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

Sergej Nadalin, 1 Alena Buretić-Tomljanović, 2 Gordana Rubeša, 1 Jasmina Giacometti, 4 Suzana Jonovska, 1 Vesna Šendula Jengić, 1 Miljenko Kapović

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 acids (AA, 20:4n-6), in 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 important means for studying gene-environment interactions in schizophrenia because enzymes that regulate phospholipid metabolism (i.e., PLA2) are genetically determined and the 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 PLA2G6A gene (cytosolic PLA2; cPLA2) and schizophrenia 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 (A/A2; BanI) of the PLA2G4A and rs4375 (T/C) of the PLA2G6A, and we also examined 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 χ² test. Association between mean age at first hospital admission and data of PANSS scale (positive and negative symptom scale) with SNPs’ allelic and genotypic variations was statistically significant (P < 0.05).

RESULTS
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Table 1. Clinical characteristics of 81 schizophrenic patients with PLA2G4C-T allele, increased symptom severity only of the A2A2 genotype (Table 3). Increased symptom that lower mean age at first hospitalisation could be impacted the onset of disease in male patients indicating schizophrenic patients and healthy controls (Table 2).

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

Table 3. Mean age at first hospitalization in correlation to BanI genotype in PLA2G4A.

Table 4. Associations between scores from PANSS psychopathology scale and PLA2G4A alleles, and their combinations.

REFERENCES

CONCLUSIONS
- Allelic and genotype frequencies of SNPs: rs1549637, BanI and rs4375 in our population resulted close 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 hormones 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 schizophrenia evaluated by PANSS psychopathology 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 environmental factors (diet, medications, nicotine usage), as well as influence of age and gender, could be more helpful in elucidating the possible relationship between PLA2’s activity and pathogenesis of schizophrenia.