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ORIGINAL PAPER

Evaluation of CNTNAP2 gene rs2107856 polymorphism in Turkish population with pseudoexfoliation syndrome

Irmak Karaca · Suzan Guven Yilmaz · Melis Palamar · Huseyin Onay · Bilcag Akgun · Burcu Aytacoglu · Ayca Aykut · Feristah Ferda Ozkinay

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Abstract

Purpose To investigate rs2107856 single-nucleotide polymorphism (SNP) of CNTNAP2 gene in Turkish population with pseudoexfoliation and to correlate clinical characteristics with the genotypic profile.

Materials and methods Forty-three patients with pseudoexfoliation syndrome (PXS), 46 patients with pseudoexfoliation glaucoma (PXG) and 99 healthy controls were enrolled. Comprehensive ophthalmological examination, central corneal thickness measurement and retinal nerve fiber layer thickness analysis of the peripapillary area were performed. Blood samples of 2 mL with EDTA were obtained and sent for genetic analysis. The role of the detected polymorphism on disease tendency along with the genotype and allele frequencies in each group was evaluated.

Results The mean age of the groups was 70.0 ± 8.0 (range 51–86) in PXS, 71.2 ± 8.8 (range 51–93) in PXG and 64.6 ± 8.3 (range 51–91) in controls. The percentages of homozygote individuals were 11.6, 10.9, 21.2%, and heterozygote individuals were 41.9, 45.7, 42.4% in patients with PXS, PXG and controls, respectively. There was no statistically significant difference between groups in terms of both genotype and allele frequencies of rs2107856 ($p = 0.429$ and $p = 0.178$, respectively). Retinal nerve fiber layer thickness did not differ between SNP-positive and SNP-negative individuals in PXG, and there was no significant difference between genotype and age, sex, best corrected visual acuity, intraocular pressure, central corneal thickness, cup/disk ratio and retinal nerve fiber layer thickness in any of the groups ($p > 0.05$).

Conclusion rs2107856 SNP of CNTNAP2 gene has no association with PXS and PXG in the evaluated Turkish population.

Keywords Pseudoexfoliation · Glaucoma · CNTNAP2 gene · Polymorphism

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I. Karaca · S. G. Yilmaz · M. Palamar (✉)
Department of Ophthalmology, Ege University Faculty of Medicine, 35040 Bornova, Izmir, Turkey
e-mail: melispalamar@hotmail.com

H. Onay · B. Akgun · A. Aykut · F. F. Ozkinay
Department of Medical Genetics, Ege University Faculty of Medicine, Izmir, Turkey

B. Aytacoglu
Department of Statistics, Ege University, Izmir, Turkey

Introduction

Pseudoexfoliation syndrome (PXS) is identified by pathological abnormal fibrillar material deposition on the corneal endothelium, iris or lens capsule [1].

Although varied widely in different populations [2–4], estimated prevalence is around 10–15%, in Turkey [5]. The existence of subsequent increased intraocular pressure (IOP) and glaucomatous optic nerve injury is diagnosed as pseudoexfoliation glaucoma (PXG). PXG is one of the most commonly identified cause of open-angle glaucoma [6]. PXG requires prompt diagnosis due to its rapid progressive course with severe optic neuropathy at the time of diagnosis [7].

Proposed mechanism for the development of PXG is thought to be the accumulation of exfoliative deposits in the juxtacanalicular area and trabeculum ending up with endothelial cell dysfunction and subsequent Schlemm canal disruption [7]. Although the exact cause of exfoliative material is still investigated, several genes are shown to have a significant impact in this process. Differences in the prevalence of PXG in various populations also suggest a significant evidence of genetic factors in disease pathogenesis [8, 9]. Firstly, Thorleifsson et al. [10] reported a strong relationship between the lysyl oxidase-like 1 (LOXL1) gene-related single-nucleotide polymorphisms (SNPs) and PXS, in genome-wide association study (GWAS). This relationship was also established in many populations [11–17]. Yilmaz et al. [18] recently reported that none of the PXG patients from Turkish population had mutation in LOXL1 gene; however, 17 subjects showed 3 SNPs termed as R141L (rs1048661), A320A (rs41435250) and F184F. In addition to LOXL1, there are some candidate genes like contactin-associated protein-like 2 (CNTNAP2), clusterin, apolipoprotein E (APOE), gluthathion-*S*-transferase (GST), as well. However, unlike strongly established LOXL1, these genes show relationships in certain populations proposing that there are either weak associations or specificity for certain ethnic societies.

CNTNAP2 is a large gene located on chromosome 7. CNTNAP2 protein (also called Caspr2) belongs to neurexin superfamily [19, 20] and known as stabilizing transmembrane potassium channels localized to juxtaparanodal region of the neuron [20, 21]. Besides its role in neurodevelopmental disorders [22–24], CNTNAP2 protein is particularly localized to membranes of cell types responsible for PXS material formation in ocular tissues. This suggests CNTNAP2 as a candidate gene for PXS [25]. Recently, GWAS with DNA-pooling technology showed strong relationship between PXS, PXG and two SNPs (rs2107856 and rs2141388) of CNTNAP2 [26]. This SNP is located in intron 11 of the CNTNAP2 gene. rs2107856 is an G>T single-nucleotide variation, and presence of G allele is accepted to be related with disease process in PXS. Global G allele frequency is 67.5%, and T allele frequency is 32.5% [27]. Despite no functional outcome of being in intronic region, localization next to exons which codes for epidermal growth factor (EGF)-repeat domains explains its role in specific protein–protein interactions [28]. This association was observed in German patients' cohort with a modest odds ratio (OR) of about 1.4. However, the risk attributed to the disease was thought to be typical for many susceptible variants related with complex diseases. As opposed, no evident association was present in Italian patients' cohort [26]. However, further evidence is still required for this association especially in different populations. This study aims to investigate the prevalence of CNTNAP2 gene rs2107856 SNP in patients with PXS and/or PXG, also healthy controls in Turkish population.

Materials and methods

Subjects

In this prospective cross-sectional study, 43 (mean age 70.0 ± 8.0 years; 27 male, 16 female) patients with PXS, 46 (mean age 71.2 ± 8.8 years; 33 male, 13 female) patients with PXG and 99 healthy controls (mean age 64.6 ± 8.3 years; 47 male, 52 female) evaluated at Ege University Faculty of Medicine, Department of Ophthalmology, Izmir, Turkey, between December 2014 and May 2016 were recruited. Each participant stated written informed consent for examination and procedures. The study was approved by the Institutional Ethics Review Board of Ege University, Turkey, and is compliant with the precepts of Declaration of Helsinki.

Comprehensive ophthalmic examination was performed to all participants involving best corrected visual acuity (BCVA), slit-lamp evaluation, IOP measurement with Goldmann applanation tonometry, central corneal thickness measurement, optic disk evaluation and retinal nerve fiber layer (RNFL) thickness analysis of the peripapillary area with Spectral Domain Optical Coherence Tomography (Topcon 3D-OCT 2000 Corporation, Tokyo, Japan) following dilatation of the pupil.

PXS was determined if exfoliative material was seen either on the corneal endothelium, iris or lens capsule with consecutive IOP values < 21 mmHg and absence of glaucomatous optic nerve injury in either eye. All participants underwent dilatation of pupils to identify the exfoliative deposits in the anterior segment. PXG was defined if the patient met the criteria for PXS and had an evidence for glaucomatous optic nerve damage, loss in the visual field, and IOP ≥ 21 mmHg or IOP under control with anti-glaucomatous treatment in at least one eye. Control subjects composed of individuals with the age of 55 or more, absence of exfoliative deposits in the anterior segment, consecutive IOP values < 21 mmHg and clinically physiologic optic nerve head.

Genetic analysis

Samples of blood (2 mL) with EDTA were taken and directed to Medical Genetics Department, Molecular Genetics Laboratory for the investigation of CNTNAP2 rs2107856 SNP (PCR and agarose gel imaging). Genomic DNA was obtained from the leukocytes then sequestered with the MagNa Pure LC DNA Isolation Kit I (Product No: 0300039900001; Roche, USA). rs2107856 SNP was chosen from the previous studies. The localized gene region for this SNP was amplified by polymerase chain reaction (PCR). Restriction Fragment Length Polymorphism (RFLP) technique is conducted to reveal fragments relevant to SNP region. Obtained fragments are separated according to their lengths by agarose gel electrophoresis (Fig. 1). The genotypes and allele frequencies of the CNTNAP2 rs2107856 SNP were identified.

Statistical analysis

Statistical analysis was executed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Allelic frequencies between groups were compared using MiniTab (Minitab Ltd., Coventry, UK). Chi-square and One-way ANOVA tests were performed to compare data between PXS, PXG and control groups and also SNP-positive and SNP-negative subjects. For the genotypes and alleles of the SNPs, the ORs, p values and 95% confidence intervals were calculated. A p value of < 0.05 was accepted statistically significant.

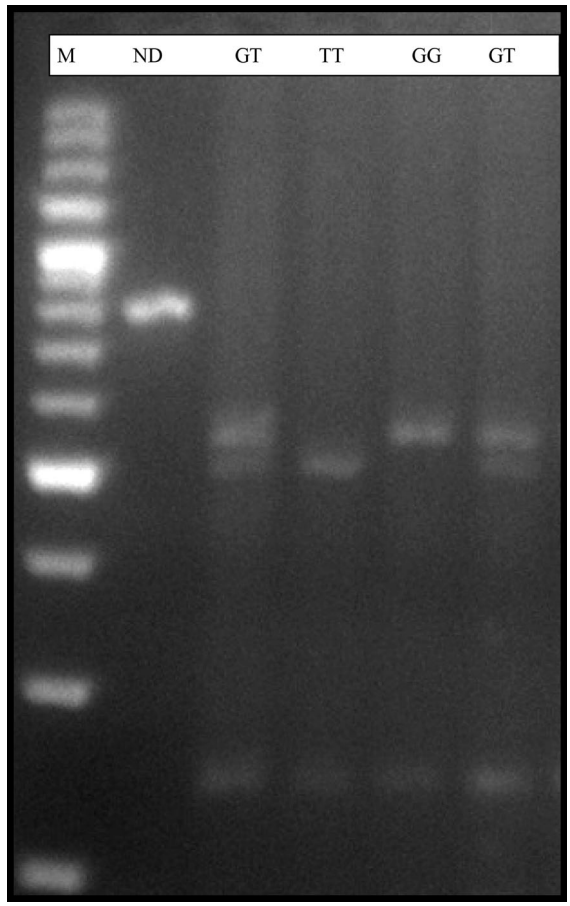

Fig. 1 Agarose gel electrophoresis imaging after RFLP analysis revealed 3 genotypes: GG genotype: 41 + 244 + 487 bp (41 bp band was not seen), GT genotype: 41 + 244 + 487 + 528 bp 88 + 67 bp; TT genotype: 244 + 528 bp. M: 100 bp DNA Ladder, ND: non-digested PCR product: 772 bp

Results

The mean age of the groups was 70.0 ± 8.0 (range 51–86), 71.2 ± 8.8 (range 51–93) and 64.6 ± 8.3 (range 51–91) in PXS, PXG and healthy controls, respectively. Demographic and clinical parameters of the participants are shown in detail in Table 1.

Allele and genotype frequencies were not significantly different between the subjects with pseudoexfoliation (PXS and PXG) and controls ($p = 0.157$; Chi-square test). In detail, the genotype frequencies of CNTNAP2 rs2107856 SNP did not show significant difference between the groups (OR 0.429, 95% CI 0.140–1.311 for both PXS and PXG, $p = 0.429$; Chi-square test; Table 2). Prevalence of homozygosity was

Table 1 Demographic and clinical features of subjects

	PXS ($n = 43$)	PXG ($n = 46$)	Control ($n = 99$)	
Age (years)	70.0 ± 8.0 (51–86)	71.2 ± 8.8 (51–93)	64.6 ± 8.3 (51–91)	$p < 0.001$*
Gender (F/M)	16/27	13/33	52/47	$p = 0.016$*
BCVA (logMAR)	0.15 ± 0.08 (0.04–0.30)	0.57 ± 0.81 (0–3)	0.17 ± 0.08 (0.04–0.30)	$p = 0.026$**
IOP (mmHg)	14.12 ± 1.49 (12–17)	14.78 ± 2.97 (8–23)	14.36 ± 1.36 (12–16)	$p = 0.310$**
CCT (μm)	555.05 ± 22.00 (512–582)	554.87 ± 31.02 (503–640)	548.38 ± 19.43 (509–582)	$p = 0.197$**
Cup-to-disk ratio (c/d)	0.23 ± 0.08 (0.1–0.3)	0.74 ± 0.28 (0.1–1.0)	0.24 ± 0.06 (0.1–0.3)	$p < 0.001$**
RNFL (μm)	97.72 ± 8.81 (86–120)	64.72 ± 18.39 (25–101)	101.10 ± 9.91 (88–127)	$p < 0.001$**

PXS pseudoexfoliative syndrome, *PXG* pseudoexfoliative glaucoma, *BCVA* best corrected visual acuity, *IOP* intraocular pressure, *CCT* central corneal thickness, *RNFL* retinal nerve fiber layer thickness

*Chi-square test

Table 2 Allele and genotype frequencies of rs2107856 in PXS, PXG and control subjects

SNP	PXS ($n = 43$)	PXG ($n = 46$)	Control ($n = 99$)	
rs2107856 Allele				$p = 0.178$*
T	28 (32.6%)	31 (33.7%)	84 (42.4%)	
G	58 (67.4%)	61 (66.3%)	114 (57.6%)	
Genotype				$p = 0.429$*
TT	5 (11.9%)	5 (10.9%)	21 (20.9%)	
GT	18 (41.9%)	21 (45.7%)	42 (42.4%)	
GG	20 (46.5%)	20 (43.4%)	36 (36.7%)	

PXS pseudoexfoliative syndrome, *PXG* pseudoexfoliative glaucoma

*Chi-square test

11.6, 10.9 and 21.2%, while prevalence of heterozygosity was 41.9, 45.7 and 42.4% in patients with PXS, PXG and healthy controls, respectively. Minor T allele frequency was 0.33 in PXS/PXG and 0.44 in healthy controls. The allele frequencies had no statistically significant difference in between the groups (OR 0.655, 95% CI 0.385–1.115 for PXS and OR 0.690, 95% CI 0.412–1.156 for PXG, $p = 0.178$).

CNTNAP2 rs2107856 SNP genotype and age, sex, BCVA, IOP, cup-to-disk ratio, central corneal thickness, RNFL thickness in the whole study population and additionally number of currently used anti-glaucomatous agents and history of previous glaucoma surgery for patients with PXG were compared; however, values did not significantly differ ($p > 0.05$; Tables 3, 4). There was no significant difference in RNFL thickness between SNP-positive (homozygotes + heterozygotes) and SNP-negative PXG subjects (66.9 ± 16.9 micron and 61.9 ± 20.3 micron; $p = 0.503$, Kruskal–Wallis test).

Discussion

Relatively significant prevalence of PXS in Turkish population (10–15%) [5] makes the possible underlying genetic and non-genetic factors come into question for this population. In the literature, increased exposure to ultraviolet radiation, hot temperature, living closer to equator, reduced plasma and ocular selenium levels and increased caffeine intake are some non-genetic factors that are found to be related with PXS/PXG [8, 29–31]. Regarding genetic background, Aboobakar et al. [32] emphasized the significant

Table 3 Comparison of clinical parameters between rs2107856 SNP positive and negatives in subjects with pseudoexfoliation

	PXS and PXG ($n = 89$)		
	rs2107856 SNP positive (TG/TT) mean (min–max)	rs2107856 SNP negative (GG) mean (min–max)	
BCVA (logMAR)	0.309 (0.001–3)	0.447 (0.001–3)	$p = 0.874$*
IOP (mmHg)	14.06 (8–21)	14.95 (11–23)	$p = 0.135$*
CCT (μm)	555.12 (503–592)	554.75 (512–584)	$p = 0.757$*
Cup-to-disk ratio (c/d)	0.495 (0.1–1.0)	0.483 (0.1–1.0)	$p = 0.857$*
RNFL (μm)	81.33 (43–120)	79.85 (35–116)	$p = 0.801$*

PXS pseudoexfoliative syndrome, *PXG* pseudoexfoliative glaucoma, *BCVA* best corrected visual acuity, *IOP* intraocular pressure, *CCT* central corneal thickness, *RNFL* retinal nerve fiber layer thickness

*One way ANOVA test

Table 4 Comparison of clinical parameters between rs2107856 SNP positive and negatives in control subjects

	Control ($n = 99$)		
	rs2107856 SNP positive(TG/TT) mean (min–max)	rs2107856 SNP negative (GG) mean (min–max)	
BCVA (logMAR)	0.175 (0.045–0.301)	0.155 (0.045–0.301)	$p = 0.815$*
IOP (mmHg)	14.37 (10–16)	14.36 (12–18)	$p = 0.758$*
CCT (μm)	547.02 (509–582)	550.02 (512–582)	$p = 0.355$*
Cup-to-disk ratio (c/d)	0.24 (0.1–0.3)	0.24 (0.1–0.3)	$p = 0.967$*
RNFL (μm)	102.62 (89–127)	98.44 (88–122)	$p = 0.068$*

PXS pseudoexfoliative syndrome, *PXG* pseudoexfoliative glaucoma, *BCVA* best corrected visual acuity, *IOP* intraocular pressure, *CCT* central corneal thickness, *RNFL* retinal nerve fiber layer thickness

*One way ANOVA test

association of LOXL1 and CACNA1A with PXS and PXG in various populations. Although LOXL1 is the strongly established gene for PXS [10–17], Yilmaz et al. [18] recently revealed that only 35% of Turkish population had 1 of 3 types of SNPs in LOXL1 gene. In addition to investigation of the impact of environmental factors, uncovering the other gene associations will also enable us to understand the disease pathogenesis and control the PXS/PXG more appropriately.

The role of CNTNAP2 gene in PXS is firstly encountered by Krumbiegel et al. [26] in 2011 in GWAS. mRNA and protein expression analysis showed the extensive presence of CNTNAP2 protein in almost all ocular tissues. However, there were no statistically significant difference in levels of expression between PXS and controls. Immunohistochemical evaluation revealed the localization of CNTNAP2 mainly to epithelial and endothelial cell membranes including trabeculum and Schlemm's canal. Taking all these data into consideration, it seems reasonable to associate CNTNAP2 gene as a part of an underlying mechanism for PXS. The study also investigated 19 discovered SNPs in a replication group of German (610 PXS/PXG, 364 controls) and Italian (249 PXS/PXG, 190 controls) cohorts. Two SNPs (rs2107856 and rs2141388), located in intron 11 of the CNTNAP2 gene, showed significant association both with PXS/PXG in a German cohort. However, no relationship was established in an Italian cohort. There was also increased risk, given of OR 1.42, for TT haplotype in German population. Although these two SNPs have no known functional role since they are placed in an intronic area, their close localization to exons coding for EGF-repeat domains suggests that relationship of cytoskeletal elements with CNTNAP2 might be important for stabilization of the membranes [33].

Based on the evidence that CNTNAP2 is found in the cell membranes playing a role in exfoliative fibrillar material formation in the anterior segment in PXS [26], significant impact of CNTNAP2 in the pathogenesis of PXS is conceivable.

Malukiewicz et al. [33] investigated two SNPs, rs2107856 and rs2141388, of CNTNAP2 gene in Polish (48 PXS, 30 controls) population. No significant association was determined in neither allele nor haplotype frequencies between PXS and controls. Analysis also revealed that these two SNPs correlated well with each other. In Japanese population (108 PXS, 199 controls), 8 SNPs of CNTNAP2 gene were analyzed [34]. Differently, rs1404699 and rs7803992 SNPs, located in intron 9 of the gene, were reported to be significantly associated with PXS in terms of allele and genotype frequencies in this population. They did not found significant relationship between PXS and previously determined rs2107856 and rs2141388 SNPs.

To the best of our knowledge, this is the first study investigating CNTNAP2 as a candidate gene for PXS in Turkish population. We chose to investigate rs2107856 SNP of the gene, since Turkish population share similar ethnic features and geographic localization with European people. However, we did not found significant relationship between rs2107856 SNP and PXS/PXG in regard to neither allele nor genotype frequencies. In our study, minor T allele frequency was 0.33 in PXS/PXG and 0.44 in healthy controls. While T frequency for PXS/PXG seems to be relatively similar to German (0.29) and Polish (0.28) cohorts, it is higher in healthy controls (0.44 vs. 0.22 and 0.35, respectively). This might be explained by heterogeneity in genotypes of the populations, despite their close geographic localization. Thus, other SNPs may also play a role and require further investigation in order to determine the exact role of this gene for PXS in Turkish population. Smaller sample size, as compared to GWAS, might also be confounding. On the other hand, in any of the studies impact of environmental factors was not rationalized.

To the best of our knowledge, this is also the first time for CNTNAP2 gene in PXS, and association of clinical data with genetic features was made. Peripapillary RNFL is an important indicator for glaucomatous change and helpful in differentiating normal and glaucomatous eyes especially in early stages objectively [35]. In our study, we did not found significant association between genotype and RNFL thickness neither in PXS, PXG nor in control groups. This also supports the finding that no association was revealed between rs2107856 SNP and pseudoexfoliation.

In conclusion, despite the previous studies [26, 33, 34], the present study did not unveil any association between rs2107856 SNP of CNTNAP2 gene and PXS/PXG in Turkish population. Nevertheless, investigation of other SNPs in Turkish population might be helpful. Further studies are required to search for possible SNPs of CNTNAP2 gene in other populations, as well. In addition, ascertainment of contributing environmental factors will also enable us to justify the results of these genetic associations. Determining PXS-associated genes is also desirable to identify the population under risk independent from their clinical characteristics. Lastly, there is also need for advance studies correlating clinical data with genetic properties to clarify the complex etiology of PXS in detail. By this way, it will be possible to identify the high-risk group and to prevent disease progression at an early stage.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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