Genetic variability at IMPA2, INPP1 and GSK3β increases the risk of suicidal behavior in bipolar patients


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Abstract
Bipolar patients (BP) are at high risk of suicide. Causal factors underlying suicidal behavior are still unclear. However, it has been shown that lithium has antisuicidal properties. Genes involved in its putative mechanism of action such as the phosphoinositol and the Wnt/β-catenine pathways could be considered candidates for suicidal behavior (SB). Our aim was to investigate the association of the IMPA1 and 2, INPP1, GSK3α and β genes with suicidal behavior in BP. 199 BP were recruited. Polymorphisms at the IMPA1 (rs915, rs1058401 and rs2268432) and IMPA2 (rs66938, rs1020294, rs1250171 and rs630110), INPP1 (rs3791809, rs4853694 and 909270), GSK3α (rs3745233) and GSK3β (rs334558, rs1732170 and rs11921360) genes were genotyped. All patients were grouped and compared according to the presence or not of history of SB (defined as the presence of at least one previous suicidal attempt). Single SNP analyses showed that suicide attempters had higher frequencies of AA genotype of the rs66938-IMPA2 and GG genotype of the rs4853694-INPP1gene compared to non-attempters. Results also revealed that T-allele carriers of the rs1732170-GSK3β gene and A-allele carriers of the rs11921360-GSK3β gene had a higher risk for attempting suicide. Haplotype analysis showed that attempters had lower frequencies of A:A haplotype (rs4853694:rs909270) at the INPP1 gene. Higher frequencies of the C:A haplotype and lower frequencies of the A:C haplotype at the GSK-3β gene (rs1732170:rs11921360) were also found to be associated to SB in BP.
1. Introduction

Bipolar disorder (BD) exerts a substantial impact on morbidity, mortality and functional outcome and is ranked one of the most disabling diseases worldwide (World Health Organization, 2008). BD spectrum’s prevalence has been recently estimated at around 2.4% worldwide (Merikangas et al., 2011) with heritability ranging as high as 80% (Kieseppa et al., 2004). Rates of suicidal ideation and suicide attempts in bipolar patients (BP) are amongst the highest in psychiatric illnesses (Valtonen et al., 2005; Chen and Dilsaver, 1996) and it has been estimated that around 15-20% die by suicide (Baldeckarini et al., 2006a; Abreu et al., 2009).

Causal factors underlying suicidal behavior are complex and its emergence is likely due to the interaction of clinical, psychosocial and genetic variables (Correa et al., 2004). Some known clinical and sociodemographic factor associated with SB in BP include gender (Nivoli et al., 2011), previous suicidal attempt (Hawton et al., 2005), presence of suicidal ideation (Valtonen et al., 2005; Leverich et al., 2003; Oquendo et al., 2000; Roy-Byrne et al., 1988), early age at onset (Slama et al., 2004; Perlis et al., 2004; Lopez et al., 2001; Tsai et al., 1999), BD II diagnosis (Pompili et al., 2009; Rihmer and Pestality, 1999) alcohol abuse/misuse (Dalton et al., 2003; Lopez et al., 2001), stimulant abuse (Gonzalez-Pinto et al., 2007), depressive episodes, mixed episodes (Dalton et al., 2003; Oquendo et al., 2000; Goodwin and Jamison, 1990; Pacchiarotti et al., 2011a), family history of suicide (Lopez et al., 2001; Romero et al., 2007), illness duration (Oquendo et al., 2000; Roy-Byrne et al., 1988), any comorbidity (Viesta et al., 1999; Viesta et al., 2000), first-episode polarity (Chaudhury et al., 2007; Ryu et al., 2010; Daban et al., 2006), depressive predomina-

The systems traditionally examined in genetic studies are those involved in the pathophysiology of affective and other psychiatric disorders with high rates of suicidal behaviors: systems such as the serotonergic and dopaminergic systems, the hypothalamic-pituitary-adrenal axis and systems key to neuroplasticity (Ernst et al., 2009; Carballo et al., 2008). In the case of BP, the presence of 5 allele-5HTTLPR polymorphism of the serotonin transporter (5ERT) gene (SLC6A4) has been associated to violent suicide attempts among this group of patients (Neves et al., 2008; Neves et al., 2010). On the other hand, a Genome Wide Association Study (GWAS) carried out by Perlis et al. (2010) provide modest support of an association between FKBP5 and NGRF (p75NTR) genes and SB in BD. Nevertheless, it should be noted that this associations did not survive to multiple comparison correction. In addition, an association between Brain Derived Neurotrophic Factor (BDNF) Val66Met polymorphism and SB in BP has been also reported (Vincze et al., 2008; Kim et al., 2008). Moreover, an association between BDNF gene and violent SA has been also detected in a sample of this patients (Neves et al., 2011).

However, given naturalistic evidence that lithium may reduce risk for suicidal behavior, biological systems related to its mechanism of action may be also of interest (Cipriani et al., 2005; Baldessarini et al., 2006b; Nivoli et al., 2010). Although the molecular basis for lithium’s therapeutic effects remains to be fully elucidated, evidence supporting the involvement of both the phosphoinositol and the Wnt/β-catenine pathways have been consolidated in recent years (Serretti et al., 2009). It is known that at therapeutic concentrations, lithium immediately inhibits several enzymes, such as both isoenzymes (1 and 2) of inositol monophosphatase (IMPA), inositol polyphosphate-1-phosphatase (INPP1), and glycogen synthase kinase-3β (GSK3β) (Quiroz et al., 2004; Serretti et al., 2009), all related to the aforementioned pathways.

The phosphoinositol pathway is associated with cellular activities such as metabolism, secretion, phototransduction, cell growth and differentiation (Serretti et al., 2009). Some evidence links phosphoinositol pathway to suicidal behavior. A study using post-mortem brain tissue found that phosphoinositol pathway was altered in the PFC of depressed suicides compared to healthy matched controls (Pacheco et al., 1996; Pandey and Dwivedi, 2010). In addition, this second messenger system has been linked with some of the most studied neurochemical markers concerning the neurobiology of suicide. For instance, the 5HT2A receptor, the increased binding of which has been reported in some brain areas, mainly PFC, of suicide victims (Stockmeier, 2003; Gross-Isseroff et al., 1998), is linked to the phosphoinositol pathway by means the agonist-activation of G protein-coupled to this receptor (Sanders-Bush, 1998; Pandey and Dwivedi, 2010). Moreover, this system is involved in protein kinase C activation which, in turn, regulates genes including BDNF, decreased levels and altered receptors of which have
been linked to the pathophysiology of both suicidal behavior and depressive states (Dwivedi, 2010).

On the other hand, glycogen synthase kinase-3 (GSK3), a key component of Wnt signaling, exerts effects on neurotransmission, neuropsychology, neuronal growth and metabolism (Rowe et al., 2007). In addition, the genetic variability at the gene encoding the beta isomorph has been proposed to be a good candidate gene not only in pathophysiology of BD, but also in lithium response (Serretti et al., 2009). Moreover, a microarray study with brain post-mortem tissue carried out by Kim et al. (2007), found that glutamine synthetase, a target gene of the Wnt/β-catenine signaling pathway whose transcription is related to GSK3 inhibition, was expressed less in suicides with schizophrenia compared to those who died by other causes. The notion of a potential role of genetic variability in GSK3 comports with studies reporting that glutamine synthetase activity was significantly reduced, not only in depressed suicides, but also in suicides free of depressive symptomatology (Sequeira et al., 2009; Klempan et al., 2009). Furthermore, another study found that the enzyme activity of GSK3 was substantially increased in depressed suicides (Karege et al., 2007). However, a study carried out failed to detect an association between two promoter polymorphisms of the GSK3-β gene and suicidal behavior in a sample of patients with depression (Yoon and Kim, 2010).

By virtue of its putative antisuicidal properties, one might argue that lithium targets, at least to some extent, the underlying pathophysiology of suicidal behavior. However, less is known about the impact of genetic variability of lithium targeted pathways on suicidal behavior.

As far as we know, this is the first study to analyze the link between genetic variability at the phosphoinositol and the Wnt/β-catenine pathways and suicidal behavior in BD. Our aim was to evaluate the potential association between genetic variability at both the phosphoinositol and Wnt-β-catenine pathways and suicidal behavior in BP by testing 14 Single Nucleotide Polymorphisms (SNPs) at the inositol monophosphatase 1 (IMPA1), IMPA2, inositol polyphosphate-1-phosphatase (INPP1) and GSK3β and γ genes in a sample of suicide attempters and non attempters bipolar patients.

2. Experimental procedures

2.1. Patients

One hundred and ninety-nine unrelated Caucasian bipolar type I or II outpatients (102 males and 97 females) were recruited from the Bipolar Disorder Program (BDP) of the Hospital Clinic of Barcelona and from mental health services in Oviedo. The BDP provides integrated care for high-complexity BP not only from its catchment area in Barcelona, but also from all over Spain (Vieta, 2011a; Vieta, 2011b). The BDP has been conducting a prospective data collection on course of illness of all patients in the program since 1992. This systematic follow-up bimonthly systematically collects clinical and sociodemographic data of all patients included in the Bipolar Disorders Program. Patients are subsequently followed up and monitored. In order to be included in the database patients should provide written informed consent for the collection of their data with research purposes, always preserving confidentiality. (Colom et al., 2006; Daban et al., 2006; Nivoli et al., 2011). Therefore, this cross-sectional analysis includes both prospective and retrospective data, meaning that the former was obtained from the follow-up carried out at the BDP and the later from the patients at baseline assessment.

Inclusion criteria were as follows: (a) bipolar I or II DSM-IV-TR diagnosis, (b) age over 18 years, (c) being descended from at least two generations of Caucasian, (d) fulfilling criteria for euthymia defined as a score < 8 on the Hamilton Depression Rating Scale (HDRS) (Ramos-Brieva and Cordero, 1986; Hamilton, 1960) and a score ≤ 6 on the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978) at inclusion and during the assessment period and (e) written informed consent. Exclusion criteria were the presence of (a) mental retardation (defined as IQ < 70) and/or (b) severe organic disease. Approval from each institution’s ethics committees was obtained.

2.2. Assessment

All patients were assessed with a semi-structured interview based on the Structured Clinical Interview for DSM Disorders (SCID), which also considered available data from medical records. Presence of depressive and manic features was assessed using HDRS and YMRS, respectively. Suicidal ideation was defined as the presence of any thoughts about the desire, intent and method for committing suicide (Beck et al., 1988). Suicidal attempt was defined as a self-injurious act committed with at least some intention to die. Methods such as defenestration, hanging, deep cutting and electrocution were defined as violent, while overdoses and self-poisoning was considered non violent.

2.3. Genotyping

DNA was extracted from blood samples according to standard protocols. Several SNPs at IMPA1 gene (rs915, rs1058401 and rs2268432), IMPA2 gene (rs669838, rs1020294, rs1250171 and rs303110), INPP1 gene (rs3791809, rs4853694 and rs909270), GSK3β gene (rs3745233) and GSK3β gene (rs334558, rs1732170 and rs1921360) were selected based on literature and the SYSNPS program (www.sysnps.org). SNPs were selected with SYSNPS program only if they were TagSNPs of the candidate gene with a Minor Allele Frequency (MAF) > 0.3. This MAF criterion was used to increase the statistical power. Genotyping, blind to clinical assessment, was performed by competitive quantitative PCR using allele specific probes with FRET signal detection. A random subsample of individuals was re-genotyped in order to confirm the pattern reproducibility.

The percentage of genotyping success for each SNP according to the total sample (n = 199) was: 97.5% for rs915 (n = 194), 96.5% for rs1058401 (n = 192), 97.5% for rs2268432 (n = 194), 97.5% for rs669838 (n = 194), 98.5% for rs1020294 (n = 196), 97.5% for rs1250171 (n = 195), 97.5% for rs630110 (n = 195), 97.5% for rs3791809 (n = 194), 97.5% for rs4853694 (n = 194), 99.6% for rs909270 (n = 195), 97.5% for rs334558 (n = 192), 98.5% for rs1732170 (n = 196) and 96.9% for rs1921360 (n = 193).

2.4. Statistical analysis

Hardy-Weinberg equilibrium (HWE) for genotype frequencies was calculated using Chi-square test. Afterwards, we classified patients according to the presence or not of suicidal behavior (defined as the presence of at least one previous suicidal attempt). Genotype and allele frequencies were compared between groups using Chi-square contingency analysis. Odds ratios (OR) with 95% confidence intervals (CI) were estimated for the effects of high-risk genotypes. Statistical significance was fixed at p < 0.05. All statistical procedures were performed using PASW (version 18.0.0) and EpiInfo (version 3.5.3).

Haplotype 3.2 (Barrett et al., 2005) was used to generate a linkage disequilibrium map and to test for HWE. The ”haplo.stat” package from the “R” software (R Development Core Team, 2008) was employed to calculate haplotype frequencies. Permutation analyses (50,000 permutations) were also used to estimate the
3. Results

Sociodemographic and clinical features of patients are shown in Table 1. The sample comprised 150 BP I and 49 BP II with a mean age of 47.32 (range: 23–81). Of the total sample, 69 (34.7%) patients made at least one lifetime suicide attempt, of which 50.7% were categorized as violent.

There were no differences in age, gender and educational level. Comparing BP according to their history of suicidal behavior, we found that suicide attempters were more likely...
to be not married (p=0.011) and unemployed (p=0.024), had higher rates of suicidal ideation (p<0.001), had a higher number of depressive episodes (p=0.003) and hospitalizations (p=0.001), had more subsyndromal depressive features (p=0.001), were more likely to present a depressive onset of the illness (p<0.001) had higher rates of comorbidity in Axis II (p=0.036), had a higher prevalence of lifetime history of psychotic depression (p<0.001) and atypical features (p<0.001) and were more likely to receive antidepressant treatment (p=0.001) compared to non attempters (see Table 1).

Genotype distribution were all in HWE (p=0.89 for IMPA gene-rs915; p=0.72 for the IMPA gene-rs1058401; p=0.55 for the IMPA gene-rs2268432; p=0.49 for the IMPA2 gene-rs669838; p=0.6 for the IMPA2 gene-rs1020294; p=0.97 for the IMPA2 gene-rs1250171; p=0.97 for the IMPA2 gene-rs630110; p=1.00 for the INPP1 gene-rs3791809; p=0.99 for the INPP1 gene-rs4853694; p=0.99 for the INPP1 gene-rs909270; p=0.44 for the GSK3β gene-rs334558; p=0.42 for the GSK3β gene-rs1732170; p=0.67 for the GSK3β gene-rs11921360; p=1.00 for the GSK3β gene-rs3745233).

3.1. Single marker analysis

Single marker analysis revealed several associations between some variants in the IMPA2, INPP1 and GSK3β genes and suicidal behavior at both genotypic and allelic level. No association was detected between the IMPA1 and GSK3-α gene polymorphisms and suicidal behavior (See Table 2).

Carriers of the AA genotype for rs669838-IMPA2 gene were more likely to have a history of suicide attempt in comparison to C-allele carriers (CC or CA) (OR=2.92; CI95% [1.19–7.015]; p=0.029). Similarly, patients carrying GG genotype of the rs4853694-INPP1 gene were more likely to be suicide attempters than A-allele carriers (AA or AG) (OR=3.69; CI95% [1.05-14.56]; χ²=5.665; p=0.020).

Two SNPs in the GSK3β gene were associated with suicide attempts. Patients carrying T allele (TT or CT genotypes) of the rs1732170 (OR=2.05; CI95% [1.02-4.21]; χ²=4.753; p=0.029) and A carriers (AA or AC genotypes) of the rs11921360 gene (OR=3.25; CI95% [1.03-13.49]; χ²=4.726; p=0.029) were more likely to be suicide attempters compared to those who carried CC homozygous genotypes, respectively.

3.2. Haplotype analysis

Fig. 1 presents the results of linkage disequilibrium tests among markers at the IMPA1, IMPA2, INPP1 genes from the phosphoinositide second messenger system and the GSK3β gene from the Wnt/β-catenine signaling pathway. Haplotype frequencies and associations with suicide attempters and non-attempters are shown at Table 3. Haplotype analysis of the IMPA1 gene revealed no significant differences between suicide attempters and non-attempters.

With regard to the IMPA2 gene, single analyses have shown significant differences between suicide attempters and non-attempters when comparing genotype frequencies of the rs669838. However, this polymorphism was not in linkage disequilibrium with the other analyzed SNPs. Taking into account those in linkage disequilibrium (rs1250171 and rs630110), no significant differences were found when attempters and non-attempters were compared in terms of haplotype frequencies.

Concerning the INPP1 gene, the frequency of the A:A haplotype (rs4853694:rs909270) was lower in suicide attempters compared to non-attempters (0.223:0.324; p=0.027; sim-p=0.028). The global score statistic was also significant (Global-stat=6.05; df=2; p value=0.048; Global sim. p-val=0.049).

Regarding the GSK3β gene, those with a history of suicide attempt had both higher frequencies of the C:A haplotype and lower frequencies of the A:C haplotype (rs1732170:rs630110) when compared to non-attempters (0.522:0.387; p=0.015; sim-p=0.012 and 0.259:0.377; p=0.023; sim-p=0.021, respectively; Global-stat=6.61; df=2; p value=0.036; Global sim. p-val=0.035) (See Table 3).

4. Discussion

To the best of our knowledge, this is the first study to examine whether molecular variation at IMPA1, IMPA2, INPP1 and GSK3-α and GSK3β genes are potential genetic markers for suicidal behavior in BD. Our results suggest that genetic variability at rs669838-IMPA2, rs4853694-INPP1, rs1732170-GSK3β and rs11921360-GSK3β genes is associated with a higher risk of attempting suicide in bipolar patients.

Our study suggest that, bipolar patients with AA homozygous genotype at rs669838 at the IMPA2 gene are more likely to be suicide attempters compared to C-allele carriers. Thus, our data would complement results from two genetic association studies which reported that variability at the above mentioned gene may confer risk for BD (Sjoholt et al., 2004; Ohnishi et al., 2007). In addition, the IMPA2 gene has also emerged a potential candidate gene for pharmacogenetic studies of lithium response (Dimitrova et al., 2005), given it is a potential target for lithium’s action (Sjoholt et al., 1997). In this sense, our results would provide a possible explanation for lithium’s putative antisuicidal properties.

Our finding suggests that genetic variability at INPP1 gene increases the liability for committing suicide attempts in BD, especially for those presenting homozygous GG genotype at the rs4853694 SNP. Our study also indicated that A:A haplotype (rs4853694:rs909270) was less frequent among BP with history of SB. Therefore, our results would add some data to those studies concerning SNPs at the gene encoding INPP1 which have supported a role for genetic variability at the INPP1 gene in terms of lithium’s effect on mood stability (Michelon et al., 2006; Steen et al., 1998), although one study failed to replicate this association (Piccardi et al., 2002). This molecular variability in both IMPA2 and INPP1 genes comports with studies reporting alterations in the phosphoinositide pathway in suicides (Pacheco et al., 1996; Pandey and Dwivedi, 2010).

Genetic variability at the gene encoding GSK3β may be a potential risk factor for attempting suicide in BD: T-allele carriers of the rs1732170 and A-allele carriers of the rs11921360-GSK3β gene had approximately two-fold and three-fold greater risk of being suicide attempters, respectively, compared to those homozygous for the alternative allele. We also found higher frequencies of C:A haplotype and lower frequencies of A:C haplotype (rs1732170:rs11921360)
Table 2  Genotype and allele frequencies of variations in the IMPA1, IMPA2, INPP1, GSK3α and GSK3β genes.

<table>
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<th>SNP</th>
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<th>n</th>
<th>Genotype distribution n (f)</th>
<th>$\chi^2$</th>
<th>p</th>
<th>Allele distribution n (f)</th>
<th>$\chi^2$</th>
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<td>T 177 (0.697)</td>
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<td>C 96 (0.716)</td>
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<td>G 119 (0.875)</td>
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</table>
among attempters compared to non attempters. This is in line with work which suggest that Wnt/β-catenine signaling pathway may be involved in suicidal behavior, based on reports of alteration in glutamine synthetase activity in suicide brains (Kim et al., 2007; Sequeira et al., 2009; Klempan et al., 2009; Karege et al., 2007). Bearing in mind that lithium, at optimal concentrations, inhibits GSK3 and that some authors consider that its possible antisuicidal effects could be related to its capacity to increase glutamine synthetase, expression (Kalkman, 2011), genetic variability at genes linked to this pathway may confer an increased liability to suicidal behavior.

Last but not least, due to some limitations, our results should be interpreted with caution. Firstly, our sample is relatively small, although our sample allows detection of an OR ≥ 1.5 with statistical power higher than 80%. Secondly, we have examined a total of 14 SNPs from five different genes and analyses were not corrected for multiple testing. Despite the fact that Bonferroni correction could be used to correct multiple testing, it was considered that the use of this procedure would be too restrictive in this exploratory study. Moreover, haplotype analysis, a more powerful genetic and statistical approach, confirmed the analyses conducted on single SNPs. Thirdly, SNPs that showed a significant effect on suicidal phenotype are located in intronic regions and its functional relevance has not been described. However, these variants could be in linkage disequilibrium with functional ones or they could be affecting splice sites as has been described for other intronic variability (Baralle and Baralle, 2005). Unfortunately, testing for SNP functionality is not a simple task and studies of complex disease often fail to verify causality of individual SNP for the phenotype (Olivier, 2004). Another limitation remains in the fact that no specific scale concerning suicide assessment was used. Finally, none of the patients of this study committed suicide, therefore, we did not obtain data from this group of patients, probably the most severe phenotype of suicidal behavior in BD and in general.

In summary, despite limitations, our results indicate an association between SNPs in the genes encoding IMPA2, INNP1 and GSK3β proteins and suicide attempts in BD and provide insight into the potential impact of genetic variability in both the phosphoinositide second messenger system and the Wnt/β-catenine pathway on suicidal behavior. Expanding our knowledge and understanding about the impact of these pathways on suicidal behavior may improve its prevention and management by providing new biological tools for the early detection of patients at high risk, but also providing guidance in the design of new drugs with antisuicidal properties. Further studies with larger samples and novel targets focused on genetic variability of genes linked to underlying molecular basis of BD are needed, not only to disentangle the pathophysiology of this illness, but also to decipher the potential contributory role of genetic variation at those pathways to the multiple comorbidities associated with BD.

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Contributors

All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Antoni Benabarre has received research grants and served as a speaker for the following companies: Grants: Janssen-Cilag and Pfizer. Speaker: Bristol-Myers Squibb, Eli Lilly, Glaxo-Smith-Kline and Janssen-Cilag.

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Dr. Garcia-Portilla has been a consultant to or has received honoraria or grants from Bristol-Myers Squibb, CIBERSAM, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Merck Sharpe and Dohme, Otsuka, Pfizer, Sanofi-Aventis.

Dr. Oquendo received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript, and was the recipient of a grant from Eli Lilly to support a year of the salary for the Lilly Suicide Scholar, Enrique Baca-García, MD, PhD. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb.

Dr. Saiz has been a consultant to or has received honoraria or grants from Adamed, Brainpharma, Bristol-Myers Squibb, CIBERSAM, Eli Lilly, GlaxoSmithKline, Instituto de Salud Carlos III, Janssen, Lundbeck, Ministerio de Ciencia e Innovación, Ministerio de Salud, Pfizer, Plan Nacional de Drogas, Reckitt-Benckiser, Sanofi-Aventis, Shering-Plough and Servier.

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Table 3 Haplotype frequencies according to Fig. 1 between suicide attempters and non-attempters.

<table>
<thead>
<tr>
<th>Haplotype (rs915:rs1058401:rs2268432)</th>
<th>Frequencies</th>
<th>SA:NA</th>
<th>p</th>
<th>Sim-p</th>
<th>Global Score Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>C:C:G</td>
<td>0.677</td>
<td>0.639:0.695</td>
<td>0.246</td>
<td>0.277</td>
<td>Global-stat=2.34; df=3; p value=0.505 Global sim. p-val=0.503</td>
</tr>
<tr>
<td>T:T:T</td>
<td>0.125</td>
<td>0.125:0.127</td>
<td>0.962</td>
<td>0.949</td>
<td></td>
</tr>
<tr>
<td>T:C:G</td>
<td>0.053</td>
<td>0.074:0.047</td>
<td>0.250</td>
<td>0.280</td>
<td></td>
</tr>
</tbody>
</table>

**IMPA2 gene (rs1250171:rs630110)**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequencies</th>
<th>SA:NA</th>
<th>p</th>
<th>Sim-p</th>
<th>Global Score Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>C:G</td>
<td>0.384</td>
<td>0.457:0.348</td>
<td>0.034</td>
<td>0.036</td>
<td>Global-stat=5.01; df=3; p value=0.171 Global sim. p-val=0.144</td>
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<tr>
<td>C:A</td>
<td>0.312</td>
<td>0.264:0.336</td>
<td>0.135</td>
<td>0.150</td>
<td></td>
</tr>
<tr>
<td>T:G</td>
<td>0.300</td>
<td>0.278:0.310</td>
<td>0.510</td>
<td>0.557</td>
<td></td>
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</table>

**INPP1 gene (rs4853694:rs909270)**

<table>
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<tr>
<th>Haplotype</th>
<th>Frequencies</th>
<th>SA:NA</th>
<th>p</th>
<th>Sim-p</th>
<th>Global Score Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A:G</td>
<td>0.443</td>
<td>0.453:0.438</td>
<td>0.767</td>
<td>0.768</td>
<td>Global-stat=6.05; df=2; p value=0.048 Global sim. p-val=0.049</td>
</tr>
<tr>
<td>A:A</td>
<td>0.288</td>
<td>0.223:0.324</td>
<td>0.027</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>G:A</td>
<td>0.269</td>
<td>0.324:0.238</td>
<td>0.068</td>
<td>0.067</td>
<td></td>
</tr>
</tbody>
</table>

**GSK3β gene (rs1732170:rs11921360)**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequencies</th>
<th>SA:NA</th>
<th>p</th>
<th>Sim-p</th>
<th>Global Score Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>T:A</td>
<td>0.431</td>
<td>0.522:0.387</td>
<td>0.015</td>
<td>0.012</td>
<td>Global-stat=6.61; df=2; p value=0.036 Global sim. p-val=0.035</td>
</tr>
<tr>
<td>C:C</td>
<td>0.337</td>
<td>0.259:0.377</td>
<td>0.023</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>C:A</td>
<td>0.232</td>
<td>0.219:0.236</td>
<td>0.700</td>
<td>0.711</td>
<td></td>
</tr>
</tbody>
</table>

Abreviations: SA=suicide attempters; NA=non attempters; Sim-p=simulated p-value.
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Reference
Genetic variability at IMPA2, INPP1 and GSK3β increases the risk of suicidal behavior in bipolar patients


