GENETIC VARIABILITY AT IMPA2, INPP1 AND GSK-3β INCREASES THE RISK OF SUICIDAL BEHAVIOUR IN BIPOLAR PATIENTS

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INTRODUCTION

Among other psychiatric illnesses, Bipolar disorder (BD) presents the highest rates of suicidality[1]. Lithium, one of the most widely used mood stabilizers in BD, has been reported to present antisuicidal properties[2]. Although its mechanism of action has not been fully elucidated, there is further insight regarding the implication of both the Phosphoinositol and the Wnt/β-catenine pathways in it[3].

OBJECTIVES

Our goal was to verify whether molecular variation at IMPA, IMPA2, INPP1 and GSK-3α and GSK-3β genes could be considered as potential genetic markers for suicide behaviour (SB) in BP.

METHODS

199 unrelated Caucasian bipolar type I or II outpatients (102 males and 97 females) were recruited from the Bipolar Disorder Unit of the Hospital Clinic of Barcelona and from primary care settings from Oviedo. All patients were grouped and compared according to the presence or the absence of history of SB (defined as the presence of at least one suicide attempt). Genomic DNA was extracted from blood samples from each participant, according to standard protocols. Several polymorphisms at the IMPA1, IMPA2, INPP1, GSK3α and GSK3β genes were genotyped.

RESULTS

Single marker analysis revealed several associations between some of the variants at the IMPA2, INPP and GSK-3β genes and SB in our BP sample, on both genotypic and allelic level (Table 1 and 2). No association was detected between the IMPA1 and GSK-3α gene polymorphisms and SB.

Gen IMPA2-rs669838

		Genotype distribution n (f)			*Allele distribution n (f)*	
Sample	***n***	***CC***	***CA***	***AA***	***C***	***A***
SA	68	33 (0.485)	19 (0.279)	16 (0.235)	85 (0.625)	51 (0.375)
NA	126	56 (0.444)	58 (0.460)	12 (0.095)	170 (0.675)	82 (0.325)
		X^2= 9.805; p= .007			X^2= 0.86; p= .350	
AA genotype →OR= 2.92; IC95% [1.19-7.26]; χ^2= 7.015; p=.008						

Gen INNP1-rs4853694

Sample	***n***	***AA***	***AG***	***GG***	***A***	***G***
SA	68	33 (0.485)	26 (0.382)	9 (0.132)	92 (0.676)	44 (0.324)
NA	126	71 (0.563)	50 (0.397)	5 (0.004)	192 (0.762)	60 (0.238)
		X^2= 5.783; p= .055			X^2= 3.29; p= .069	
GG genotype → OR=3.69;IC95%[1.05-14.56];χ^2=5.665;p=.020						

Table 1. Genotype and allele frequencies of variations at the IMPA2 and INPP1 genes. (SA= Suicide attempters; NA= Non-attempters).

Patients carrying AA and GG genotypes of the rs669838-IMPA2 gene and the rs4853694-INPP1 gene, respectively, presented higher risk of committing a SA. Concerning the GSK-3β gene, two SNPs were found to be associated with the emergence of SB.

Patients carrying T allele of the rs1732170 and A carriers of the rs11921360 presented a higher risk of attempting suicide compared to those patients who carried CC genotypes, respectively.

Gen GSK3B-rs1732170

		Genotype distribution n (f)			*Allele distribution n (f)*	
Sample	***n***	***CC***	***CT***	***TT***	***C***	***T***
SA	68	17 (0.250)	31 (0.456)	20 (0.294)	65 (0.478)	71 (0.522)
NA	128	52 (0.406)	53 (0.414)	23 (0.180)	157 (0.613)	99 (0.387)
		X^2= 5.911; p= .052			X^2= 6.62;p= .010	
T-allele carriers →OR=2.05; IC95% [1.02-4.21];χ^2=4.753;p=.029						

rs11921360- GSK3β gene

Sample	***n***	***AA***	***AC***	***CC***	***A***	***C***
SA	66	36 (0.545)	26 (0.394)	4 (0.061)	98 (0.742)	34 (0.258)
NA	127	53 (0.417)	52 (0.409)	22 (0.173)	158 (0.622)	96 (0.378)
		X^2= 5.661;p= .059			X^2= .564; p= .017	
A-allele carriers → OR=3.25;IC95%[1.03-13.49];χ^2=4.726;p=.029						

Table 2. Genotype and allele frequencies of variations at the GSK3β genes. (SA= Suicide attempters; NA= Non-attempters).

Moreover, haplotype analysis also revealed significant differences in haplotype distributions concerning INPP1 and GSK3β genes (Table 2).

Haplotype	***Frequencies***	***SA:NA***	***χ^2***	***p***	***Global Score Statistics***
INPP1 gene (rs4853694:rs909270)					
A:C	0.443	0.453:0.438	0.086	.768	*Global-stat=6.05* *p=.048*
A:A	0.288	0.223:0.324	4.395	**.036**	
C:A	0.269	0.324:0.238	3.302	.069	
GSK3β gene (rs1732170:rs11921360)					
C:A	0.431	0.522:0.387	6.624	**.010**	*Global-stat=6.61* *p =.036*
A:C	0.337	0.259:0.377	5.598	**.018**	
A:A	0.232	0.219:0.236	0.140	.707	

Table 3. Haplotype distribution between suicide attempeters (SA) and non-attempters (NA).

CONCLUSIONS

Our results suggest that genetic variability at IMPA2, INPP1 and GSK3β is associated with the emergence of SB in BP. Therefore our data would strengthen those studies which have suggested the potential significant role of genetic variability at the phosphoinositol signaling pathway and the Wnt/β-catenine pathway in both suicide and bipolar disorder.

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