress response, and the 116C/G polymorphism in the promoter region of the corresponding gene is known to be associated with BD. An association between this polymorphism and the response to VPA has been reported (91): in a sample of 51 BD patients the G allele was associated with a better response to VPA than the C allele (91). The transcription activity of *XBP1* was lower for the G allele than for the C allele. Thus VPA increases the endoplasmic reticulum (ER)-stress response, which is compromised by the G allele. Similarly, association between the -116C/G polymorphism and the clinical efficacy of lithium has been observed consistent with the notion that the *XBP1* gene product is involved in the response to MS (91).

The Val158Met polymorphism in the *COMT* gene is another candidate gene in the response to VPA and to lithium; its role was examined in a sample of 144 BDI patients and 157 controls (92). The study found that the Met/Met genotype was more frequent in non-responders than in responders to MS (either lithium, VPA or carbamazepine), whereas no differences were detected between BD patients and controls. Unfortunately, the sample was pooled for types of MS and therefore the study is uninformative about the role of *COMT* Val66Met in the response to individual mood stabilizers (92). Further studies with a larger numbers of subjects are required to elucidate the role of *COMT* gene polymorphism in the therapeutic response of BD patients to mood stabilizer.

5.2.2. Lamotrigine (LTG)

A pharmacogenetic study based on the response to LTG has been performed in 85 LTG-treated BD I depression patients. Polymorphisms in the dopamine D2 receptor (*DRD2*), dopamine β-hydroxylase (*DBH*), glucocorticoid receptor (*NR3C1*), histamine H1 receptor (*HRH1*) and melanocortin 2 receptor (*MCR2*) genes were associated with the response to treatment (93). As far as we are aware, this is the only pharmacogenetic study addressing LTG to be reported, no other results of studies of this type, relevant to conventional MS, have been published. Several pathways seem to be involved in the response to LTG, and might be, at least in part, shared by lithium and other conventional MS.

5.2.3. Atypical antipsychotics (AAP)

Antipsychotic medication is widely used, being prescribed to between 72% and 92% of patients with mania (94). Despite this extensive use of AAP in the treatment of BD, pharmacogenetic studies are again lacking and very few studies have investigated the genetic underpinnings of the therapeutic response. Furthermore, these few studies only included patients during acute phases of BD.

Perlis *et al.* investigated common genetic variations for association with clinical improvement in a cohort of 88 BD I depression patients following treatment with an olanzapine/fluoxetine combination (OFC) (93). They found significant associations between polymorphisms in the dopamine D (3) receptor (*DRD3*) and *HRH1* genes, and response to OFC (93). Subsequently, in the same population, they found an association between the response to OFC and polymorphisms in the norepinephrine transporter (*SLC6A2*) gene, the melanocortin 3 receptor (*MC3R*) gene and the tryptophan hydroxylase 2 (*TPH2*) gene (95).

Furthermore, Dávila *et al.* investigated the role of the *COMT* Val158Met polymorphism in the plasma concentration of catecholamine metabolites and clinical features in 42 BD I patients (96). Authors found no significant association with the response to olanzapine treatment or with any of the markers tested, including the plasma concentrations of metabolites of dopamine (homovanillic acid; HVA) and of noradrenaline (3-methoxy-4-hydroxyphenylglycol; MHPG). Nevertheless, in the homozygous Val-Val group, a non-significant aggregation of BD patients presenting with psychosis was found; and clinical improvement significantly correlated with the plasma concentration of MHPG prior to treatment. The preliminary findings of these two studies are of interest and further work on these issues would be fruitful.

Table 2 presents published pharmacogenetic studies of the response to various mood-stabilizing medications. In view of the widespread and increasing prescription of antipsychotics to patients with BD further research efforts in pharmacogenetics to identify possible genetic predictors of response would be extremely valuable.

6. SUMMARY AND PERSPECTIVES

To prescribe MS appropriately to patients, predictors of the response are required. Various genetic markers are considered to be promising candidates. In this review, we present diverse findings that are promising, and further investigation is warranted for confirmation. It seems very likely that the response to MS has a complex genetic heritability. Candidate genes associated with BD display relatively low odds ratios (OR) and minor allele frequencies (MAF), and therefore it is unlikely that the response to MS is determined by common variants with large effect-sizes.

Furthermore, specific clinical features, family history, comorbidities and clinical course are factors that may be closely linked to the MS response phenotype and thus may help to understand its complex genetic heritability. For example, A. Bremer *et al* observed that polymorphisms in *NTRK2* and *INPP1* genes were associated with the response to lithium, and also with both suicidal ideation and post-traumatic stress disorder; this indicates that the response to lithium in BD and clinical co-morbidities share, at least partly, genetic determinants (84).

This review leads us to suggest several putative goals for pharmacogenomics research in BD: genetic research in mood disorders can be reasonably expected to contribute in the following areas associated with treatment effects: 1) prediction of treatment response in individual patients; 2) prediction of side effects; 3) development of personalized therapies; 4) identification of homogeneous clinical subgroups of BD for genetic studies; 5) identification of causative determinants of BD; 6) identification of new treatment pathways; 7) development of gene therapy for BD; and 8) findings that are relevant to other psychiatric diseases. Some of the goals that we believe are important for pharmacogenomics research in BD are summarized in Figure 1.

These approaches are however subject to several limitations, and as a consequence of some of them, the interpretation of pharmacogenetic results can be difficult (summarized in Table 1 as relevant to the efficacy of lithium prophylaxis). First, diagnostic heterogeneity in patient groups prevents rigorous comparison between studies. The definitions of the response to MS (see table 1 and 2) are not consensual and differ between studies. Clearly, valid and consensual definitions of probands and clear criteria for the definition of the response to MS are needed for results to be reliable and comparable.

Also, most of the candidate genes studied were chosen for their possible association with mood disorders, rather than for their putative role in the mechanism of action of lithium or other MS. Future studies on biological and genetic factors associated with lithium response will have to consider potential confounders such as compliance and co-administration of circadian rhythm therapy, other psychotropic drugs or psychotherapy. Finally, sample sizes in these studies are often small; prospective studies with larger samples are required to study the response to MS.

7. CONCLUSION

To date, the results from pharmacogenomics studies are not sufficiently abundant, informative or conclusive to have significantly changed daily practice in the management of BD. The clinical assessment of a subject with the identification of specific individual phenotypic and pharmacogenetics data may nevertheless become a powerful approach for the development of

personalized therapies. Further pharmacogenomics studies are needed to validate reliable and reproducible predictors of individual responses to MS and MS safety. Advances made in pharmacogenomics may help the clinician select appropriate effective treatment and monitoring, leading to more personalized treatment algorithms that are currently lacking for BD.

8. ACKNOWLEDGEMENTS

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Table 1. Pharmacogenetic studies on the response to lithium in bipolar disorder

Gene	Sample	Association (Yes/No)	Study design	Definition of response	Reference
The inositol pathway					
INPP1	a) 23 BD + 20 controls b) 54 BD I + 50 controls	a) Yes b) No	Retrospective	a) R: demonstrated "complete lithium response" b) R: demonstrated "long and complete remission" on lithium alone	(39)
	134 BD I	No	Retrospective	R '' Good responders'': no recurrence of impairing symptoms, or recurrence of mild symptoms, promptly controlled by adjusting the lithium dose or with short courses of benzodiazepines but no other medication. PR : lithium level ≥0.6 mEq/l with improvement of the recurrence pattern in spite of being mildly depressed or hypomanic while on monotherapy.	(40)
	184 BD (92R, 92NR)	Yes (in BD with post-traumatic stress disorder)	Retrospective	R: rated retrospectively from standardized interviews and medical records	(84)
IMPA2	237 parents-offspring trios and 174 cases ascertained for their response to lithium and 170 controls	Yes	Retrospective	'' Good responders'': patients recruited for genetic association studies had clearly shown a good response to lithium ''Poor responders'': some of these patients experienced no benefit at all	(41)
	a)44 Norwegian lithium-treated patients with BD b) 75 nuclear families from a Palestinian Arab trio sample with BD	a) No b) Yes	Retrospective	a) classified retrospectively according to the clinical history, with comparison of the frequency, duration and severity of episodes before and after treatment b) demonstrated "long and complete remission" on lithium alone	(42)
	184 BD (92R, 92NR)	No	Retrospective	R: rated retrospectively from standardized interviews and medical records	(84)
IMPA1	184 BD (92R, 92NR)	No	Retrospective	R: rated retrospectively from standardized interviews and medical records	(84)
	a)44 Norwegian lithium-treated patients with BD b) 75 nuclear families from a Palestinian Arab trio sample with BD	a) No b) No	Retrospective	a) classified retrospectively according to the clinical history, with comparison of the frequency, duration and severity of episodes before and after treatment b) demonstrated "long and complete remission" on lithium alone	(42)
	21 BD patients (7R, 7NR, 7UN)	No	Retrospective	classified retrospectively according to the clinical history	(43)
DGKH	91 BD lithium responders (24FR, 67PR+NR)	No	Retrospective	Response to lithium: assessed using the scale of Grof *et al.* (24).	(46)
	199 BD lithium responders (57FR, 142PR+NR)	No	Retrospective	Response to lithium: assessed using the scale of Grof *et al.* (24).	(45)
PLCG1	a) 136 BD lithium responders 163 controls b) 32 families ascertained through lithium-responsive BD probands	a) Yes b) Yes (when unilineal families were considered)	Prospective	Response to lithium was evaluated prospectively with an average follow-up of 14.4 ± 6.8 years.	(47)
	133 BD lithium responders	No	Prospective	Patients were stabilized on lithium monotherapy for an average of 14.4 ± 9 years	(48)

	99 controls				
	61 BD (29R, 16NR, 16PR/UN)	No (only a PLCG1-8 repeat was more frequent among R)	Retrospective	Retrospectively subclassified as lithium R, NR, or PR/UN according to the clinical history, with comparison of the frequency, duration and severity of episodes before and after lithium therapy.	(49)
The circadian signaling system					
NR1D1	199 BD lithium responders (57FR, 142PR+NR)	No	Retrospective	Response to lithium: assessed using the scale of Grof *et al.* (24).	(45)
	170 BD	Yes	Prospective	R: minor or modest improvement in frequency of episodes or admissions.	(54)
	282 BD (148R, 134NR)	Yes	Retrospective	R: if there was a 50% reduction in the frequency and/or severity of symptoms on Li. NR: if less than 50% symptom reduction.	(55)
NR3C1	115 BD (30ER, 58PR, 27NR)	Yes	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to pre-lithium period NR: < 50% reduction, no change or worsening in the episode index, defined as number of episodes per year compared to the pre-lithium period.	(56)
GSK3β	88 BD I lithium responders	Yes	Prospective	Efficacy of lithium was evaluated by calculating the difference between the "pre-lithium treatment recurrence index" and the "on-lithium treatment recurrence index".	(51)
	134 BD I	No	Retrospective	R '' Good responders'': no recurrence of impairing symptoms, or recurrence of mild symptoms, promptly controlled by adjusting the lithium dose or with short courses of benzodiazepines but no other medication. PR: lithium level ≥0.6 mEq/l with improvement of the recurrence pattern in spite of being mildly depressed or hypomanic while on monotherapy.	(40)
	89 BD (23 ER, 47 PR, 19 NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to pre-lithium period NR: < 50% reduction, no change or worsening in the episode index, defined as number of episodes per year compared to the pre-lithium period.	(52)
	184 BD (92R, 92NR)	No	Retrospective	R: rated retrospectively from standardized interviews and medical records	(84)
	282 BR (148R, 134NR)	No: alone Yes: when GSK3β and NR1D1 genotypes were considered together	Retrospective	R: if there was a 50% reduction in the frequency and/or severity of symptoms on Li. NR: if less than 50% reduction of symptoms.	(55)
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to pre-lithium period NR: < 50% reduction, no change or worsening in the episode index	(86)
CRY1	282 BR (148R, 134NR)	Yes	Retrospective	R: if there was a 50% reduction in the frequency and/or severity of symptoms on Li. NR: if less than 50% reduction of the symptoms.	(55)
The neurotransmitter system: serotonin, dopamine and GABA pathways					
DRD1	155 BD (43R, 112PR + NR)	No	Retrospective	The response to lithium was assessed using the scale developed by Grof *et al.* (24)	(45)
	92 BD (24ER, 48PR, 20NR)	Yes	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening in the episode index, defined as number of episodes per year compared to the pre-lithium period.	(63)
	101 BD (24ER, 51PR, 26NR)	Yes	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to pre-lithium period NR: < 50% reduction, no change or worsening in the episode index	(86)
DRD2	125 patients (100BD; 25MD)	No	Prospective	Efficacy evaluated by the difference between a pre-treatment index and an ongoing treatment index	(57)
	155 BD (43R, 112PR +	No	Retrospective	The response to lithium was assessed using the scale developed by Grof *et al.* (24)	(45)

	NR)				
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
DRD3	155 BD (43R, 112PR + NR)	No	Retrospective	The response to lithium was assessed using the scale developed by Grof *et al.* (24)	(45)
	55 patients (43BD; 12MD)	No	Prospective	Efficacy evaluated as the difference between a pre-treatment index and an ongoing treatment index	(58)
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
DRD4	125 patients (100BD; 25MD)	No	Prospective	Efficacy evaluated as the difference between a pre-treatment index and an ongoing treatment index	(57)
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
DAT1	155 BD (43R, 112PR + NR)	No	Retrospective	The response to lithium response was assessed using the scale developed by Grof *et al.* (24)	(45)
GABRA1	125 patients (100BD; 25MD)	No	Prospective	Efficacy evaluated as the difference between a pre-treatment index and an ongoing treatment index	(57)
GABRA3	a) 138 BDI lithium responders and 108 controls b) 24 families ascertained through lithium-responsive BD probands	a) No b) No	Prospective	Patients were stabilized on lithium monotherapy	(67)
GABRA5	a) 138 BDI lithium responders and 108 controls b) 24 families ascertained through lithium-responsive BD probands	a) No b) No	Prospective	Patients were stabilized on lithium monotherapy	(67)
GABRB3	a) 138 BDI lithium responders and 108 controls b) 24 families ascertained through lithium-responsive BD probands	a) No b) No	Prospective	Patients were stabilized on lithium monotherapy	(67)
5-HT1A	124 patients (102BD; 22MD)	No	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(59)
5-HT2A	124 patients (102BD; 22MD)	No	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(59)
	155 BD (43R, 112PR + NR)	No	Retrospective	The response to lithium response was assessed using the scale developed by Grof *et al.* (24)	(45)
	92 BD (24ER, 48PR, 20NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index, defined as number of episodes per year compared to the pre-lithium period.	(64)
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening of the	(86)

				episode index	
5-HT2C	124 patients (102BD; 22MD)	No	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(59)
	92 BD (24ER, 48PR, 20NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening in the episode index, defined as number of episodes per year compared to the pre-lithium period.	(64)
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
5-HTTLPR	201 patients (167BD, 34MD)	Yes (s/s and worse response)	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(60)
	83 BD (36R, 47NR)	Yes (l/s and better response)	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(65)
	67 BD (18ER, 35PR, 14NR)	Yes (s/s and s and worse response)	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to pre-lithium period NR: < 50% reduction, no change or worsening of the episode index, defined as number of episodes per year compared to the pre-lithium period.	(66)
	121 BD (31ER, 54PR, 26NR)	Interaction between BDNF and 5HTTLPR polymorphism and the response to lithium	Retrospective	ER: no affective episodes PR: 50% reduction in the number of episodes per year compared to the pre-lithium period	(61)
	134 BD I	No	Retrospective	R '' Good responders'': no recurrence of impairing symptoms, or recurrence of mild symptoms, promptly controlled by adjusting the lithium dose or with short courses of benzodiazepines but no other medication. PR: lithium level ≥0.6 mEq/l with improvement of the recurrence pattern in spite of being mildly depressed or hypomanic while on monotherapy.	(40)
	155 BD (43R, 112PR + NR)	No	Retrospective	The response to lithium was assessed using the scale developed by Grof *et al.* (24)	(45)
	101 BD (24ER, 51PR, 26NR)	Yes	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
COMT	201 patients (160 BD + 41MD characterized for lithium response)	No	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(68)
	101 BD (24ER, 51PR, 26NR)	Yes	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year compared to pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
MAO-A	201 patients (160 BD + 41MD characterized for lithium response)	No	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(68)
	a) 138 BD and 108 controls b) 25 families ascertained through lithium-responsive BD probands	a) No b) No	Prospective	The response to lithium was evaluated prospectively with an average follow-up of 14.4 ± 6.8 years.	(69)
Gβ3	201 patients (160 BD +	No	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment	(68)

	41MD characterized for lithium response)			recurrence index	
TPH	108 patients (90BD + 18MD characterized for lithium response)	Yes	Prospective	Efficacy evaluated as the difference between a pre-lithium treatment recurrence index and an on-lithium treatment recurrence index	(70)
TH	54 BD lithium responders (48 BD and 6 RU) 94 controls	No	Retrospective	ER: patients judged to have a high risk of recurrence on the basis of the number and frequency of episodes before lithium therapy. Maintained on lithium monotherapy for ≥3 years, at plasma levels ≥0.6 mEq/l, with no further episodes of the illness while on adequate treatment. No additional biological or pharmacological interventions allowed.	(71)
The BDNF/TrkB signaling pathway					
BDNF	88 BD characterized for response to lithium	Yes	Retrospective	ER: had no affective episodes on lithium; PR: showed 50% reduction in the episode index (number of episodes per year relative to that during the pre-lithium period); NR : showed <50% reduction, no change, or worsening of the episode index.	(45)
	108 BD (25ER, 55PR, 28NR)	Yes	Retrospective	ER: had no affective episodes on lithium; PR: showed 50% reduction in the episode index (number of episodes per year relative to that during the pre-lithium period); NR: showed <50% reduction, no change, or worsening of the episode index.	(73)
	134 BD I	No	Retrospective	R '' Good responders'': no recurrence of impairing symptoms, or recurrence of mild symptoms, promptly controlled by adjusting the lithium dose or with short courses of benzodiazepines but no other medication. PR: lithium level ≥0.6 mEq/l with improvement of the recurrence pattern in spite of being mildly depressed or hypomanic while on monotherapy.	(40)
	184 BD (92R, 92NR)	No	Retrospective	The response to lithium was rated retrospectively from standardized interviews and medical records	(84)
	121 BD (31ER, 54PR, 26NR)	Yes	Retrospective	ER: had no affective episodes on lithium; PR: showed 50% reduction in the episode index (number of episodes per year relative to that during the pre-lithium period); NR: showed <50% reduction, no change, or worsening of the episode index.	(61)
	161 BD	No	Retrospective	R: Less frequent and/or severe relapses, including no relapse, by comparison with the period before the initiation of lithium treatment	(74)
	101 BD (24ER, 51PR, 26NR)	Yes	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, defined as number of episodes per year, since the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
NTRK2	108 BD (25ER, 55PR, 28NR)	No	Retrospective	ER: had no affective episodes on lithium; PR: showed 50% reduction in the episode index (relative to that during the pre-lithium period); NR: showed <50% reduction, no change, or worsening of the episode index.	(73)
	184 BD (92R, 92NR)	Yes (in BD with suicidal ideation)	Retrospective	The response to lithium was rated retrospectively from a standardized interviews and medical records	(84)
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, from that during the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
FYN	101 BD (24ER, 51PR, 26NR)	Yes	Retrospective	ER: had no affective episodes on lithium; PR: showed 50% reduction in the episode index (from that during the pre-lithium period); NR: showed <50% reduction, no change, or worsening of the episode index.	(75)
	101 BD (24ER, 51PR, 26NR)	Yes	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, from that during the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
GRIN2B	105 BD (24ER, 53PR, 28NR)	No	Retrospective	ER: had no affective episodes on lithium; PR: showed 50% reduction in the episode index (from that during the pre-lithium period);	(76)

				NR: showed <50% reduction, no change, or worsening of the episode index.	
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, from that during the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)
Other signaling pathways					
CREB1	249 BD (180R, 69NR) and 127 controls	Yes	Prospective	ER: Each patient had to fulfill several criteria: A) Diagnosis of primary episodic bipolar disorder based on the SADS-L (lifetime version) interview and Research Diagnostic Criteria (RDC); B) High recurrence risk; and C) Unequivocal response to lithium NR: had to experience at least two recurrences during lithium treatment with confirmed therapeutic levels of lithium	(77)
CREB2 CREB3	249 BD (180R, 69NR) and 127 controls	No	Prospective	ER: Each patient had to fulfill the following criteria: A) Diagnosis of primary episodic bipolar disorder based on the SADS-L (lifetime version) interview and Research Diagnostic Criteria (RDC) ; B) High recurrence risk ; and C) Unequivocal response to lithium NR: had to experience at least two recurrences during lithium treatment with confirmed therapeutic levels of lithium	(77)
PREP	249 BD (180R, 69NR) and 127 controls	No	Prospective	ER: Each patient had to fulfill the following criteria: A) Diagnosis of primary episodic bipolar disorder based on the SADS-L (lifetime version) interview and Research Diagnostic Criteria (RDC) ; B) High recurrence risk ; and C) Unequivocal response to lithium NR: had to experience at least two recurrences during lithium treatment with confirmed therapeutic levels of lithium	(78)
XBP1	66 BD	Yes	Retrospective	R: Less frequent and/or severe relapse, including no relapse, than during the period before the initiation of lithium treatment	(80)
BCR	161 BD (43R, 118NR)	Yes	Retrospective	R: full response without any affective episode during lithium treatment (=ER).	(81)
AP2-B	134 BD I	No	Retrospective	R '' Good responders'': no recurrence of impairing symptoms, or recurrence of mild symptoms, promptly controlled by adjusting the lithium dose or with short courses of benzodiazepines but no other medication. PR: lithium level ≥0.6 mEq/l with improvement of the recurrence pattern in spite of being mildly depressed or hypomanic while on monotherapy.	(40)
PDLIM5	155 BD (43R, 112PR + NR)	No	Retrospective	The response to lithium was assessed using the scale developed by Grof *et al.* (24)	(82)
CACNG2	a) 213 BD I b) 170 BD	a) Yes b) Yes	Retrospective	NR: no improvement or worsening of illness PR: minor or modest improvement in frequency of episodes or admissions; significant morbidity R: partial good response (marked improvement but not episode-free) FR: good response (complete remission).	(83)
MMP-9	109 BD (26ER, 55PR, 28NR)	No	Prospective	ER: no affective episodes during lithium treatment; PR: 50% or more reduction in the episode index; NR: less than 50% reduction, no change or worsening of the episode index.	(85)
	101 BD (24ER, 51PR, 26NR)	No	Retrospective	ER: no affective episodes on lithium PR: 50% reduction in the episode index, since the pre-lithium period NR: < 50% reduction, no change or worsening of the episode index	(86)

BD: bipolar disorder; MD: major depression; RU: recurrent unipolar; ER: excellent responders; FR: full responders; R: responders; PR: partial or poor responders; NR: non responders; UN: unclassified. 5-HT1A: 5-hydroxytryptamine receptor 1A; 5-HT2A: 5-hydroxytryptamine receptor 2A; 5-HT2C: 5- hydroxytryptamine receptor 2C; 5-HTT: solute-carrier family 6 member 4 (serotonin transporter); 5-HTTLPR: serotonin-transporter-linked promoter region; AP2-B: activating enhancer- binding protein 2 beta 3; BCR: breakpoint cluster region; BDNF: brain-derived neurotrophic factor; CREB1: cAMP-responsive element-binding protein 1; COMT: catechol-O-methyl transferase; CREB2: cAMP-responsive element-binding protein 2; CREB3: cAMP-responsive element-binding protein 3; CRY1: cryptochrome-1 ; DAT1: dopamine transporter 1; DGKH: diacylglycerol kinase, eta; DRD1: dopamine receptor D1; DRD2: dopamine receptor D2; DRD3: dopamine receptor D3; DRD4: dopamine receptor D4; GABRA1: gamma-aminobutyric acid A receptor, alfa 1; GABRA3: gamma-aminobutyric acid A receptor, alfa 3; GABRA5: gamma-aminobutyric acid A receptor, alfa 5; GABRB3: gamma-aminobutyric acid A receptor, beta 3; Gβ3: G protein beta 3; GRIN2B: NMDA receptor 2B subunit ; GRK3: beta-adrenergic receptor kinase 2 (BARK2); GSK3B: glycogen synthase kinase 3 beta; FYN: Src-family tyrosine kinases; IMPA1: inositol(myo)-1(or 4)-monophosphatase 1; IMPA2: inositol(myo)-1(or 4)-monophosphatase 2; INPP1: inositol polyphosphate-1-phosphatase; MAO-A: monoamine oxidase A; MARKS: myristoylated

alanine-rich C-kinase substrate; group D, member 1; MMP-9: matrix metalloproteinase-9; NR1D1: nuclear receptor subfamily 1, group D, member 1; NR3C1: nuclear-receptor subfamily 3, group C, member 1 ; NTRK2: neurotrophic tyrosine kinase, receptor, type 2; PDLIM5: PDZ and LIM domain 5; PLCG1: phospholipase C, gamma 1; PREP: propyl endopeptidase; TH: tyrosine hydroxylase; TPH: tryptophan hydroxylase; XBP1: X-box-binding protein 1.

Table 2. Pharmacogenetic studies of the response of bipolar disorder patients to non-lithium mood stabilizers

Gene	Sample	Association (Yes/No)	Study design	Definition of response	References
Valproate (VPA)					
XBPI	51 BD patients	Yes	Retrospective	Less frequent and/or severe relapse, including no relapse, than during the period before the initiation of valproate treatment	(91)
Lamotrigine					
DRD2	85 lamotrigine-treated, BD I depression patients	Yes	Prospective	Reduction in Montgomery-Asberg Depression Rating Scale (MADRS) total score between baseline and week 7.	(93)
DRD3		No			
DRD4		No			
DBH		Yes			
HRH1		Yes			
ANKK1		No			
MCR2		Yes			
NR3C1		Yes			
Atypical antipsychotics					
DRD2	88 olanzapine/fluoxetine combination (OFC)-treated BD I depression patients	No	Prospective	Reduction in Montgomery-Asberg Depression Rating Scale (MADRS) total score between baseline and week 7.	(93)
DRD3		Yes			
DRD4		No			
DBH		No			
HRH1		Yes			
ANKK1		No			
MCR2		No			
NR3C1		No			
SLC6A2	88 olanzapine/fluoxetine combination (OFC)-treated BD I depression patients	Yes	Prospective	Reduction in Montgomery-Asberg Depression Rating Scale (MADRS) total score between baseline and week 7.	(95)
MCR3		Yes			
TPH2		Yes			
COMT	42 BD patients characterized for response to olanzapine	No	Prospective	Clinical status evaluated before treatment, after 4 days of treatment and subsequently every week, with the Young scales for mania and the Andreasen scale for positive symptoms.	(96)
Common to Lithium, VPA and carbamazepine					
COMT	144 BD patients characterized for response to mood stabilizers (Li, VPA, CBZ) and 157 controls.	Yes	Prospective	Response defined as subjects exhibiting a decrease of at least 50% in the YMRS score after 6 weeks of medication.	(92)

BD: bipolar disorder; R: responders; NR: non responders. ANKK1: ankyrin repeat and kinase domain containing 1; COMT: catechol-O-methyl transferase; DBH: dopamine beta-hydroxylase; DRD2: dopamine receptor D2; DRD3: dopamine receptor D3; DRD4: dopamine receptor D4; HRH1: histamine H1 receptor; MCR2: melanocortin 2 receptor; MCR3: melanocortin 3 receptor ; NR3C1: nuclear receptor subfamily 3, group C, member; SLC6A2: norepinephrine transporter ; TPH2: tryptophan hydroxylase 2 ; XBP1: X-box-binding protein 1.

Figure 1. Goals of the pharmacogenomics research in bipolar disorder.
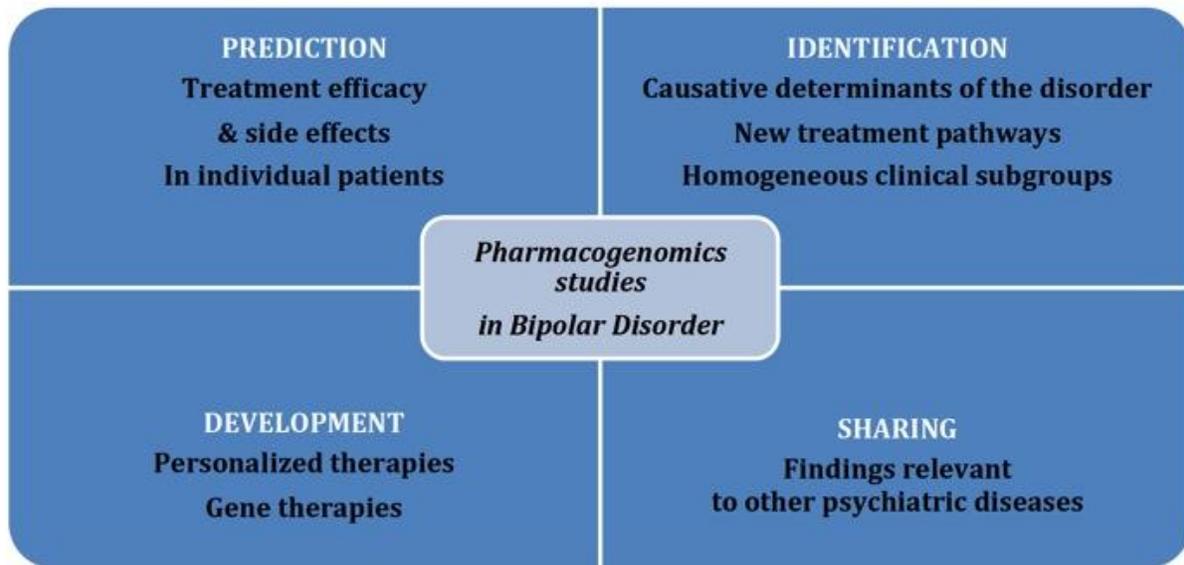
Running title: Predicting response to mood stabilizers