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Twenty years of Lithium pharmacogenetics: A systematic review

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ABSTRACT

Lithium is among the best proven treatments for patients diagnosed with Bipolar Disorder, however response to Lithium appears to be considerably variable among individuals and it has been suggested that this inconstancy in Lithium response could be genetically determined. Starting from this perspective, in the last few decades, a number of pharmacogenetic studies have attempted to identify genetic variants, which might be associated with response to Lithium in bipolar patients, in order to develop a pharmacogenetics test to tailor treatment on patients, identifying who will benefit the most from therapy with Lithium. Within this context, authors have critically reviewed pharmacogenetic studies of Lithium response in bipolar disorder, suggesting strategies for future work in this field. Computerized searches of PubMed and Embase databases, for studies published between 1998 and January 2018, was performed: 1162 studies were identified but only 37 relevant papers were selected for detailed review. Despite some interesting preliminary findings, the pharmacogenetics of Lithium and the development of a specific pharmacogenetics test in bipolar disorder appears to be a field still in its infancy, even though the advent of genome-wide association studies holds particular promise for future studies, which should include larger samples.

1. Introduction

Although, Lithium was first approved, by the Food and Drug Administration (FDA), for the treatment of maniac episodes in 1970 and, four years later, for the maintenance therapy in Bipolar Disorder, Lithium's properties were first observed in 1949 by John Cade, who described its efficacy in treating maniac episodes (Cade, 2000). Since the publication of early trials of Lithium treatment in the 60s and 70s, Lithium has become the standard treatment for relapse prevention in Bipolar Disorder (Geddes, 2004); its use for more than half a century has generated a wealth of empirical evidence in addition to which it has been found to have a unique therapeutic profile that includes for instance its anti-suicidal and neuroprotective properties (Grunze et al., 2009; Malhi and Gershon, 2009; Malhi, 2012; Van Erp et al., 2011). Since its discover, several molecular mechanisms have been identified as possible targets of Lithium, which is an inhibitor of at least four key molecules: Inositol monophosphatase (IMP), Glycogen Sinthase Kinase 3 (GSK3), adenyl-cyclase and G-proteins (Agam et al., 2009; Chen and Manji, 2006; Quiroz et al., 2004; Zarate et al., 2006). By directly inhibiting these targets, Lithium has widespread indirect effects, which in turn might alter gene expression, neurotransmitter receptors' distribution and cellular processes, including neuronal differentiation, apoptosis and circadian rhythms.

Despite its effectiveness and the existence of an inexpensive and accurate monitoring tool, in clinical practice the use of Lithium has diminished somewhat in favour of other agents, such as mood stabilizers and second generation antipsychotics, even though these medications are not free from side effects (Diurni et al., 2009; Malhi, 2010). Compared to Lithium, much less evidences are available on the pharmacogenomics of other treatments for BD (Squassina et al., 2010). Polymorphisms in dopaminergic receptors were associated with response to lamotrigine and olanzapine/fluoxetine combination, whereas polymorphisms in the catechol-O-methyl transferase gene were associated with non-response to mood stabilizers, including valproate and carbamazepine (Dàvila et al., 2006; Lee et al., 2010).

That underutilization of Lithium appears to be related to the fear for its toxicity, to its narrow therapeutic window and to the need of a long-term follow-up (Malhi, 2012; Young, 2007). Furthermore, even though Lithium's side effects have been investigated for decades and guide lines for their prevention and treatment are currently available

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(NICE guidelines, 2006), the use of Lithium remains limited. In recent years, the introduction of Lithium prolonged-release (PR) formulations could facilitate the use of this molecule in view of their advantages over immediate-release (IR) formulations (Martinotti et al., 2018). Some side effects seem to be related to fluctuations in Lithium plasma levels that appear more pronounced with the use of IR formulations; on the other hand, PR preparations provide more stable patterns of drug plasma levels, allowing for a more stable response and reducing the incidence of side effects, thus, along with once-daily administration, improving patients' compliance (Durbano et al., 2002).

About 30% of patients treated with Lithium can be classified as "excellent responder", as defined by the total absence of affective episodes through-out a 10-years period of Lithium treatment (Rybakowski et al., 2009). Building on that, interest of scientific community focused on the search of common factors to this subset of patients with the aim to use them as markers to identify the best candidates for treatment with Lithium Salts. During decades, several studies have highlighted that a family history positive for Bipolar Disorder was associated with a better response to Lithium (Grof, 2010; Maj, 1985; Mendlewicz, 1973). Furthermore, in 2014, Kliwicki et al. observed that excellent responders' first-degree relatives had a better response to therapy compared to non-responders' relatives (Kliwicki et al., 2014). These results, in line with what Duffy observed in 2007 (Duffy, 2007), seem to confirm the hypothesis whereby response to Lithium could be genetically determined.

With this systematic review authors want to assess existing evidences and data related to genetic polymorphisms potentially capable of modulating patients' response to Lithium in order to evaluate the state-of-the-art in finding a genetic marker useful to identify those patients who will benefit the most from Lithium treatment both in terms of effectiveness and tolerability. The opportunity to tailor pharmacologic therapies on each individual, through the use of genetic information (Bolla et al., 2011; Ferrari et al., 2012), could lead to shorter waiting time between the diagnosis and the beginning of an effective treatment and, consequently, to a reduction of costs (Gardner et al., 2014; Ielmini et al., 2018a, 2018b).

2. Material and methods

A literature search was conducted from PubMed and EmBase databases from 1998 to January 2018 using the combination of terms *Lithium* OR *Mood Stabilizer* AND *Personalized Medicine* OR *Precision Medicine* OR *Pharmacogenetics*. Inclusion criteria are the following:

- Articles published in English
- Randomized controlled trials, observational studies and case-control studies were included. Genome Wide Association Studies were also included.
- Patients between the ages of 18 and 65 years old.

Fig. 1 shows the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow-chart of the search. A total of 1162 records was returned after the exclusion of duplicates. Articles were examined independently by two researchers and a third researcher was involved whenever there was a dissenting opinion among the main investigators. 258 articles were identified as potentially eligible for this study based on title and abstract; of these only 55 studies were retrieved for full-text review. All relevant references were checked for additional records and a total of 37 articles was considered eligible according to the aim of this review (Fig. 1).

3. Results

As shown in Table 1, several genes have been investigated in the last twenty years: candidate genes participating in monoaminergic neurotransmitter systems, the circadian system, neurotrophic mechanisms, or the inositol signalling pathway have been the most studied in the literature (Papiol et al., 2018) (Table 1).

Polymorphisms in dopaminergic receptors genes were the first to be investigated, since the dopaminergic neurotransmitter system seems to play a pivotal role in the pathophysiology of Bipolar Disorder, as highlighted by several authors over the last decades (Berk et al., 2007; Cousins et al., 2009; Wittenborn, 1974). Nonetheless, at the end of 90s', Serretti et al., in two retrospective studies involving respectively 55 and 125 patients, did not find any association between polymorphisms in dopaminergic receptor genes (DRD2, DRD3 and DRD4) and patients' response to Lithium (Serretti et al., 1998, 1999). However, approximately ten years later, Rybakowsy et al., in a retrospective study on 92 patients diagnosed with Bipolar Disorder, have highlighted the existence of strong association between polymorphism −48A/G in gene coding for dopaminergic receptor-1 and the response to Lithium: specifically, the genotype G/G seems to be associated with an excellent response (Rybakowski et al., 2009). These results had been confirmed subsequently in another retrospective study on 101 patients affected by BD, in which 14 genes, previously reported as potentially involved in patients' response to Lithium, were investigated (Rybakowski et al., 2012).

Serotonin is one of the most important neurotransmitters and a large body of evidence supports the association between the serotonergic system with Mood Disorders, including Bipolar Disorder (Lin et al., 2014). In the light of the above, the interest shown by scientific community in finding polymorphisms on genes involved in serotonin's metabolism, that could explain the variability in response to Lithium, is pretty much explained. Serretti and co-authors first and, subsequently Rybakowski and his colleagues, failed to identify any polymorphisms on genes coding for serotoninergic receptors 5HT2A and 5HT2C that could account for the differences, commonly observed in the population, in Lithium response (Rybakowski et al., 2012; Serretti et al., 2000). In recent years, the role of the functional polymorphism in the regulatory region of the serotonin transporter gene in BD has been a matter of intensive research (Cho et al., 2005). The 44-base pair insertion/deletion within the promoter region of the serotonin transporter gene (5-HTTLPR) can exist in two allelic forms: the long variant (L) and the short variant (S) (Mynett-Johnson et al., 2000); the presence of the latter, both in homozygosis and heterozygosis, has been associated with a lower transcriptional activity and a consequent reduction in serotoninergic transmission (Collier et al., 1996; Lesch et al., 1996). Thus, the presence of the allele S has been investigated as a predictive factor for clinical response to Lithium. Furthermore, variants of this gene have been associated with individuals' variation in harm avoidance; this personality traits seems to mediate the effects of functional polymorphisms in the regulatory region of the serotonin transporter gene on response to treatment in bipolar patients (Mandelli et al., 2009). As shown in Table 1, to date the association between clinical Lithium's efficacy and polymorphism in the regulatory region of the serotonin transporter gene remains not clear and unconvincing. In fact, some studies had pointed out as the presence of the allele S is associated with a worse response to therapy (Rybakowski et al., 2005a; Serretti et al., 2001, 2004), whereas others did not confirm these results (Michelon et al., 2006). Moreover, in a retrospective study involving 111 patients diagnosed with BD, Rybakowski et al. have shown that excellent Lithium responders presented the simultaneous presence of allele S and polymorphism Val66Met on gene coding for Brain Derived Neurotrophic Factor (BDFN) (Rybakowski et al., 2007).

As mentioned above, inositol signalling pathway has been matter of intensive study in the last two decades, in view of the hypothesis according to which Lithium-blockable enzyme inositol polyphosphate 1-phosphatase is a putative target for the mood-stabilizing effects of Lithium. An association with such a response was obtained with polymorphism C973A of the inositol polyphosphate 1-phosphatase (*INPP1*) gene (Steen et al., 1998). Moreover, Bremer et al., in a study on 184 patients recruited from family for linkage studies, found a significant

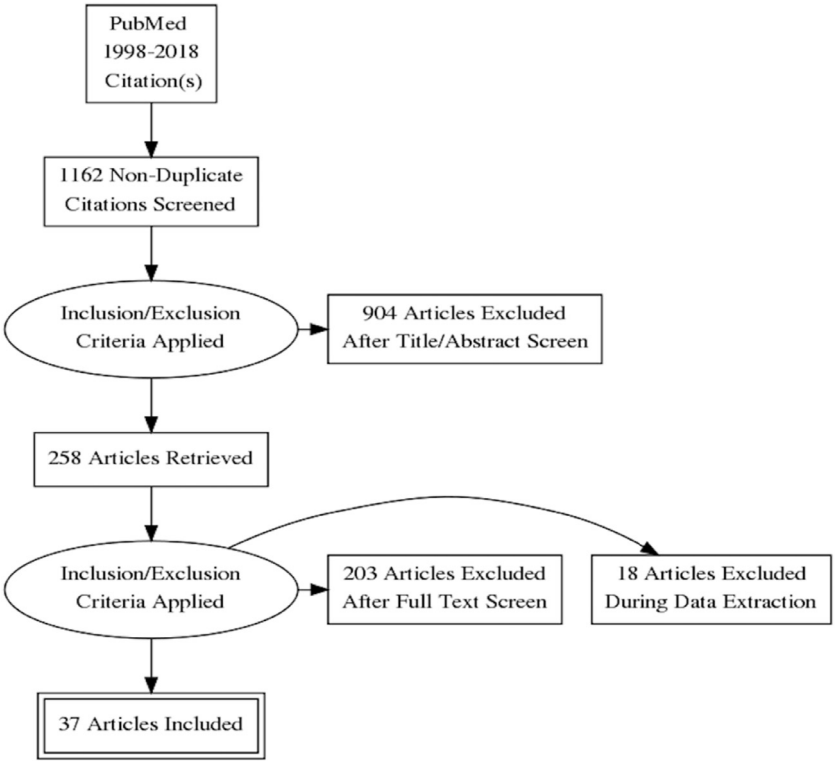

Fig. 1. PRISMA flow chart.

interaction between Lithium response and single-nucleotide polymorphism (SNP) rs2064721 in INNP1 gene, particularly in patient with an associated post-traumatic stress disorder (Bremer et al., 2007). More recently, Mitjans and colleagues (Mitjans et al., 2015), investigating the potential association of genetic variability at genes related to INNP1, glycogen synthetase kinase-3 (GSK3), hypothalamic-pituitary-adrenal and glutamatergic pathways with Lithium response, in a sample of 131 patients diagnosed with BD, identified a significant association for the SNPs rs3791809, rs4853694 and rs909270 in INNP1 gene with a better response to Lithium therapy.

Bipolar Disorder was first linked to glycogen synthetase kinase-3 hyper-activation in 1996 (Klein and Melton, 1996), following the observation that Lithium is a direct inhibitor of this enzyme. From this perspective, it is easy to understand the interest shown by researchers for the gene coding for GSK3 as a potential genetic marker to predict patients' response to Lithium. Notwithstanding these assumptions, most studies failed to find any association between Lithium response and SNPs on gene coding for GSK3 (Michelon et al., 2006; Serretti et al., 2002). However, there are several evidences which highlight the possible role of this gene in modulating response to Lithium: Benedetti et al., in 2005, showed that carriers of the allele C had a better improvement on Lithium therapy (Benedetti et al., 2005), as later confirmed in a more recent study, carried out by Rybakowski and other, in which authors highlighted that the presence of this allele is associated with a greater tolerability, particularly for what concern renal functioning (Rybakowski et al., 2013). Contrary to the claim of Benedetti and his group, the study of Iwahashi and co-workers, in 2014, pointed out that carriers of GSK3 haplotype T-A presented a higher Lithium response; this might suggest that patient with the T allele, which gives greater transcriptional activity, are more affected by Lithium, which inhibits GSK3 activity, compering to those with the C allele (Iwahashi et al., 2014).

Concerning neurotrophic factors, one of the most investigated is Brain-Derived Neurotrophic Factors (BDFN), whose serum levels could represent a potential biomarker of disease activity in Bipolar Disorder (Fernandes et al., 2015). Furthermore, the presence of the SNP Val66Met on gene coding for BDFN has been associated with a greater susceptibility for the development of BP (Green et al., 2006; Sklar et al., 2002). Rybakowski and colleagues, in a retrospective study involving 88 patients with BD, were the first to highlight the existence of a strong association between this SNP and an excellent response to Lithium (Rybakowski et al., 2005a). Such evidence was later confirmed by Dmirtzak and his group, in 2008 (Dmitrzak et al., 2008), and by Rybakowski himself, in 2012 (Rybakowski et al., 2012). Furthermore, it seems to be a significant interaction between BDFN gene and 5-HTTLPR polymorphism in determining patients' response to Lithium: the combination of Val66Met polymorphism and allele S seems to be more common in poor responders (Rybakowski et al., 2007).

Starting from the evidence that BDFN could be involved in BD pathogenesis, several researchers have wondered whether Neurotrophic Tyrosine Kinase Receptor 2 (NTRK2), a specific BDFN receptor that regulates neuronal differentiation (Luberg et al., 2010), might has some role in modulating response to therapy with Lithium. Despite these premises, only Bremer and co-workers, in a study on 184 patients with Bipolar Disorder, successfully demonstrated a strong association between SNP rs1387923 and Lithium response, but only in a subset of patients with euphoric rather than dysphoric mania and without suicidal intention (Bremer et al., 2007).

In recent years, interest of scientific community shifted on "clock" genes and their possible role as predictive factors to identify patients who will benefit the most from therapy with Lithium. It is well known, from many years now, that abnormalities in circadian rhythms often are the first sign of illness acute exacerbation (Kripke et al., 1978; Shi et al., 2008). Lithium salts acts by correcting these abnormalities through the modulation of "clock" genes' expression (Kripke et al., 2009; McClung, 2007). Campos De Sousa and his colleagues were the first to investigate the role of seven SNPs on Rev-Erb-α in determining response to therapy, in a sample of 170 patients under long-term treatment with Lithium, demonstrating how the presence of SPN rs2314339 was associated with a poor response to treatment (Campos de Sousa et al., 2010). One year

Table 1
Lithium pharmacogenetic.

Study	Sample	Definition of response	Gene	Marker	Risk	Note
Serretti et al. (1998)	55	Difference between a pretreatment index and an ongoing treatment index	DRD-3	DRD-3 variants	No association	Prospective study
Serretti et al. (1999)	25	Difference between a pretreatment index and an ongoing treatment index	DRD-2, DRD-4 and GABA- 1	Genes variants	No association	Prospective study
Steen et al. (1998)	a) 23 DSM-III-R bipolar patients and 20 controls b) 54 DSM-IV bipolar I patients and 50 controls	(a) Demonstrated "complete Lithium response (b) Demonstrated "long and complete remission" on Lithium alone	INNP1	A682G, G153T, G348A, C973A	C973A better response in sample a); did not replicate in sample b).	Retrospective study
Turecki et al. (1998)	136 excellent responders and 163 controls	No affective episodes	PLCG-1	Dinucleotide repeat	More common in responders	Case-control association study
Ftouhi et al. (2001)	133 excellent responders and 99 controls	No affective episodes	PLCG-1	Gene variants	Uncertain association	Case-control association study
Løvlie et al. (2011)	61	Number of affective episodes before and after treatment	PLCG-1	Gene variants	Uncertain association	Retrospective study
Serretti et al. (2000)	124	Number of affective episodes before and after treatment	5HT2A and 5HT2C	Genes variants	No association	Prospective study
Serretti et al. (2001)	201	Difference between a pre- Lithium treatment recurrence index and an on-Lithium treatment recurrence index	5-HTTLPR	Alleles S and L	s/s genotype showed a worse response than s/l and l/l	Prospective study
Serretti et al. (2002)	201	Difference between a pre- Lithium treatment recurrence index and an on-Lithium treatment recurrence index	COMT, GSK3, MAO-A	Genes variants	No association	Prospective study
Washizuka et al. (2003)	54	No affective episodes defines an excellent responder	mtDNA	SNPs 5178 and 10,398	Significant association between 10398A polymorphism and Lithium response	Retrospective study
Serretti et al. (2004)	83	Number of affective episodes before and after treatment	5-HTTLPR	Alleles s and l	Genotype l/s associated with a better response	Retrospective study
Benedetti et al. (2005)	88	Number of affective episodes before and after treatment	GSK3	rs334558 (−50T/C)	C allele associated with a better response	Prospective study
Kakiuchi et al. (2005)	56	Clinical improvement greater than 50%	XBP1	−116C/G	C allele associated with a better response	Transcriptional factor involved in Valproic Acid response
Rybakowski et al. (2005a)	67	No affective episodes	5-HTTLPR	Alleles s and l	Genotype s/s and s allele more frequent in poor responder	Retrospective study
Rybakowski et al. (2005b)	88	No affective episodes	BDNF	Val66Met and 270C/T	Val/Met genotype of BDNF occurred more frequently in excellent than in poor responders	Retrospective study
Masui et al. (2006a)	161	Less frequent and/or severe relapse, including no relapse, compared with the period before the initiation of Lithium treatment	BDNF	Val66Met	No association	Retrospective study
Masui et al. (2006b)	66	Less frequent and/or severe relapse, including no relapse, compared with the period before the initiation of Lithium treatment	XBP1	−116C/G	Lithium more effective in −116C allele carriers than in −116 G homozygotes	Retrospective study
Michelon et al. (2006)	134	No recurrence of impairing symptoms, or recurrence of mild symptoms, promptly controlled by adjusting the Lithium dose	INNP-1, BDNF, 5HTTLPR, GSK-3β	C973A, rs6265, rs3755557	No association	Retrospective study
Bremer et al. (2007)	184	Clinical improvement greater than 50%	NTRK2	rs1387923	NTRK2: genotype T/T associated with a better response.	NTRK2 associated with Bipolar Disorder in Genome Wide Association Studies
			INPP1	rs2067421	INNP1: nominal association in patients with comorbid post-traumatic stress disorder	

(*continued on next page*)

Table 1 (*continued*)

Study	Sample	Definition of response	Gene	Marker	Risk	Note
Rybakowski et al. (2007)	111	No affective episodes	5HTTLPR and BDNF	5HTTLPR and Val66Met interaction	Worse response in genotype S/*S* + Val/Val	Retrospective studies
Dmitrzak et al. (2008)	108	No affective episodes	BDNF	rs2030324, rs988748, Val66Met, rs2203877	rs988748 and Val66Met associated with a better response	
			NTRK2	rs1187326, rs2289656 e rs1187327		
Rybakowski et al. (2009)	92	No affective episodes	DRD1	−48A/G	G allele poor response	
Campos-de-Sousa et al. (2010)	170	Alda Scale	Rev-Erb-α	7 SNPs	rs2314339 poor response	
Mc Carthy et al. (2011)	282	Alda Scale	16 SNPs on seven clock genes		Rev-Erb-α: NR1D1 and CRY1 better response	
Rybakowski et al. (2012)	101	No affective episodes	Multiple SNPs on 14 different genes		Possible role in Lithium response of 5HTT, DRD1, COMT, BDFN and FYN	
Rybakowski et al. (2013)	78	No affective episodes	GSK3	−50T/C	Genotype −50C/C better response in terms of tolerability	Retrospective study
Iwahashi et al. (2014)	42	Clinical improvement greater than 50%	GSK3	−50T/C and 1727A/T	Genotype −50T/T e −1727A/A associated with a better response to Lithium	
Rybakowski et al. (2014)	115	No affective episodes in patients in monotherapy	Several clock genes		6 SNPs of ARNTL and three haplotypes of TIMELESS associated with a better response	
Mitjans et al. (2015)	131	Clinical improvement greater than 50%	Multiple SNPs on 16 genes		INPP1: rs3791809, rs4853694 e rs909270 associated with Lithium response GSK3: rs1732170, rs11921360 e rs334558 associated with Lithium response	Polypharmacotherapy did not allow patients to be considered excellent responders
Cruceanu et al. (2015)	41 Caucasia families with high bipolar disorder incidence	Alda Scale	GADL1	rs1702668 e rs 17,026,651	No association	
Kotambail et al. (2015)	151	No affective episodes	GADL1	rs1702668 e rs 17,026,651	No association	Indian ethnicity
Geoffroy et al. (2016)	151	Alda Scale	22 Clock genes	Several SNPs	PGC-1α and RORA involved in Lithium response	
Moreira et al. (2017)	36 patients and 20 controls	Alda Scale	GADL-1		No association	Caucasian ethnicity

DRD-3: Dopamine Receptor D3; DRD-2: Dopamine Receptor D2; DRD-4: Dopamine Receptor D4; GABA- 1: gamma-aminobutyric acid; INNP1: inositol polyphosphatase-1-phosphatase; PLCG-1: plyphospholipase C-gamma 1; 5HT2A: Serotonin 2A receptor; 5HT2C: Serotonin 2C receptor; 5-HTTLPR: serotonin transporter linked polymorphic region; COMT: catechol-O-methyltransferase; GSK3: glycogen synthase kinase 3; MAO-A: monoamine oxidase A; XBP1: X-box binding protein 1; BDNF: brain derived neutrophic factor; NTRK2: neurotrophic receptor tyrosine kinase 2; Dopamine Receptor D1; GADL1: glutamate decarboxylase like 1.

Table 2
Genome wide association study.

Study	Sample	Definition of response	Gene	Results	Notes
Perlis et al. (2009)	1177	Pre- and post-treatment psychometric tests	GWAS	SNPs in a region on chromosome 4q32	Only 458 were under treatment with Lithium
Chen et al. (2014)	188	Alda Scale	GWAS	rs1702668 and rs 17,026,651 on GADL1 high sensibility	Patients of Han Chinese descent
Song et al. (2016)	3874	Pre- and post-treatment psychometric tests	GWAS	rs116323614 on SESTD1	No significant association within bipolar patients, but strong association comparing Lithium responders with healthy controls
Hou et al. (2016)	2563	Alda Scale	GWAS	rs79663003, rs78015114, rs74795342, rs75222709 on chromosome 21 associated with Lithium response	Patients collected by 22 participating sites from the International Consortium on Lithium Genetics

Single Nucleotide Polymorphisms (SNPs) associated with Lithium response. GADL: glutamate decarboxylase like-1; SESTD1: SEC14 and spectrin domain containing 1.

later, McCarthy and collaborators identified two SNPs of on Rev-Erb-α (rs2071427, rs8192440) which were nominally associated with a better response to Lithium (McCarthy et al., 2011), confirming the involvement of Rev-Erb-α in patients' Lithium response. Over the following years, the interest in the possible role of clock genes in determining response to Lithium has spread through researchers, and others genes were identified as possibly involved. In 2014, Rybakowski and colleagues suggested that the six SNPs and three haplotypes of ARNTL gene and two SNPs and one haplotype of TIMELESS gene might be associated with the Lithium prophylactic response in bipolar patients (Rybakowski et al., 2014). Two years later, Geoffrey et al. by testing the association between 22 core clock genes with Lithium response in BD in two independent samples, found an association between PPARGC1A (PGC-1α) and RORA genes and Lithium response (Geoffroy et al., 2016).

Separate mention should be made with respect to Genome Wide Association Studies (GWAS) (Table 2). As shown in Table 2, as concerns Lithium pharmacogenetic, at present only four GWAS were made the first of which dates back to 2009. Perlis et al. examined the hazard for mood episode recurrence among 1177 patients with bipolar disorder, including 458 individuals treated with Lithium. SNPs showing the greatest evidence of association were then examined for association with positive Lithium response among patients treated with Lithium. Of the regions showing suggestive evidence of association with Lithium response, five were further associated with positive Lithium response (Perlis et al., 2009), including SNPs in a region on chromosome 4q32 spanning a gene coding for the glutamate/alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionate (AMPA) receptor *GRIA2,* which expression has been shown to be regulated by Lithium treatment (Seelan et al., 2008). In 2014, Chen and colleagues, performed a genome wide association study on samples from one subgroup of 294 patients of Han Chinese descent, with BD treated with Lithium. They identified two SNPS, rs17026688 and rs17026651, located in the introns of GADL1, that showed a sensitivity of 93% for predicting response to Lithium (Chen et al., 2014). However, this surprising result was not confirmed by subsequent studies involving different ethnicities (Cruceanu et al., 2015; Kotambail et al., 2015; Moreira et al., 2017). Two years later, Song and his group performed a GWAS on 2698 patients with subjectively defined Lithium response and 1176 patients with objectively defined Lithium response; no significant association were found within bipolar patients. However, in a second stage, Song's working group conducted GWAS comparing Lithium responders with healthy controls, finding out a strong association with SPN rs116323614 on chromosome 2q31.2 in the gene SEC14 and spectrin domains 1 (SESTD1), which encodes a protein involved in regulation of phospholipids (Song et al., 2016). In the same year, Hou and colleagues, in a GWAS involving 2563 patients collected by 22 participating sites from the International Consortium on Lithium Genetics, identified four SNPs on chromosome 21 meeting the genome-wide significance criteria for association with Lithium response (rs79663003, rs78015114, rs74795342, rs75222709) (Hou et al., 2016).

4. Discussion

There are currently a number of positive findings in Lithium pharmacogenetics' studies but none of them have been replicated in a satisfactory manner and, according to available data, patients' response to Lithium appears to be polygenic; furthermore, a single gene, which at best account for a small portion of the observed variability, could have multiple polymorphic alleles.

Moreover, at present, there are number of limitations within the available studies on Lithium response pharmacogenetics. One of these is the selection of candidate genes which was based on the supposed mechanism of action of Lithium; however, the reality is that our understanding is far from be clearly complete. From this perspective, it appears clear how GWAS could by-pass this by permitting large

numbers of single nucleotide polymorphisms (SNPs) to be examined across whole regions of interest within the genome.

Another important limitation, according to authors' opinion, is sample's selection, particularly in view of the considerable clinical heterogeneity in BD: future works should as far as possible recruit large and representative samples of patients, including those with significant comorbidities, in order to offer a picture closer to reality. Moreover, as shown in Table 1, there is a great deal of variability about what constitutes a good response to Lithium. In order to define treatment response clinicians have to make judgments about adequacy and tolerability of therapy as well as assess in disease's severity and episodes frequency and there is an increasing need of adequate new tools (Poloni et al., 2010, 2013). Concerning, Lithium response, one scale that includes such data is the scale developed by Alda and his colleagues (Grof et al., 2002). It is therefore desirable that future studies should specify precise *a priori* definitions of Lithium response, which could be assessed through the use of this scale in order to obtain more replicable results.

It is evident that in recent years, research techniques have gradually become more precise and technically reliable. Despite the enormous number of patients analysed so far, with a high number of SNPs possibly implicated in Lithium response, it is important not to overestimate the evidence available for now, even though it is becoming increasingly precise and reproducible.

The theme of the personalization of psychopharmacological therapy is as alive as ever in recent years, and succeeding in identifying patients who will benefit the most from treatment with Lithium both in terms of efficacy and tolerability, represents the main objective to which geneticists and psychiatrists should focus in future studies, trying to ensure the patient more tailored solutions and therefore more effective and safe therapies, also reducing healthcare costs. While current studies show a correlation between genetic variations and response to therapy for patients with bipolar disorder, research is still unclear on the type of therapeutic recommendations that should occur based on the results of the pharmacogenetics testing. Future studies, including larger sample sizes, are needed.

Authors' contribution

R.P. and M.I: provided the conception and design of the study. I.C. and N.P.: provided acquisition of data, analysis and interpretation of data A.G. was responsible to Writing-Original Draft Preparation and supplied analysis and interpretation of data. F.M. and M.F.: were responsible for critically review the article for important intellectual content; and C.C.: provided the revised the article critically for important intellectual content and gave final approval of the version to be submitted.

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Declaration of Competing Interest

All authors have no conflict of interest to report

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