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Pyroptosis-Related Genetic Variants and Protein Levels Determination in Prostate Cancer

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Abstract

Background: Our study examined genetic variants of Gasdermin A (GSDMA) rs7212938, Gasdermin B (GSDMB) rs7216389, Gasdermin C (GSDMC) rs4527833, and Gasdermin D (GSDMD) rs2305492 gene variants and the level of GSDMA, GSDMB, GSDMC, GSDMD proteins, which are related to pyroptosis.

Methods and Results: In our study, 100 patients diagnosed with prostate cancer and 120 healthy controls who applied with various complaints but without evident malignancies were included. SNP-Genotyping was used for Gasdermin family gene variant analysis and ELISA method for protein levels and the results were statistically evaluated. As a result of our study, when the GSDMD genetic variant (rs2305492) associated with pyroptosis was examined in terms of allele frequencies, a significant difference in allele A was observed between prostate cancer patients and control individuals (P=0.007). Furthermore, a significant difference was also observed in genotype variables between prostate cancer patients and control individuals for the GSDMD genetic variant (P=0.016). In terms of protein level, a substantial difference was determined between GSDMC, prostate cancer and control groups (P=0.013).

Conclusion: Our findings suggest that GSDMD (rs2305492) and GSDMC are associated with prostate cancer. The significant differences in allele frequencies, genotypes, and protein levels highlight their potential as biomarkers and therapeutic targets for prostate cancer, warranting further research.

INTRODUCTION

The leading cause of death for middle-aged men between the ages of 45 and 60 is prostate cancer, a malignant disease. Prostate cancer is linked to a number of environmental factors, including age, race, obesity, and family risk [1]. In recent years, death of tumor cells and the activation of antitumor immunity caused by radiation therapy, which causes necrosis and apoptosis, has been studied thoroughly, but recent studies have shown that radiotherapy also causes pyroptosis, necroptosis and ferroptosis [2].

Cell swelling, disruption to the cell membrane, and the discharge of cytoplasmic contents are the hallmarks of inflammatory cell death, or pyroptosis [3]. As GSDM oligomerizes and forms pores in the plasma membrane with a diameter of 10–15 nm, it integrates into the plasma membrane via the N-terminal domain with phosphatidylinositol phosphates, phosphatidylserine, and cardiolipin [4]. The main members of the gasdermin family GSDMA, GSDMB, GSDMC, GSDMD and GSDME are the main causes of pyroptosis, all these members share a similar activation mechanism [5].

The plasma membrane pores open up to release a variety of inflammatory factors, including lactate dehydrogenase, IL-18, IL-1β, and high mobility group protein-1 (HMGB1) [6].

Through the cleavage of GSDMD, the aggregation of inflammasomes, and the release of interleukins (mostly IL-18 and IL-1β), caspase-1 mediates canonical pyroptosis. The release of pro-inflammatory cytokines and GSDMD-mediated cell death are followed by intracellular and extracellular signals and pattern recognition receptors (PRRs), such as danger-associated molecular patterns (DAMPs) and

pathogen-associated molecular patterns (PAMPs) [7]. GSDMB is cleaved by lymphocyte-derived Granzyme A (GZMA), resulting in GSDMB pore formation and resulting in pyroptic cell death of GSDMB-expressing cancer cells. Inflammatory signals in the tumor microenvironment (TME) mediated by granzymes can promote cancer cells to pyroptosis, thus recruiting more immune cells and also triggering antitumor immunity [8].

In humans, the GSDMA gene is located on chromosome 17q21.2. In humans, there is only one copy of the gene encoding GSDMA. GSDMA are often suppressed in primary gastric cancer and gastric cancer cell lines [9].

Chromosomally, the GSDMB gene maps to 17q12 [9]. GSDMB can be detected in the epithelium of the gastrointestinal tract, lungs, liver, lymphocytes, and esophagus [10].

The human chromosome's 8q24 region is where the GSDMC gene is located. GSDMC, often referred to as melanoma-induced leucine chain-containing extranuclear factor (MLZE), was first discovered to be substantially expressed in metastatic melanoma cells [9]. GSDME is activated by senescence of neutrophils, leading to the death of lytic neutrophils [11].

The human chromosome 8q24.3 contains the GSDMD gene, which regulates the growth of the stomach, esophageal, and cutaneous epithelium. GSDMD is regarded as a tumor suppressor gene because of its potent inhibition of cell proliferation. Additionally, GSDMD regulates the process of cancer development [9].

GSDMD is the main executor of the occurrence of pyroptosis, forming pores in the membrane and causing cytokine secretion after cleavage of inflammatory caspases [12]. Separation of GSDMD, the N-terminal is released, causing pyroptosis and the death of tumor cells [13].

Based on this information, the aim of our study is to determine the relationship between pyroptosis and prostate cancer.

MATERIALS AND METHODS

Patients

The subject group consisted of 120 control individuals and 100 prostate cancer patients, both groups were of Turkish origin. The samples were collected from the Faculty of Medicine of Eskisehir Osmangazi University, Department of Urology, Turkey, between August 2022 and July 2023.

DNA isolation and purity determination

Genomic DNA isolation was performed from collected blood samples using the Monarch® Genomic DNA Purification Kit (New England Biolabs) was used for DNA isolation. Quantity and purity of DNA

samples were determined using a Thermo Scientific NanoDropTM 1000 spectrophotometer (Thermo Fisher Scientific Inc., Wilmington, DE, USA).

SNP-genotyping

Genetic alterations were determined by SNP genotyping in isolated DNA samples using the appropriate primer assay (TaqMan®) and q-PCR master mix (TaqMan®). 40X TaqMan® SNP Genotyping assay working solution, containing reverse and forward primers, dyes and probes, was diluted into 20X working stock solution with 1X TE buffer as specified in the protocol.

Elisa

To determine serum protein levels, 4 ml of venous blood samples were collected from each patient and controlled individually in biochemical gel tubes. Blood samples were centrifuged at 2500 rpm for 15 minutes at 4°C to separate the serum fraction. Venous blood was collected from patients and controlled samples in EDTA tubes. Protein levels were measured spectrophotometrically after the incubation and pipetting steps and following the instructions. In the protein analysis phase; GSDMA, GSDMB, GSDMC and GSDMD Elisa Kits (BT-LAB, CHINA) was used. The results were calculated according to the standard curve plot.

Statistical analysis

For continuous data, the Shapiro-Wilks normality test was used in this investigation. The mean±standard deviation (mean ± SD), median (25%–75%), and frequency and percentage of categorical variables were displayed as descriptive statistics. The Mann Whitney U test, Kruskal Wallis test, and Dunn's multiple comparison test were used for variables that did not have a normal distribution. For categorical variables, the Chi-square test was used, and the results were displayed as frequency and percentage. The threshold for statistical significance was set at $P < 0.05$. The statistical software utilized was IBM SPSS Statistics 23.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Genotype variables; A substantial association was determined between prostate cancer patients and control individuals for the GSDMD rs2305492 genetic variant ($P = 0.016$). However, there is no relationship between GSDMC rs4527833, GSDMB rs7216389, GSDMA rs7212938, and prostate cancer and control group variables. Comparison results are shown in (Table 1).

Table 1 Comparison results of genotype variables between prostate cancer and control groups

Gene (Risk)	Variation	Allele	Control n(%)	Prostate cancer n(%)	Statistics p
GSDMA (T/G)	rs7212938	TT (%)	34 (28.3)	21 (21.0)	0.457
		TG (%)	57 (47.5)	52 (52.0)	
		GG (%)	29 (24.2)	27 (27.0)	
		n	120	100	
GSDMB (C/T)	rs7216389	TT (%)	31 (25.8)	19 (19.0)	0.472
		TC (%)	59 (49.2)	55 (55.0)	
		CC (%)	30 (25.0)	26 (26.0)	
		n	120	100	
GSDMC (C/T)	rs4527833	TT (%)	32 (26.7)	29 (29.0)	0.201
		TC (%)	67 (55.8)	45 (45.0)	
		CC (%)	21 (17.5)	26 (26.0)	
		n	120	100	
GSDMD (A/C)	rs2305492	AA (%)	54 (45.0)	52 (52.0)	**0.016**
		AC (%)	63 (52.5)	38 (38.0)	
		CC (%)	3 (2.5)	10 (10.0)	
		n	120	100	

Abbreviations: Gasdermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD). **Bold**: Represents statistically significant p values ($p<0.05$).

Pyroptosis Related Gene Variants allele frequencies: For GSDMD (A/C) rs2305492 alleles, a substantial association was determined between prostate cancer patients and control individuals in terms of the A allele ($P = 0.007$). However, no significant relationship could be determined between GSDMA (T/G) rs7212938, GSDMB (C/T) rs7216389, GSDMC (C/T) rs4527833 alleles and prostate cancer patients and control individuals. Comparison results are shown in (Table 2).

Table 2 Comparison of allele variants between prostate cancer and control group

Gene (Risk)	Variation	Allele	Control	Prostate cancer	Statistics p	OR %95 (CI)
GSDMA	rs7212938	T (%)	125 (52.0)	94 (47.0)	0.532	0.843 (0.446_1.517)
		G (%)	115 (48.0)	106 (53.0)		
					0.211	1.487 (0.797_2.775)
		n	240	200		
GSDMB	rs7216389	T (%)	121 (50.5)	93 (46.5)	0.886	0.956 (0.516_1.770)
		C (%)	119 (49.5)	107 (53.5)		
					0.307	1.393 (0.736_2.637)
		n	240	200		
GSDMC	rs4527833	T (%)	131 (54.5)	103 (51.5)	0.297	0.711 (0.375_1.351)
		C (%)	109 (45.5)	97 (48.5)		
					0.407	0.778 (0.429_1.410)
		n	240	200		
GSDMD	rs2305492	A (%)	171 (71.2)	142 (71)	**0.007**	0.153 (0.033_0.714)
		C (%)	69 (28.8)	58 (29)		
					0.639	0.861 (0.518_1.499)
		n	240	200		

Abbreviations: Odds Ratio (OR), Gasdermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD). **Bold**: Represents statistically significant p values (p<0.05).

Measure of Pyroptosis-Related Protein Levels in Serum: Pyroptosis-related GSDMA, GSDMB, GSDMC, and GSDMD protein levels and comparison results of prostate cancer and control groups are given in (Table 3).

Table 3 Comparison of protein variables with prostate cancer and control groups

Protein variants	**Control** **Median (%25-%75)** **Mean±sd**	**Prostate cancer** **Median (%25-%75)** **Mean±sd**	**Statistics** **p**
GSDMA	51.1 (112.9) 110.3±109.1	52.7(30.6) 82.6±73.8	0.539
GSDMB	65.4 (77.4) 117.3±112.5	78.0(89.9) 105.3±108.7	0.408
GSDMC	60.9 (72.5) 116.0±116.9	57.7(79.5) 80.1±77.3	**0.013**
GSDMD	58.4 (71.7) 110.5±110.2	66.4(44.1) 94.4±79.6	0.265

Abbreviations: mean±standard deviation (Mean±SD), Gasdermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD). **Bold**: Represents statistically significant p values (p<0.05).

A substantial difference was determined in the GSDMC protein variable between prostate cancer and control groups (P = 0.013). However, no difference was found in GSDMA, GSDMB, and GSDMD proteins between prostate cancer and control groups (P>0.05).

No difference was found between genotypes of rs7212938, rs7216389, rs4527833, and rs2305492 gene variants of GSDMA, GSDMB, GSDMC, and GSDMD protein variants (P>0.05). These results are given in (Table 4).

Table 4 Comparison results between protein variants and genotypes of gene variants

Protein variants	GSDMA - rs7212938			**Protein variants**	GSDMB - rs7216389		
	Genotype	**Median (%25-%75) mean±sd**	**P**		**Genotype**	**Median (%25-%75) mean±sd**	**P**
GSDMA	TT	55.8 (89.5) 107.5±103.8	0.652	GSDMB	TT	65.2 (55.7) 100.9±103.2	0.143
	TG	51.1 (50) 93.9±91.5			TC	71.5 (90.9) 124.9±118.1	
	GG	50.7 (52) 95.6±95.8			CC	62.4 (71.7) 95.0±99.2	
Protein variants	GSDMC - rs4527833			**Protein variants**	GSDMD - rs2305492		
	Genotype	**Median (%25-%75) mean±sd**	**P**		**Genotype**	**Median (%25-%75) mean±sd**	**P**
GSDMC	TT	58.8 (65.4) 98.4±110.3	0.642	GSDMD	AA	63.8 (65.7) 104.4±94.3	0.813
	TC	60.4 (62.8) 105.1±106.7			AC	6.7 (47.6) 100.7±98.9	
	CC	59.9 (68.7) 88.5±78.7			CC	60.0 (121.2) 112.7±119.6	

Abbreviations: mean±standard deviation (Mean±SD), Gasdermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD). Bold: Represents statistically significant p values ($p<0.05$). **Bold**: Represents statistically significant p values ($p<0.05$).

DISCUSSION

The association between pyroptosis and cancer has drawn a lot of attention in recent years. The Gasdermin family has six members who have different biological roles in malignant tumors. The differential expression of the Gasdermin family gene between tumor and normal tissues, as well as its prognostic significance in pan-cancer, were investigated in this work by a thorough investigation. Furthermore, a thorough analysis was conducted on the possible relationships between the expression

of genes belonging to the Gasdermin family and genetic changes. We examined its relationship with prostate cancer risk. Our findings are discussed below, evaluated together with literature data.

Gasdermin family genes have been identified as potential therapeutic cancer targets in pan-cancer [14]. Saeki et al. claimed that GSDMA inhibits cell growth; this Gasdermin is expressed in differentiated cells in the esophageal and gastric epithelium [15]. GSDMA is also expressed in mammary glands, bladder, skin epithelial cells, tongue, umbilical cord and gastrointestinal tract. GSDMA was also detected in T lymphocytes. GSDMA is silenced in esophageal cancer and gastric cancer cells as a result of epigenetic modifications that appear, especially methylation, in mucin cells of the gastric epithelium [13]. Compared to normal tissues, human gastric and esophageal cancers express less GSDMA. Cancers of the stomach, head, and neck overexpress GSDMB [16].

In our study, we determined the association of these two variants, GSDMA (rs7212938) and GSDMB (rs7216389), which have not been previously associated with cancer in the literature, with prostate cancer. In our study, no substantial difference was detected in GSDMA protein levels between the prostate cancer and control groups. No substantial difference could be determined between patient and control individuals in terms of GSDMA rs7212938 variant genotype and allele frequencies. In addition, according to the results of multiple comparisons, no substantial difference was detected between the genotypes of this variant and the serum protein levels examined in our study.

The fact that GSDMB is expressed in areas where stem cells are located indicates that it may play a role in the proliferation of stem cells [15]. Many studies have shown that GSDMB has anti-cancer properties, such as stomach and cervical cancer. Has been shown to be expressed in cells, therefore, it is known as an oncogene. Samples with hepatocellular carcinoma (HCC) have been proven to have higher levels of GSDMB than normal samples [9].

Studies on GSDMB show that it has an important role in epithelial responses against infections, inflammations, and tumorigenesis [17]. The mechanisms by which GSDMB affects epithelial cell proliferation are unknown, but in bladder cancer, GSDMB interacts with STAT3 and regulates STAT3 activation. STAT3 activation affects glycolysis through overexpression of various metabolic enzymes [18]. Studies by Molina and colleagues have provided strong evidence proving that GSDMB expression in HER2 breast cancers promotes aggressive behavior by stimulating migration, cell proliferation, and metastatic behavior, as well as resistance to anti-HER2 therapy [19].

In our study, no significant difference could be determined in GSDMB protein levels between the prostate cancer and control groups. At the same time, no substantial difference could be determined between patient and control individuals in terms of GSDMB rs7216389 variant genotype and allele frequencies. In addition, according to the results of multiple comparisons, no substantial difference could be detected between the genotypes of this variant and the serum protein levels examined in our study.

Because Miguchi and colleagues found that silencing GSDMC reduced the proliferation and tumorigenesis of colorectal cancer cell lines and its overexpression increased the proliferation of cells,

they found that GSDMC functions as an oncogene that promotes cell proliferation in colorectal carcinogenesis [20]. The large and small intestine, the esophagus, and some cancers such metastatic melanoma, esophageal cancer, and colorectal cancer express GSDMC [21].

Hou et al. in 2020 detected unknown functions of the PD-L1 molecule, which increases GSDMC expression, in the nucleus. GSDMC through TNF-α by creating a GSDMC N-terminal domain that creates membrane holes and causes pyroptosis. In breast cancer, antibiotic chemotherapy treatments cause pyroptosis. These results suggest that GSDMC/caspase-8 mediates a non-canonical pyroptosis pathway in cancer cells, which leads to tumor necrosis, and that PD-L1 has a non-immune checkpoint role [22].

GSDMC causes inflammation in the tumor microenvironment and pyroptosis in cancer cells. It is unclear, nevertheless, if GSDMC expression in pancreatic adenocarcinoma (PAAD) is linked to immunotherapy response or survival. In the 2023 study by Xia et al., a positive link was found between GSDMC expression and PD-L1 expression in patient-derived human tissue microarray (TMA) obtained from 139 local PAAD patients, while a negative correlation was found between GSDMC expression and poor infiltration of CD8+ T cells. Furthermore, a worse overall survival (OS) rate has been linked to GSDMC overexpression [23].

In our study, a significant difference was determined in GSDMC protein levels between the prostate cancer and control groups. However, no substantial difference could be determined between patient and control individuals in terms of GSDMC (rs4527833) variant genotype and allele frequencies. In addition, according to the results of multiple comparisons, no substantial difference could be detected between the genotypes of this variant and the serum protein levels examined in our study. These results showed that, as seen in the above studies, GSDMC expression and therefore protein levels differ between various cancer groups and control groups, but the GSDMC (rs4527833) variant we examined in our study did not affect the change in protein level.

According to the findings of Wang et al.'s investigation, GSDMD inhibits the growth of gastric cancer cells. In a similar vein, GSDMD expression was found to be downregulated in the malignant tissues of stomach cancer patients. GSDMD is also related to a number of human diseases, such as inflammatory bowel diseases, cancer, type II diabetes, Alzheimer's disease, and cardiovascular diseases [24].

GSDMD also plays a role in regulating pyroptosis in colon cancer [25]. In endometrial cancer, significantly higher expression of GSDMD is observed in cancerous cells in comparison to normal endometrial cells [26]. Saeki and colleagues concluded that GSDMA has a role in differentiated cells, GSDMB and GSDMD have a role in undifferentiated cells, and GSDMC may have a role in both [15]. Gao et al. discovered that GSDMD protein level was substantially higher in NSCLC and lung adenocarcinoma than in adjacent tissues. They also reported that GSDMD knockdown reduced tumor proliferation in NSCLC [27]. Peng and colleagues discovered a novel GSDMD pathway in colorectal cancer in another investigation. According to their findings, GSDMD is a crucial molecule that mediates hypoxia and apoptosis caused by chemotherapeutic drugs by translocating from the cytoplasm to the nucleus, in addition to its role in

pyroptosis. GSDMD blocks the ability of cell nuclei to repair DNA by directly interacting with PARP-1 [28]. In their study, Shen and colleagues found that GSDMD was expressed much more in adenoid cystic carcinoma (ACC) than in adjacent non-cancerous tissue (ANC), suggesting that the expression level of GSDMD is related to the behavior of ACC [29]. Berkel and colleagues determined that GSDMD and GSDMC were more expressed in serous ovarian cancer compared to normal ovaries. Based on these findings, they showed that in ovarian cancer, the incidence of copy number increases in these two gasdermins is 50% [30].

Our study is the first in the literature in which the GSDMD gene rs2305492 polymorphism and GSDMD protein level are associated with prostate cancer. In addition, literature reviews have shown that GSDMD has an antiproliferative effect in some types of cancer and supports tumor formation and progression in others. In our study, no significant difference was detected in GSDMD protein levels between the prostate cancer and control groups. However, a substanstial difference was determined between patient and control individuals in respect of GSDMD rs2305492 variant genotype and allele frequencies. In addition, according to the results of multiple comparisons, no substantial difference could be detected between the genotypes of this variant and the serum protein levels examined in our study. These results showed that, as seen in the above studies, GSDMD expression and therefore protein levels differ between various cancer groups and control groups, but the GSDMD rs2305492 variant we examined in our study did not affect the change in protein level.

Based on this information, the purpose of our study is to determine the relationship between these pyroptosis-related gene variants and the disease by determining their protein levels. Thus, the findings we will obtain to elucidate the molecular mechanism of the disease will contribute to the development of a new method alternative to the prognosis of the disease and routine measurements for the determination of the disease.

CONCLUSION

From the results of our study, we conclude that GSDMD and GSDMC were associated with prostate cancer specifically GSDMD (A/C) rs2305492 alleles, a significant association was determined between prostate cancer patients and control individuals in terms of allele A (P = 0.007) and GSDMD rs2305492 genetic variant for prostate cancer a significant relationship was determined between patients and control individuals. While a significant difference was determined between the GSDMC protein variable and prostate cancer and control groups.

Abbreviations

ACC
Adenoid cystic carcinoma
ANC
Adjacent non-cancerous tissue

CI
Confidence interval
DAMPs
Damage-associated molecular patterns
GSDMA
Gasdermin A
GSDMB
Gasdermin B
GSDMC
Gasdermin C
GSDMD
Gasdermin D
GSDME
Gasdermin E
GSDMs
Gasdermin family proteins
GZMA
Granzyme A
HCC
Hepatocellular carcinoma
HER2
Human epidermal growth factor receptor 2
HMGB1
High mobility group box 1
IL-1β
Interleukin-1 beta
IL-18
Interleukin-18
MLZE
Melanoma-derived leucine zipper-containing extranuclear factor
NSCLC
Non-small cell lung cancer
PAAD
Pancreatic adenocarcinoma
PAMPs
Pathogen-associated molecular patterns
PARP-1
Poly (ADP-ribose) polymerase 1
PD-L1
Programmed death-ligand 1

PRRs
Pattern recognition receptors
SNP
Single nucleotide polymorphism
SPSS
Statistical Package for the Social Sciences
STAT3
Signal transducer and activator of transcription 3
TMA
Tissue microarray
TME
Tumor microenvironment
TNF-α
Tumor necrosis factor alpha

Declarations

Conflict of interest

The authors declare that they have no competing interests.

Ethics statement

The study was conducted with the approval of the Clinical Research Ethics Committee of Eskisehir Osmangazi University, as per their decision number 2022/194, dated July 26, 2022. The participants provided informed consent forms.

Consent to participate

Written informed consent was obtained from all the participants included in the study.

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Author Contribution

Y.K., E.Y., and H.K. conceived and designed the study. E.Y., A.O., and Y.K. provided study materials and patient samples. F.M. performed the statistical analysis. C.O., F.M., H.K., Y.K., and E.Y. contributed to data analysis and interpretation. Y.K. drafted the manuscript. H.K., E.Y., and C.O. critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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