IMPACT OF PLA2 GENE POLYMORPHISMS ON ONSET OF SCHIZOPHRENIA AND ILLNESS SEVERITY

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INTRODUCTION

Abnormal membrane phospholipid metabolism was repeatedly implicated in the etiology of schizophrenia.

Reduced levels of n-3 and n-6 polyunsaturated fatty acids (PUFAs), namely docosahexaenoic (DHA, 22:6n-3) and arachidonic (AA, 20:4n-6) acids in the brain and red blood cell (RBC) membranes of schizophrenic patients were accompanied with increased activity of phospholipase A2 (PLA2) enzymes in temporal cortex and serum. Brain phospholipids provide an interesting means for studying gene-environment interactions in schizophrenia because enzymes that regulate phospholipid metabolism (i. e. PLA2) are genetically determined and fatty acid composition of cell membranes is largely influenced by nutrition, medications and oxidative stress.

A number of studies have investigated the association between genes coding for different classes of PLA2 enzymes and etiology of schizophrenia. Positive association has been reported between BanI polymorphic site of the PLA2G4A gene (cytosolic PLA2; cPLA2) and schizofrenia in British, US Caucasian, Brazilian, Indian and Korean population, two polymorphisms of other cPLA2 genes (PLA2G4B and PLA2G4C) in Chinese population, as well as between polymorphism of the PLA2G6A (calcium-independent PLA2; iPLA2) and illness in Brazilian population.

In our study we tested whether the risk for schizophrenia was associated with allelic and genotype frequencies of single nucleotide polymorphisms (SNPs) in three genes of PLA2 superfamily: rs1549637 (A/T) of the PLA2G4C, rs10798059 (A1/A2; BanI) of the PLA2G4A and rs4375 (T/C) of the PLA2G6A and we also examinated SNPs' possible impact on age of onset and symptom severity.

METHODS

Allelic and genotype frequencies or their combinations were determined in 159 Croatian patients with schizophrenia from Department of Psychiatry, Clinical Medical Centre, Rijeka and in 187 healthy controls, who were blood donors, using polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP) analysis and the significance of the differences was performed using x^2 test. Association between mean age at first hospital admission and data of PANSS score (positive and negative symptom scale) with SNPs' allelic and genotypic variations or their combinations in 81 schizophrenic patients (their clinical features are presented in Table 1.) were tested by nonparametric Kendall Tau correlations. Probability (P) values less than 0.05 were considered statistically significant. All statistical analyses were conducted using the Statistica software package for Windows, StatSoft, Inc. (2005), Version 7.1.

RESULTS

x^2 test did not show significant difference of allelic and genotype frequencies or their combinations between schizophrenic patients and healthy controls (Table 2). BanI polymorphism of the PLA2G4A gene significantly impacted the onset of disease in male patients indicating that lower mean age at first hospitalisation could be correlated to the absence of the allele A1 or the presence of the A2A2 genotype (Table 3). Increased symptom severity during a psychotic state rated by PANSS psychopatology scale correlated significantly (in all patients as well in males separately) with the presence of the PLA2G4C-T and absence of the PLA2G4A-A2 allele. The presence of the PLA2G6A-C, alone or synergizing with PLA2G4C-T allele, increased symptom severity only in males, while PLA2G4A-A2 alone, in combination with PLA2G4C-A or PLA2G6A-T, tended to decrease symptom severity (Table 4).

Table 1. Clinical characteristics of 81 shizophrenic patients[a]

	age (years)	age at first hospitalisation[b]	PANSS positive score	PANSS negative score	PANSS general psychopatholoy score	PANSS total score	CGI (clinical global impression)
males (N=43)	37.67 ± 10.35	24.23 ± 5.76	26.45 ± 5.07	29.36 ± 5.72	51.90 ± 7.19	107.71 ± 13.75	5.40 ± 0.83
females (N=38)	40.87 ± 10.63	28.37 ± 8.20	26.47 ± 5.74	29.16 ± 6.59	52.29 ± 7.01	107.92 ± 13.62	5.32 ± 0.84
total (N=81)	39.17 ± 10.54	26.17 ± 7.27	26.46 ± 5.37	29.26 ± 6.11	52.09 ± 7.06	107.81 ± 13.60	5.36 ± 0.83

[a] Values are expressed as mean ± standard deviation
[b] Statistically significant difference between males and females: P = 0.009

Table 2. The frequency of rs 1549637 (PLA2G4C), rs10798059 (PLA2G4A) and rs4375 (PLA2G6A) genotypes and alleles in schizophrenic patients and healthy controls[a]

PLA2G4C-rs1549637	genotypes			alleles	
	AA	AT	TT	A	T
Patients (N=159)	118 (74.2%)	38 (23.9%)	3 (1.9%)	274 (86.2%)	44 (13.8%)
Controls (N=187)	138 (73.8%)	44 (23.5%)	5 (2.7%)	320 (85.6%)	54 (14.4%)
PLA2G4A-rs10798059	**genotypes**			**alleles**	
	A1A1	**A1A2**	**A2A2**	**A1**	**A2**
Patients (N=159)	27 (17.0%)	68 (42.8%)	64 (40.2%)	122 (38.4%)	196 (61.6%)
Controls (N=187)	30 (16.0%)	87 (46.6%)	70 (37.4%)	147 (39.3%)	227 (60.7%)
PLA2G6A-rs4375	**genotypes**			**alleles**	
	T/T	**T/C**	**C/C**	**T**	**C**
Patients (N=159)	81 (50.9.%)	52 (32.7%)	26 (16.4%)	185 (58.2%)	133 (41.8%)
Controls (N=187)	83 (44.4%)	66 (35.3%)	38 (20.3%)	215 (57.5%)	159 (42.5%)

[a] Differences in frequency are not statistically significant: P > 0.05

Table 3. Mean age at first hospitalization in correlation to *BanI* genotype in

	PLA2G4A total[a] (N=81)	males[b] (N=43)	females[a] (N=38)
A1 allele positive (A1A1 and A1A2)	27.14 ± 6.92	25.62 ± 5.41	28.78 ± 8.02
A1 allele negative (A2A2)	24.00 ± 7.70	21.36 ± 5.54	27.36 ± 8.95

[a] Non-significant difference
[b] Statistically significant difference: Kendall Tau = 0.331, Z = 3.124, P = 0.002

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Table 4. Associations between scores from PANSS psychopathology scale and PLA2 genotypes, alleles and their combinations[a]

Pair of variables		All (N=81) r	z	p-level
Negative scale score	G4C-T allele present + G4A-A2 allele absent	0.158	2.076	0.038
	G4A-A2 allele present	-0.165	-2.162	0.031
	G4C-A allele present + G4A-A2 allele present	-0.170	-2.226	0.026
General psychopathology scale score	G4A-A2 allele present	-0.177	-2.328	0.020
	G4C-A allele present + G4A-A2 allele present	-0.153	-2.012	0.044
Total PANSS score	G4A-A2 allele present	-0.197	-2.591	0.009
	G4C-A allele present + G4A-A2 allele present	-0.188	-2.465	0.014
		Males (N=43)		
Negative scale score	G4C genotype	0.262	2.449	0.014
	G4C-T allele present + G4A-A2 allele absent	0.233	2.174	0.030
	G4C-T allele present	0.256	2.392	0.017
	G4C-A allele present + G4A-A2 allele present	-0.283	-2.639	0.008
	G4C-A allele present + G6A-T allele present	-0.250	-2.336	0.020
	G4C-T allele present+ G6A-C allele present	0.296	2.761	0.006
General psychopathology scale score	G6A-C allele present	0.215	2.007	0.045
Total PANSS score	G6A-C allele present	0.221	2.059	0.039
	G4C-A allele present + G4A-A2 allele present	-0.221	-2.064	0.039

[a] Associations were tested by nonparametric Kendall Tau correlations

CONCLUSIONS

- Allelic and genotype frequencies of SNPs: rs1549637, BanI and rs4375 in our population resulted closer to the allelic frequencies in other European, American population of Northern and Western European origin and Brazilian population and frequencies were quite different from the allelic ratios in Chinese and Korean populations.
- Allelic and genotype frequencies of all three investigated SNPs did not show significant difference between patients with schizophrenia and healthy controls; therefore, neither polymorphic site tested in our study could be associated with an elevated risk for schizophrenia.
- Investigated SNPs, alone or in combination, may contribute to variable clinical expression, possibly by modulating PLA2 expression/activity and implicating a role of sex hormons as well. Evidences might be:
- BanI polymorphism of the PLA2G4A showed a significant impact on the mean age of the onset of disease in males (lower mean age at admission was found in those not having A1 allele or homozygous A2A2 males);
- All investigated SNPs or their combinations affected severity of symptoms evaluated by PANSS psychopatology scale in patients with schizophrenia (in all patients and in male patients separately).
- Larger studies exploring both, genetic and biochemical markers of abnormal phospholipid metabolism and controlling for contribution of environmetal factors (diet, medications, nicotine usage), as well as influence of age and gender, could be more helpful in elucidating the possible relationship between PLA2s's activity and pathogenesis of schizophrenia.

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