Personalized Medicine in Psychiatry 13–14 (2019) 6–10

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.elsevier.com/locate/pmip

CYP2D6 metabolizer status and HTTLPR variant of *SLC6A4* associated with antidepressant-induced mania in bipolar disorder

Lindsay Melhuish Beaupre[a,b,*], Clement C. Zai[a,b,c,d], Arun K. Tiwari[b,c], Vanessa Gonçalves[b], Emanuela Mundo[b], James L. Kennedy[a,b,c,d]

[a] Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada
[b] Molecular Brain Science Research Department, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[c] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[d] Laboratory Medicine & Pathology, University of Toronto, Toronto, ON, Canada

ARTICLE INFO

Keywords:
Bipolar disorder
Antidepressants
Metabolizer status
Cytochrome P450
Pharmacogenetics

ABSTRACT

Introduction: Approximately 12% of individuals with bipolar disorder (BD) treated with an antidepressant experience antidepressant-induced mania (AIM). Numerous clinical risk factors have been identified but the only genetic risk factor found is the "S" allele or "SS" genotype of HTTLPR, a polymorphism in the promoter region of *SLC6A4*. We sought to investigate whether metabolizer status of five Cytochrome P450 genes, which encode for enzymes involved in the degradation of medications in the liver played a role in AIM.
Methods: 26 AIM+/25AIM− individuals were identified from the Toronto BD sample, via a blind retrospective analysis of two questionnaires and life charts. Genotyping was performed using pre-plated Taqman assays and metabolizer status was assigned based on the Clinical Pharmacogenetics Implementation Consortium guidelines.
Results: Concurrent use of mood stabilizer had a protective effect against AIM ($p = 0.0001$). No significant association between metabolizer status and AIM for the CYP genes was observed. When we grouped poor metabolizers (PM) and intermediate metabolizers (IM) we identified a nominal trend ($p = 0.14$) towards them being at a greater risk of experiencing AIM. In an additive model, combining *CYP2D6* metabolizer status and HTTLPR, PM and IM with the "S" allele were 9× more likely to experience AIM ($p = 0.002$).
Discussion: Our results provide further support for concurrent mood stabilizers having a protective effect against AIM. They also suggest that PM and IM of CYP2D6 may be at a greater risk of AIM. Lastly, combining the risk-allele of the HTTLPR with the risk metabolizer statuses increases the overall risk of AIM.

Bipolar disorder (BD) is a debilitating mood disorder that affects approximately 1% of the population worldwide [1]. Currently, mood stabilizers are the first-line treatment for individuals with BD, however their effectiveness in treating depressive episodes remains unclear [2,3]. As such, antidepressants still play a valuable role in treating bipolar depression [3]. Unfortunately, a potential side effect of antidepressant treatment in BD is antidepressant-induced mania (AIM). AIM is a complex phenomenon that affects approximately 12–30% of individuals with BD, depending on the study [4,5].

Given the effects AIM has on both clinical management and prognosis, efforts to identify potential factors behind this phenomenon has had limited success. The most promising clinical risk factors contributing to AIM are: a diagnosis of BD type I (BD-I), the use of tricyclic antidepressants versus selective serotonin reuptake inhibitors and not taking a concurrent mood stabilizer with the antidepressant. These results need to be interpreted with caution because the studies investigating these factors yield contradictory results. To the best of our knowledge, there has not been a risk factor that has been definitively associated with AIM. However, some risk factors have survived a meta-analysis, including antidepressant monotherapy, and use of tricyclic antidepressants instead of other classes [6].

In addition to the clinical studies, there have been several studies investigating the genetic variations associated with of AIM. Majority of the studies have studies the HTTLPR polymorphisms of the serotonin transporter gene (*SLC6A4*) for association with AIM. Mundo et al. (2001) reported that the 'S' allele and the 'SS' genotype of the HTTLPR polymorphism was associated with an increased risk of AIM in patients European ancestry [7]. Since this first report, there have been a number

* Corresponding author at: Molecular Brain Science Research Department, Campbell Family Mental Health Research Institute, Centre for Addiction & Mental Health, Toronto, 250 College Street, ON, Canada.
E-mail address: Lindsay.Melhuish@camh.ca (L.M. Beaupre).

https://doi.org/10.1016/j.pmip.2018.11.003

Available online 24 December 2018

of (N = 6) replication attempts in addition to a meta-analysis [8–13].

Besides, HTTLPR, recently poor and intermediate metabolizers of *CYP2D6* were reported to be at a higher risk for AIM than extensive metabolizers [14].

CYP2D6 is part of a hepatic set of genes known as the Cytochrome P450s (CYP). These genes encode for enzymes that are responsible for the synthesis and degradation of chemicals, including pharmaceuticals in the liver [15].

The CYP genes are known to have considerable interindividual differences in drug response and metabolism. Individuals can be categorized generally into four different metabolizer statuses based on the functionality of the alleles of each gene: an ultra-rapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM). The most common genetically predicated metabolizer status is an EM, who possesses two functional genes. An UM may carry more than two functional copies of the gene while a PM means an individual has no functional copy of the gene and thus has no enzymatic activity. Lastly, an IM may be classified as an individual who either only has one functional allele or has two partially functional alleles [16,17].

This study will investigate whether the metabolizer statuses at five CYP genes play a role in AIM. These genes include: *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP1A2*, and *CYP3A4*. These hepatic genes were included in the study because of their significant involvement in drug metabolism and previous literature findings [14,17].

CYP2D6. This gene is responsible for about 25% of drug metabolism [18,19]. Currently, over 100 allelic variants are known for this gene [20]. The two wild-type (WT) alleles, *1 and *2 are most commonly found in the Caucasian population (71%). The population also contains 5–10% of PM, with the PM status determined by the no-function alleles, *3, *4 and *5. *4 is the most common no-function allele in the Caucasian population (20%) but is lacking in the Asian population, where PM only account for 1–2% of the population [21].

CYP2C9. The most common variants for CYP2C9 are *1 (WT), *2 and *3. The two mutant alleles, *2 and *3 differ from *1 by a single amino acid substitution [22]. The predominant allele, *1 is found in 86% of Caucasians and 99% of African Americans. The *2 and *3 alleles are also found in higher quantities in the Caucasian population than African Americans or Asians, which do not carry the *2 allele [23].

CYP2C19. Similar to CYP2C9, the most common alleles for CYP2C19 are *1 (WT), *2 and *3, with the WT allele being the most prevalent in the Caucasian population. Unlike CYP2D6, individuals of Asian ancestry have a much higher prevalence of PM status (15%) of this gene compared to Caucasians (2%) [24]. The *17 allele has been linked with a UM status in psychiatric patients. Individuals that were homozygous for the allele displayed lower serum concentration levels of escitalopram [25].

CYP1A2 has over 20 variants identified, with many polymorphisms in the upstream sequence and intron 1 region (https://www.pharmvar.org/gene/CYP1A2). The WT allele for this gene is *1A with several other alleles identified as being associated with decreased enzymatic activity in vivo and invitro. These include, but are not limited to: *1C, *1F, *7, and *8 [26–28]. Studies have shown comparable frequencies of the WT allele among different ethnicities, though Caucasians and Japanese have a significantly larger number of individuals with *1F [27,29].

CYP3A4. This enzyme is involved in nearly half of the medications on the market today [30]. Currently, there are 30 different known alleles for this gene, with *1A being the WT allele (https://www.pharmvar.org/gene/CYP3A4). Like the previous genes that have been outlined, several alleles have been suggested to negatively affect the enzyme activity both in vivo and in vitro. For example, Hsieh et al. (2001) found three new deleterious alleles, *4, *5 and *6, all of which produce reduced enzyme activity [31]. Others that produce coding changes include *3 and *15 in Caucasians and *17 and *18 in Asians. However these alleles were found in only 2% of their respective populations [32].

In this study we will investigate whether metabolizer status of the 5 hepatic genes outlined plays a role in the risk of developing AIM. As suggested by Zhu et al. [33], we would also like to expand on the findings of the HTTLPR polymorphism of *SLC6A4* and determine whether this finding remains significant after controlling for *CYP2D6* metabolizer status. In addition, we would like to examine whether these two genes have an additive effect contributing to AIM. Lastly, we will also investigate a number of potential risk factors that have been studied in the literature.

1. Materials and methods

1.1. Subjects

Subjects recruited for this study have been described previously [7]. Participants were chosen from a larger sample of over 300 patients with a diagnosis of BD type I (BDI) and BD type II (BDII). These participants were recruited from hospitals and through newspaper advertisements in Toronto, Ontario and central Canada. All participants provided informed written consent to participate in the genetic studies. Trained clinical personnel administered the Diagnostic Structured Interview for DSM-IV Axis I diagnoses (SCID-I) [34], the Family Interview for Genetic Studies (FIGS) [35] and created put together the life charts for all study participants.

The SCID-I, FIGS and life charts available were blindly and independently reviewed by two clinical psychiatrists (E.M. and J.L.K.) to confirm diagnoses and create two groups of unrelated individuals: 27 individuals who experienced AIM (AIM+) and 29 individuals who did not (AIM−). All participants met the following criteria: 1) confirmed DSM-IV diagnosis of BDI or BDII and 2) experienced at least one depressive episode while taking pro-serotonergic antidepressants. The AIM+ status was defined as having experienced a manic or hypomanic episode induced by the antidepressants within the first 8 weeks of starting the antidepressant. Each participant in the AIM+ group was matched with a participant in the AIM-negative, matching for sex, age (± 5 years) and ethnicity.

Exclusionary criteria included: 1) uncertain diagnosis of BD (which includes individuals who experienced a manic or hypomanic episode induced by an antidepressant but no spontaneous episodes of mania or hypomania), 2) individuals with no exposure to pro-serotonergic antidepressants, and 3) individuals with inadequate or unreliable information pertaining to pharmacological treatment.

Due to the lack of DNA for a small subset of individuals, this analysis included 26 AIM+ and 25 AIM− individuals. For both groups the following clinical information was obtained: sex, diagnosis, age of onset, presence of rapid cycling, use of a concurrent mood stabilizer, and antidepressants each participant had taken.

1.2. Genetic analyses

Genomic DNA was extracted at the Center for Addictions and Mental Health (CAMH) using the high salts method [36]. All genotyping was done using TaqMan SNP genotyping assays using a preplated plate (Thermo Fisher Scientific). This plate contained several markers for each CYP gene. The following were included from *CYP2D6*: rs16947, rs1135840, rs35742686, rs3892097, rs5030655, rs1065852, rs28371706, rs59421388, rs28371725 and rs5030656. Other markers included were: rs1799853 and rs1057910 from *CYP2C9*, rs4244285, rs4986893 and rs12248560 from *CYP2C19*, rs2069514 and rs762551 from *CYP1A2*, and rs11773597 and rs28371759 from *CYP3A4*. Genotyping was confirmed by two independent researchers using the Viia 7 Real-Time PCR System and allelic discrimination program within Viia 7 software. 10% of the sample was re-genotyped for quality control. All ambiguous genotypes were retyped, and if they were still ambiguous then they were removed from further analyses.

Table 1
Genotypes Associated with Metabolizer Status (Adapted from CPIC Guidelines).

Gene	Ultra-rapid Metabolizers (UM)	Extensive Metabolizers (EM)	Intermediate Metabolizers (IM)	Poor Metabolizers (PM)
CYP1A2		*1/*1, *1/*1C, *1C/*1C, *1/*1F, *1/*1L, *1C/*1L, *1F/*1F, *1F/*1L, *1L/*1L		
CYP3A4		*1/*1, *1/*1F, *1F/*1F, *18/*18, *1/*18		
CYP2D6		*1/*1, *1/*2, *1/*5, *1/10, *1/*17, *1/*4, *1/*3, *1/*41, *2/*10, *2/*17, *2/*4, *2/*3, *2/*41, *2/*2, *1/*29, *2/*29, *2/*5, *1/*6, *2/*6, *1/*9, *2/*9	*10/*10, *5/*10, *10/*17, *4/*10 *3/*10, *10/*41, *17/*17, *5/*17, *4/*17, *3/*17, *17/*41, *4/*41, *3/*41, *41/*41, *5/*41, *3/*29, *4/*29, *5/*29, *10/*29, *17/*29, *29/*41, *29/*29, *6/*10, *6/*17, *6/*41, *6/*29, *9/*9, *3/*9, *4/*9, *5/*9, *6/*9, *9/*10, *9/*17, *9/29, *9/*41	*4/*4, *4/*5, *3/*4, *3/*3, *3/*5, *5/*5, *5/*6, *4/*6, *3/*6, *6/*6
CYP2C9		*1/*1	*1/*2, *1/*3	*2/*2, *2/*3, *3/*3
CYP2C19	*17/*17	*1/*1, *1/*17, *2/*17	*1/*2, *1/*3, *2/*17	*2/*2, *2/*3, *3/*3

Copy number variant (CNV) analysis was performed for *CYP2D6* exon 9 and intron 6 using TaqMan copy-number assays and analyzed using real-time polymerase chain reactions in Viia 7. Again, 10% of the samples were re-genotyped for quality control. Metabolizer status was assigned based on the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 genes (https://www.pharmgkb.org/guidelines) (see Table 1).

1.3. Statistical analyses

Clinical and demographic risk factors were analyzed using either χ^2 or *t*-test. In cases when the expected number of individuals in a group was < 5, a Fisher's Exact Test were used. Means for age of onset were compared between AIM+ and AIM− using an independent samples *t*-test. A χ^2 test was also used to analyze the association between metabolizer status for the 5 hepatic genes and AIM. Odds ratios were also conducted for each of the genes comparing the two groups: EM versus IM plus PM. A binary logistic regression analysis was conducted to examine the association of HTTLPR genotypes with AIM, considering *CYP2D6* metabolizer status as a covariate. Finally, a Fisher's Exact test was done to determine whether individuals who were PM or IM of *CYP2D6* carrying the "S" allele of HTTLPR were at a greater risk of experiencing AIM.

2. Results

The sample was a subset of the original sample used by Mundo et al. [7].The main demographic and clinical information are summarized in Table 2. Of the clinical factors studied, the concurrent mood stabilizer treatment was to be protective against AIM (p = 0.0001). All other factors studied were not associated with AIM.

The results from analyses of metabolizer status with AIM are summarized in Table 3. Analyses could not be performed for *CYP1A2* or *CYP3A4* because all the individuals in the sample were determined to be EM. There were no significant differences between metabolizer status for *CYP2D6*, *CYP2C9* or *CYP2C19* (Table 3). Following our first analyses, we grouped PMs and IMs together for the three genes we could analyze and compared EMs to PMs+ IMs (Table 4). There were still no significant findings for *CYP2C19* or *CYP2C9*. However, when we grouped PMs and IMs together for *CYP2D6*, our findings were in the same direction of those observed by Sánchez-Iglesias et al. [14]. PMs and IMs were 4× more likely to experience AIM than EMs individuals, but overall, these results were not statistically significant (p = 0.14, CI: 0.786, 22.843).

Table 2
Demographic Summary of AIM+/AIM− from the TB Sample.

	AIM+ group (N = 26)	AIM− group (N = 25)	p-value
Males/Females	9/17	5/18	0.9
Age of Onset, mean (SD)	20.88 (6.42)	20.24 (6.57)	0.73[a]
Age of Onset, N (%)			0.483
Childhood Onset (< 18)	14 (53.8)	10 (40)	
Adult Onset (≥18)	17 (65.38)	14 (53.8)	
Bipolar Diagnosis, N (%)			
BD type I	14 (53.8)	14 (56.0)	0.64[b]
BD type II	11 (42.3)	9 (36.0)	
Schizoaffective Bipolar type	1 (3.8)	0 (0)	
Rapid Cycling, N (%)	4 (15.4)	2 (8.0)	0.67[c]
Concurrent Mood Stabilizer, N (%)	4 (15.4)	19 (76)	0.0001[d]

*Data was missing for 2 individuals for age of onset and rapid cycling.
[a] Independent samples *t*-test used.
[b] BD type I vs. BD type II were analyzed.
[c] Fisher's Exact test was used.
[d] Significant at p < 0.01.

Table 3
CYP Genes in AIM.

Gene	Metabolizer Status	Antidepressant induced Mania		Chi square Analysis	p-value
		Present	Absent		
CYP2C19	UM	1	1	0.904	0.636
	EM	18	20		
	IM	7	4		
	PM	0	0		
CYP2C9	UM	0	0	0.243	0.886
	EM	12	13		
	IM	10	4		
	PM	4	4		
CYP2D6	UM	0	0	3.363	0.186
	EM	19	23		
	IM	2	1		
	PM	5	1		
CYP1A2	UM	0	0	N/A	N/A
	EM	26	25		
	IM	0	0		
	PM	0	0		
CYP3A4	UM	0	0	N/A	N/A
	EM	26	25		
	IM	0	0		
	PM	0	0		

Table 4
Grouping IM + PM compared to EM.

Gene	Metabolizer Status	Antidepressant induced Mania		Fisher's exact-test p-value	Odds Ratio	95% Confidence Intervals
		Present	Absent			
CYP2C19	EM	18	20	0.496	1.944	0.487, 7.758
	IM + PM	8	5			
CYP2C9	EM	12	13	0.782	1.264	0.421, 3.797
	IM + PM	14	8			
CYP2D6	EM	19	23	0.14	4.237	0.786, 22.843
	IM + PM	7	2			

We observed that individuals with the 'SS' genotype of the HTTLPR polymorphism of *SLC6A4* were 3.26 folds more likely to experience AIM (p = 0.02, CI: 1.2, 8.85) than individuals with the 'LS' or 'LL' genotypes, when *CYP2D6* metabolizer status was accounted for in the analysis. Lastly, we found that individuals that were PM or IM of *CYP2D6* who also carried a "S" allele of the HTTLPR of *SLC6A4* had a nine-fold greater likelihood of experiencing AIM (p = 0.002, CI: 1.82, 48.82).

3. Discussion

Our study provides further support for antidepressants (without concurrent mood stabilizer treatment) being a risk factor for AIM. This finding is in line with several previous studies [37–40] including a meta-analysis [6]. Interestingly, Lieberman et al. [41] reported higher switch rates among those taking an antidepressant without a concurrent mood stabilizer, but the results were not statistically significant. We failed to detect any associations with sex, type of BD, or rapid cycling, which have previously been associated with AIM in other studies [8,11,39,42]. Overall, while these clinical risk factors cannot be entirely ruled out as playing a role in AIM risk, they likely do not play major roles.

Our pharmacogenetic findings extend upon the findings from Sánchez-Iglesias et al. [14] in a larger sample (N = 51). Based on their study, we hypothesized that PMs and IMs of *CYP2D6* would be at a significantly greater risk of experiencing AIM. However, we were unable to find significant associations between metabolizer status of *CYP2C9*, *CYP2C19* or *CYP2D6* and risk of AIM even though our data suggest that PMs and IMs of *CYP2D6* may be at a greater risk of developing AIM than are EMs.

Given the role *CYP2D6* plays in the break-down of drugs in the liver, including many antidepressants [17], it seems quite likely that the gene is involved in side-effects. In fact, a pilot study investigating the effects of *CYP2D6* metabolizer status on antidepressant response found that PMs were four times more likely to have adverse effects from antidepressants, which suggests that PMs would be more likely to experience AIM than other metabolizers [43].

Considering the recommendation of Zhu et al. [33] we investigated whether the HTTLPR findings would remain significant when controlling for *CYP2D6* metabolizer status. The sample used for this study was the same as the one used to first implicate the HTTLPR polymorphism in AIM. In that original sample by Mundo et al. [7] (N = 57), the 'SS' genotype was associated with a greater risk for AIM (p = 0.002). Our results were in the same direction, such that individuals with the 'SS' genotype were still at a greater risk of AIM, when *CYP2D6* metabolizer status was a covariate in the analysis (p = 0.02). To extend upon these findings, we decided to see whether the two genes would have an additive effect. We found that PMs and IMs carrying the 'S' allele experienced a nine-fold increase in their chance of developing AIM, which is much greater than the five-fold increase found for just the 'S' allele in our sample.

We hypothesized that PMs and IMs of *CYP2D6* would be at a greater risk of experiencing AIM because they are not as efficient at metabolizing the antidepressant and therefore there is a greater build-up of the drug in the individual's system, and this excess is what leads to a manic switch. We did not find support for our hypothesis, as *CYP2D6* metabolizer status was not significantly associated with AIM.

This study was not without limitations. First, this study had a small sample size, especially for a genetic study. Future work should attempt to validate our findings in larger samples to determine whether *CYP2D6* metabolizer status is a significant risk factor for AIM. In addition to this, our study was based on a retrospective design, which can have more bias than a prospective design.

4. Conclusion

Overall our investigation is the first to suggest that *CYP2D6* metabolizer status is not an independent risk factor of AIM, but when combined with the risk allele of HTTLPR, it is. Individuals that are PMs or IMs of *CYP2D6* and carry the 'S' allele of HTTLPR are at a much greater risk of developing AIM. The effect size of the HTTLPR was only 5.1, but when the *CYP2D6* metabolizer status is incorporated then the effect size increases to 9.4. Lastly, we report that *CYP2D6* metabolizer status does not influence the previously reported HTTLPR findings however, when combined, they lead to an even greater risk of experiencing AIM.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2018.11.003.

References

[1] Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. Arch Gen Psychiatry 2015;64:543–52.
[2] Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004;161:1537–47. https://doi.org/10.1176/appi.ajp.161.9.1537.
[3] Malhi GS, Adams D, Lampe L, Paton M, O'connor N, Newton LA, et al. Clinical practice recommendations for bipolar disorder. Acta Psychiatr Scand 2009;119:27–46. https://doi.org/10.1111/j.1600-0447.2009.01383.x.
[4] Tondo L, Baldessarini RJ, Hennen J, Floris G. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. Am J Psychiatry 1998;155:638–45. https://doi.org/10.1176/ajp.155.5.638.

[5] Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord 2003;5:407–20.
[6] Tondo L, Vazquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand 2009;121:404–14.
[7] Mundo E, Walker M, Cate T, Macciardi F, Kennedy JL. The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder. Arch Gen Psychiatry 2001;58:539–44.
[8] Baumer FM, Howe M, Gallelli K, Simeonova DI, Hallmayer J, Chang KD. A pilot study of antidepressant-induced mania in pediatric bipolar disorder: characteristics, risk factors, and the serotonin transporter gene. Biol Psychiatry 2006;60:1005–12. https://doi.org/10.1016/j.biopsych.2006.06.010.
[9] De Aguiar A, Silva F, Filardi F, Silveira G, Romano-silva MA, Marques D, et al. The role of 5-HTTLPR polymorphism in antidepressant-associated mania in bipolar disorder. J Affect Disord 2009;112:267–72. https://doi.org/10.1016/j.jad.2008.04.012.
[10] Serretti A, Artioli P, Zanardi R, Lorenzi C, Rossini D, Cusin C, et al. Genetic features of antidepressant induced mania and hypo-mania in bipolar disorder. Psychopharmacology 2004;174:504–11. https://doi.org/10.1007/s00213-004-1948-x.
[11] Frye MA, Mcelroy SL, Prieto ML, Harper KL, Fuentes M, Cuellar-barboza AB, et al. Clinical risk factors and serotonin transporter gene variants associated with antidepressant-induced mania. J Clin Psychiatry 2015;62:174–80. https://doi.org/10.4088/JCP.14m09127.
[12] Rousseva A, Henry C, van den Bulke D, Fournier G, Laplanche J-L, Leboyer M, et al. Antidepressant-induced mania, rapid cycling and the serotonin transporter gene polymorphism. Pharmacogenomics J 2003;3:101–4. https://doi.org/10.1038/sj.tpj.6500156.
[13] Masoliver E, Menoyo A, Pérez V, Volpini V, Del Rio E, Pérez J, et al. Serotonin transporter linked promoter (polymorphism) in the serotonin transporter gene may be associated with antidepressant-induced mania in bipolar disorder. Psychiatr Genet 2006;16:25–9. https://doi.org/10.1097/01.ypg.0000180684.26288.d7.
[14] Sánchez-Iglesias S, García-Solaesa V, García-Berrocal B, Sanchez-Martín A, Lorenzo-Romo C, Martín-Pinto T, et al. Role of pharmacogenetics in improving the safety of psychiatric care by predicting the potential risks of mania in CYP2D6 poor metabolizers diagnosed with bipolar disorder. Medicine (Baltimore) 2016;95:e2473https://doi.org/10.1097/MD.0000000000002473.
[15] Zanger UM, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal Bioanal Chem 2008;392:1093–108.
[16] Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther 2007;116:496–526. https://doi.org/10.1016/j.pharmthera.2007.09.004.
[17] Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 2013;138:103–41. https://doi.org/10.1016/j.pharmthera.2012.12.007.
[18] Zhou S-F. Polymorphism of human cytochrome P450 2D6 and its clinical significance. Clin Pharmacokinet 2009;48:761–804. https://doi.org/10.2165/11318070-000000000-00000.
[19] Zhou S-F. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. Clin Pharmacokinet 2009;48:761–804. https://doi.org/10.2165/11318070-000000000-00000.
[20] Sim SC, Ingelman-Sundberg M. Update on Allele nomenclature for human cytochromes P450 and the human cytochrome P450 allele (CYP-Allele) nomenclature database. Cytochrome P450 Protoc 2013:251–9.
[21] Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Steven Leeder J. Prediction of CYP2D6 phenotype from genotype across world populations. Genet Med 2017;19:69–76. https://doi.org/10.1038/gim.2016.80.
[22] Stubbins M. Genetic analysis of the human cytochrome P450 CYP2C9 locus. Pharmacogenetics 1996;6:429–39.
[23] Sullivan-Klose TH, Ghanayem BI, Bell DA, Zhang ZY, Kaminsky LS, Shenfield GM, et al. The role of the CYP2C9-Leu359 allelic variant in the tolbutamide polymorphism. Pharmacogenetics 1996;6:341–9. https://doi.org/10.1097/00008571-199608000-00007.
[24] Goldstein JA, Ishizaki T, Chiba K, De Morais SMF, Bell D, Krahn PM, et al. Frequencies of the defective CYP2C19 alleles responsible for the mephenytoin poor metabolizer phenotype in various Oriental, Caucasian, Saudi Arabian and American black populations. Pharmacogenetics 1997;7:59–64. https://doi.org/10.1097/00008571-199702000-00008.
[25] Rudberg I, Mohebi B, Hermann M, Refsum H, Molden E. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther 2008;83:322–7.
[26] Nakajima M, Yokoi T, Mizutani M, Kinoshita M, Funayama M, Kamataki T. Genetic polymorphism in the 5'-flanking gene: effect on the CYP1A2 inducibility region of human in humans. J Biochem 1999;125:803–8.
[27] Soyama A, Saito Y, Hanioka N, Maekawa K, Komamura K, Kamakura S, et al. Single nucleotide polymorphisms and haplotypes of CYP1A2 in a Japanese population. Drug Metab Pharmacokinet 2005;20:24–33.
[28] Saito Y, Hanioka N, Maekawa K, Isobe T, Tsuneto Y, Nakamura R, et al. Functional analysis of three CYP1A2 variants found in a Japanese population. Drug Metab Dispos 2005;33:1905–10. https://doi.org/10.1124/dmd.105.005819.
[29] Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. Eur J Clin Pharmacol 2007;63:537–46. https://doi.org/10.1007/s00228-007-0288-2.
[30] Guengerich F. Human cytochrome P-450 enzymes. In: de Montellano O, editor. Cytochrome P-450. 2nd ed.New York, NY: Plenum Press; 1995. p. 473–535.
[31] Hsieh KP, Lin YY, Cheng CL, Lai ML, Lin MS, Siest JP, et al. Novel mutations of CYP3A4 in Chinese. Drug Metab Dispos 2001;29:268–73.
[32] Dai D, Tang JUN, Rose R, Hodgson E, Bienstock RJ, Mohrenweiser HW, et al. Identification of variants of CYP3A4 and characterization of their abilities to metabolize testosterone and chlorpyrifos. J Pharmacol Exp Ther 2001;299:825–31.
[33] Zhu J, Klein-Fedyshin M, Stevenson JM. Serotonin transporter gene polymorphisms and selective serotonin reuptake inhibitor tolerability: review of pharmacogenetic evidence. Pharmacotherapy 2017;37:1089–104. https://doi.org/10.1002/phar.1978.
[34] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. fourth ed. Washington, DC: American Psychiatric Association; 1994.
[35] Maxwell M, NIMH Molecular Genetics Iniative. Family Interview for Genetic Studies 1992. http://www-grb.nimh.gov/interviews.html.
[36] Lahiri D, Nurnberger Jr J. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic Acids Res 1991;19:5444.
[37] Bottlender R, Rudolf D, Strauß A. Mood-stabilisers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. J Affect Disord 2001;63:79–83.
[38] Henry C, Ph D, Sorbara F, Lacoste J, Gindre C, Leboyer M, et al. Antidepressant-induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry 2001;62:249–55.
[39] Koszewska I, Rybakowski JK. Antidepressant-induced mood conversions in bipolar disorder: a retrospective study of tricyclic versus non-tricyclic antidepressant drugs. Neuropsychobiology 2009;59:12–6. https://doi.org/10.1159/000202824.
[40] Tada M, Uchida H, Mizushima J, Suzuki T. Antidepressant dose and treatment response in bipolar depression: reanalysis of the systematic treatment enhancement program for bipolar disorder (STEP-BD) data. J Psychiatr Res 2015;68:151–6. https://doi.org/10.1016/j.jpsychires.2015.06.015.
[41] Lieberman DZ, Kolodner G, Massey SH, Williams KP. Antidepressant-induced mania with concomitant mood stabilizer in patients with comorbid substance abuse and bipolar disorder. J Addict Dis 2009;28:348–55. https://doi.org/10.1080/10550880903182994.
[42] Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck FE, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006;163:232–9. https://doi.org/10.1176/appi.ajp.163.2.232.
[43] Rau T, Wohlleben G, Wuttke H, Thuerauf N, Lunkenheimer J, Lanczik M, et al. CYP2D6 genotype: impact on adverse effects and nonresponse during treatment with antidepressants – a pilot study. Clin Pharmacol Ther 2004;75:386–93. https://doi.org/10.1016/j.clpt.2003.12.015.