



The Association of Pancreatic Cancer and *PALB2* Gene Mutations in the Turkish Population

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OBJECTIVE

The aim of the present study was to identify the prevalence of *PALB2* gene mutations in patients diagnosed with pancreatic cancer in Turkish population, and to investigate the role of *PALB2* in the pathogenesis of the disease.

METHODS

Thirty patients diagnosed with pancreatic cancer and 30 healthy controls who had no cancer history in their family and matched for age, gender, and ethnicity with the patients were analyzed in the study. The exome regions of the *PALB2* gene in the genomic DNA obtained from the peripheral blood samples of the patients and controls were investigated by the Sanger sequencing method.

RESULTS

Evaluation of the obtained data showed that the alterations of c.29G>T, c.2737C>A, c.2773G>C, and c.2840T>G were only identified in the group of patient; and the alteration of c.1676A>G was detected in the homozygous formation in the case with a familial pancreatic cancer syndrome in the group of patient.

CONCLUSION

These alterations were suggested to be possibly important in the pathogenesis, and in the inheritance of pancreatic cancer. Further study is needed with a large cohort to emphasize importance of alteration.

Keywords: DNA repair; mutation; pancreatic cancer; *PALB2* gene; sequence analysis.

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Introduction

Pancreas cancer (PC) is generally diagnosed in the advanced stage and is cancer with poor diagnosis. The data of Globocan in 2018 showed that the worldwide incidence rate of pancreas cancer was 2.5, with a ranking of 12 among the other cancers. The worldwide mortality rate is 94.2%. Pancreas cancer has a similar incidence and mortality rate in men and women. The Turkish data of pancreas cancer are compatible with

worldwide data, and PC is the 9th most frequently occurring cancer, and the mortality rate is 99.1%. [1]

It is thought that genetic factors and genetic heterogeneity are some of the causes underlying the aggressive behavior of pancreas cancer. [2] Various germline mutations associated with pancreas cancer were detected in the literature. The most significant genes increasing the pancreas cancer risk were reported as *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CDKN2A*, *APC*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PRSS1* and *STK11*. [3-5]

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Although the *PALB2* gene was first described as associated with the Fanconi anemia, further studies also described the gene as the breast cancer susceptibility gene. The monoallelic truncating mutation of *PALB2*, which increased the breast cancer risk approximately 2-3 folds, was described in 10 out of 923 patients with a history of familial breast cancer.[6] *PALB2* mutations were reported in approximately 3-4% of the families with familial pancreatic cancer syndrome.[7] In addition, the results of *PALB2* gene analysis in BRCA negative families showed that the carriers of *PALB2* mutation four folds increased the risk for male breast cancer, and six folds increased the risk for pancreas cancer.[8]

PALB2 is a gene that has a role in the DNA repair pathway by enabling the attachment and localization of BRCA2 protein to the BRCA complex. *PALB2*, which is the partner, and localizer of *BRCA2* is emerged as the key player in the preservation of genome integrity. The monoallelic mutations in *PALB2* are susceptible to breast, ovarian, and pancreatic cancer. The tumor-suppressor role of *PALB2* is closely associated with its supporting ability of homologous recombination (HR) mediated repair of DNA double-strand breaks. Understanding the functioning of *PALB2* has become the main focus point of various studies because *PALB2* has been located at the intersection point of FA, HR, and cancer susceptibility.[9]

One of the repair mechanisms of homologous recombination was used in the repair of double-strand breaks during the transformation of S phase to G₂ phase in the cell cycle, and that procedure was the main mechanism used in such repairs.[10,11] *PALB2* gene product was suggested to have a tumor-suppressor role due to its interaction with the BRCA1 and BRCA2 proteins in double-strand DNA repair. The interaction of the BRCA complex with *RAD51* enables the initiation of the homologous recombination. BRCA complex cannot establish an association with *RAD51* in the absence of *PALB2*, and thus the repair of the double-strand DNA breaks cannot be performed.[12-15]

Special molecular alterations are known to be effective in the selection of personal treatment, such as platinum-based chemotherapy in pancreatic ductal adenocarcinoma (PDAC) patients. Although *PALB2* was mainly investigated owing to its significant role in breast cancer biology, preliminary reports suggested that *PALB2* might also have a role in pancreatic ductal adenocarcinoma. PDAC patients with *PALB2* mutation were suggested to significantly benefit from the use of platinum-based chemotherapy based on a report of S. Boeck et al.[16] In addition, studies have reported that

PDAC patients carrying a mutation in homologous recombination repair-related genes may better response to oxaliplatin-based chemotherapy.[17] Platinum-based agents directly target the DNA and cause DNA breaks through cross-links between the chains. *PALB2* is suggested to be one of the potential biomarkers in genomic instability because *PALB2* is an important mediator in DNA stability. Although platinum-based agents were found to be effective in pancreas cancer patients with genomic instability, the recent evidence showed that cancer cells might be resistant against platinum agents. The results of the studies reported that PARP inhibitor resistance was in the same clones where the second mutation developed.[18]

The investigation of the literature demonstrated that the distribution of the mutations in the *PALB2* gene, which causes susceptibility to pancreas cancer, and breast cancer varied in accordance with the geographic regions.[19] The present study aims to identify the prevalence and distribution of *PALB2* gene mutations in pancreas cancer patients in the Turkish population and investigate its role in the pathogenesis of the disease.

Materials and Methods

Patients

The peripheral blood samples of 30 patients diagnosed with pancreas cancer who presented to İstanbul University, Faculty of Medicine, Oncology Institute between 2014-2015 were used in this study. Peripheral blood samples of 30 healthy individuals who had no history of cancer in the family were investigated as the control group. All the material collection process of all patients and controls were approved by the İstanbul University Ethics Board (protocol number: 2014/1961). All the DNA and clinical data of the participants used for investigation purposes were obtained after the informed consent forms were signed. This work was supported by the Scientific Research Projects Coordination Unit of İstanbul University (Project number: 54273). The clinical diagnosis of the patients was confirmed by the clinical oncologists.

Mutation Analysis

The “Sanger sequencing” method was used to sequence full exons of the *PALB2* gene in both healthy controls and patients with pancreas cancer. All exon regions and exon-intron boundaries of the *PALB2* gene were amplified in the DNA samples of each patient and healthy controls through primers designed appropriately for the target gene using the PCR method. Polymerase

chain reaction and sequencing procedures were performed for a total of 16 fragments consisting of four fragments in exon 4 and two fragments in exon 5.

The polymerase chain reaction was prepared as to provide a total final volume of 50 μ L consisting of 5 μ L from 10X PCR buffer, 1 μ L from 10 mM dNTP mixture, 0.5 μ L from each of the 0.3 mM primers, 2 μ L from the template DNA, 0.5 μ L from 5U/ μ L DreamTaq DNA polymerase, and 1 μ L $MgCl_2$. The mixture was incubated for 20 seconds 94°C, 20 seconds at 56°C, and 40 seconds at 72°C in 35 cycles, and the final elongation was incubated 10 minutes at 72 °C.

The Roche HP PCR Product Purification kit was used for the purification of the PCR products. Thirteen exons of *PALB2* gene were sequenced with a total of 16 amplicons for each case, and with 32 reactions using the DTCS Quick Start DNA Sequencing Kit. The exon sequencing after the precipitation procedures using ethanol was performed using 'Beckman Coulter GXL' Sanger Sequencing Device, and the data were analyzed on the "GenomeLab Genetic Analysis System" program.

In Silico Analysis

The pathogenicity of the missense variants was evaluated in the databases of Polymorphism phenotyping (PolyPhen2),[20] the SIFT algorithms,[21] and Mutation Taster,[22] ClinVar [23] databases which are used in the identification of the pathologic possibilities.

Statistical Analysis

In this study, the non-parametric Chi-square (χ^2) test was used in the resolution of the data because our data (Kolmogorov-Smirnov Test: Assymp.Sig (significance): $p < 0.05$) could not provide the normality assumption after conducting the single sample Kolmogorov-Smirnov test using the IBM Statistical Package for the Social Sciences (SPSS) v20.0 program.

Results

Sanger sequencing method was used to sequence full exons of the *PALB2* gene, which has a role in the repair of the double-strand DNA breaks in patients with pancreatic cancer and healthy controls in the present study.

In this study, peripheral blood samples of 30 patients with pancreatic cancer applied to the Department of Basic Oncology, Faculty of Medicine, Istanbul University, were used. Peripheral blood samples of 30 healthy age and sex-matched individuals were used as a control group.

This study included 30 patients with pancreatic cancer, 13 of whom were women and 17 of whom were men along with 30 healthy individuals, of whom 20 men were examined. 27% (8/30) of the patients were under the age of 45 years, and 73% (22/30) of the patients were over the age of 45 years (Table 1). 10% (3/30) of the patients were in the 2nd stage, 47% (14/30) were in the 3rd stage, and 43% (13/30) were in the 4th phase (Table 1). While metastasis was detected in 83% (25/30) of the 30 patients, metastasis was not observed in 17% (5/30) (Table 1). 20% (6/30) of the patients had histological grade 1 (well-differentiated), 13% (4/30) grade 2 (moderate), and 17% (5/30) grade 3 (poorly differentiated). The histological grade of the tumor could not be evaluated in 50% (15/30) of the tumor (Table 1). While 60% (18/30) of the patients with pancreas had no familial history of cancer, 10% (3/30) had a family history of pancreatic cancer, and 30% (9/30) had at least one and four patients had another type of cancer history (Table 1).

When the patients compared according to another cancer or chronic disease, 43% (13/30) of the patients had a chronic disease, 57% (17/30) had no other chronic disease (Table 1). While 30% (9/30) of the patients examined in this study were diagnosed with diabetes, 70% (21/30) of the patients had no diagnosis of diabetes (Table 1). It was observed that 53% (16/30) of the patients used more than 20 years of smoking, and 47% (14/30) of the patients had no smoking during their lifetime.

The exons sequencing of the *PALB2* gene was performed in 30 patients diagnosed with pancreas cancer, and the detected SNP alterations were compared with the results in the clinical database. The previously reported alterations of *rs80531188*, *rs876659643*, *rs152451*, *rs45532440*, *rs180177125*, and *rs45551636*, and 17 new, unreported, alterations in the literature were detected in this study (Table 2). Two of these alterations were reported as the VUS database, and the remaining four were shown as benign in the database of ClinVar Miner. In addition, 17 new SNP were found that they were not reported in the literature previously (Table 1 and Table 2). The chronograph images of alterations in DNA are indicated in Figure 1 and Figure 2, respectively (Fig. 1 and Fig. 2). In the study group, the alterations in the literature, which were determined for the first time, were evaluated using in silico algorithms, which were SIFT, Mutation Taster, PolyPhen 2. Two of these algorithms, which are used to determine the pathogenesis of a genetic change in scientific terms, are valid in the same direction. In this respect, the only change reported to be "pathogenic" in three of the three algorithms used in our study was *c.29G>T*. Changes in two of the three algorithms reported to be pathogenic "were *c.2737C>A*; *c.2773G>C*; *c.2840T>G*. Two of these changes are de-

Table 1 Clinical features of patients

Clinical features	Number of cases	Percentage of cases (%)
Gender		
Male	17	57
Female	13	43
Age at diagnosis		
≤45	8	27
>45	22	73
Stage		
II	3	10
III	14	47
IV	13	43
Metastasis status		
Yes	25	83
No	5	17
Histological grade		
Grade X (unknown)	15	50
Grade 1-well differentiated (low-grade)	6	20
Grade 2-moderately differentiated	4	13
Grade 3-poorly differentiated (high grade)	5	17
Family history		
No family history	18	60
FDR and/or SDR with PC	3	10
Other tumors	9	30
Second chronic disease		
Yes	13	43
No	17	57
Diabetes mellitus		
Yes	9	30
No	21	70
Smoking history		
Yes	16	53
No	14	47

FDR: First degree relative; SDR: Second degree relative; PC: Pancreatic cancer

finned as a Variant of Uncertain Significance (VUS) in the ClinVar database and no literature information is available on the other 2 (Table 2).

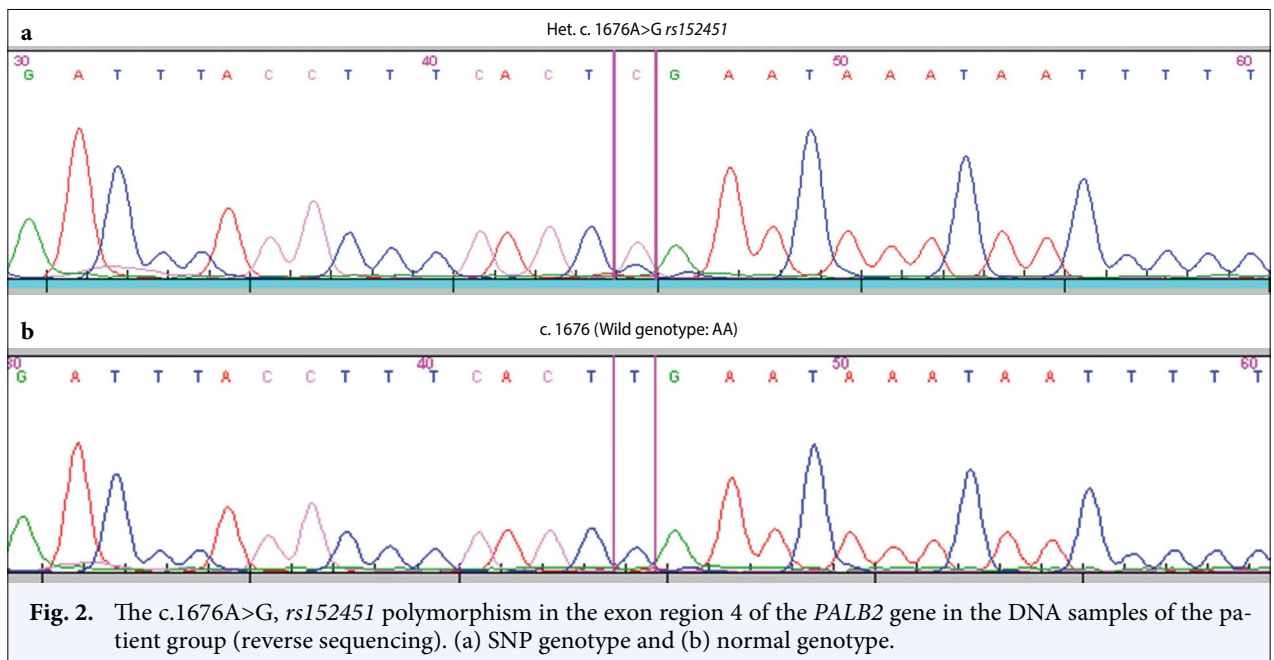
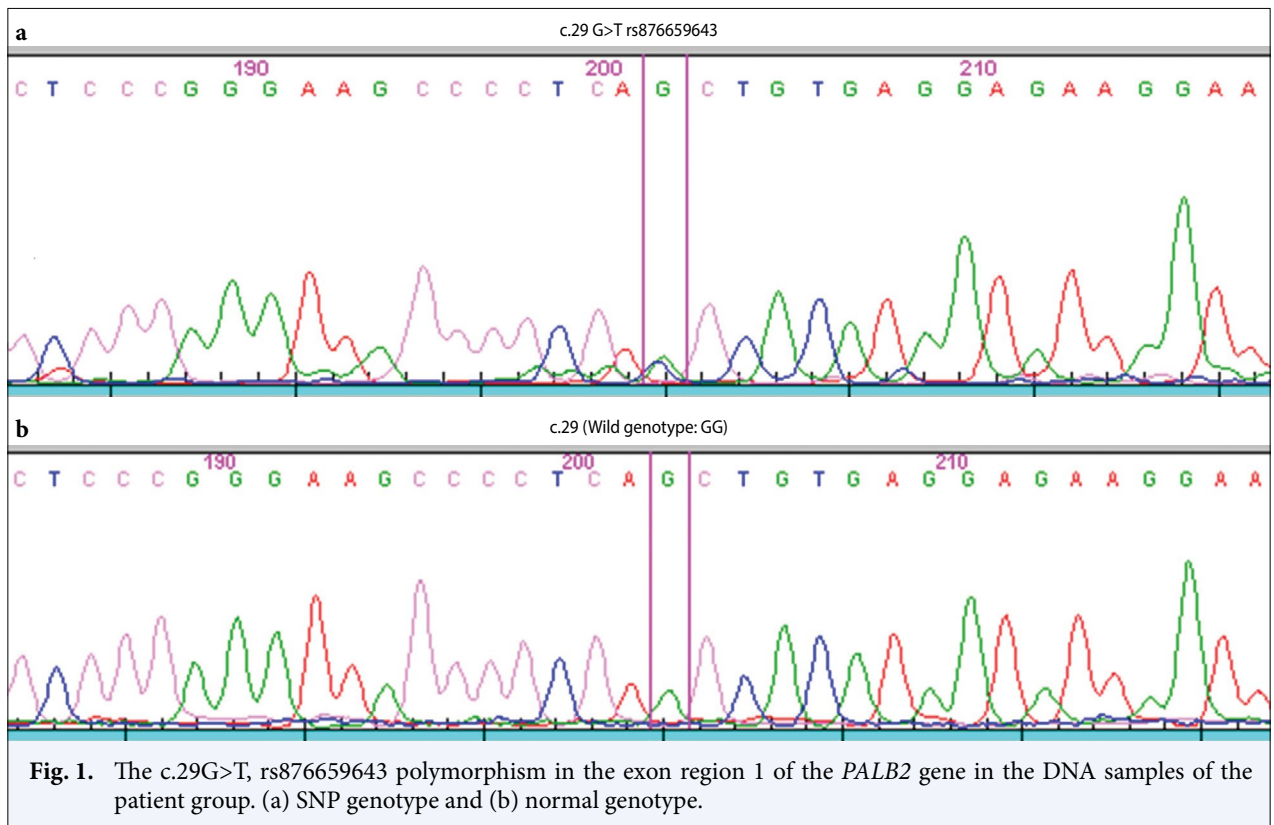
When 30 healthy controls included in this study were sequenced for the *PALB2* gene, heterozygous c.-47G>A rs8053188, c.1676A>G rs152451, c.2014G>C rs45532440, c.2993G>A rs45551636 to the previously were reported as found changes (SNP) with the rs numbers. In addition, 13 different changes heterozygote formation in the same healthy group has not been previously reported in the literature were detected (Table 3), 1807C>G, c.2280T>G, c.2299G>A, c.2441T>A, c.2840T>G, c.3114-51A>T and c.3300T>G.

The changes in the healthy control group without knowledge of the literature were calculated to be deleterious in two different in silico algorithms out of three,

in two of them. Two changes were identified as benign in the ClinVar databank (Table 3).

Discussion

The single nucleotide alterations of c.2737C>A, c.2773G>C, c.2840T>G, and c.2993G>A detected in nine patients (30%) out of 30 were located in the WD40 domain region in the C terminal region of PALB2 protein. That region was suggested to be protected phylogenetically and was suggested to have a significant role in the cellular signal transmission and in the regulation of cell cycle and in the transcriptional apoptosis.[24] The WD40 region is a highly important region in the protein-protein interaction. PALB2 protein interacts through the WD40 domain in the N terminal region of the BRCA2 protein and



contributes to the development of BRCA1 and BRCA2 complex. Therefore, the alterations in this region were suggested being effective in the formation of protein complex having a role in DNA repair and in the accurately functioning.

The c.29G>T, c.107A>G, and c.145A>G alterations were detected in a total of five patients out of 30 on the domain where the PALB2 protein interacts with BRCA1 protein and located in the N terminal region of the PALB2 protein. The alterations in this region suggested being ef-

Table 2 The detected alterations in the *PALB2* gene of the patients with PC

Exon of <i>PALB2</i>	Nucleotide change	Protein change	Variant type	rs number	SIFT	Mutation taster	Polyphen2	ClinVar Miner/Literature	Frequency n (%)
1	c.-47G>A	-	-	8053188	-	-	-	Benign in ClinVar miner	1 (3.3%)
1	c.-155T>G	-	-	-	-	-	-	Not reported in literature	1 (3.3%)
1	c.29G>T	p.Ser10Ile	Missense	876659643	Deleterious	Disease Causing	Deleterious	VUS in ClinVar miner	2 (6.6%)
1	c.107A>G	p.Gln36Arg	Missense	-	-	Disease Causing	Neutral	Not reported in literature	2 (6.6%)
1	c.145A>G	p.Lys49Glu	Missense	-	-	Polymorphism	Neutral	Not reported in literature	1 (3.3%)
2	c.183G>A	p.Gln61Gln	Synonymous	-	-	-	-	Not reported in literature	1 (3.3%)
4	c.559 C>G	p.Pro187Ala	Missense	-	Tolerated	Polymorph.	Neutral	Not reported in literature	1 (3.3%)
4	c.604C>G	p.Leu202Val	Missense	-	Tolerated	Polymorph.	Neutral	Not reported in literature	2 (6.6%)
4	c.611C>G	p.Ser204Cys	Missense	-	Tolerated	Polymorph.	Neutral	Not reported in literature	2 (6.6%)
4	c.1005T>A	p.Asn335Lys	Missense	-	Tolerated	Polymorph.	Neutral	Not reported in literature	1 (3.3%)
4	c.1027C>A	p.Gln343Lys	Missense	-	-	-	Neutral	Not reported in literature	5 (16.6%)
4	c.1308G>A	p.Lys436Lys	Synonymous	-	-	-	-	Not reported in literature	6 (20%)
4	c.1368G>T	p.Glu456Asp	Missense	-	Deleterious	Polymorph.	Neutral	Not reported in literature	1 (3.3%)
4	c.1391G>A	p.Arg464Lys	Missense	-	-	-	Neutral	Not reported in literature	2 (6.6%)
4	c.1464C>T	p.Ser489Thr	Missense	-	-	-	Neutral	Not reported in literature	2 (6.6%)
4	c.1596A>T	p.Pro532Pro	Synonymous	-	-	-	Neutral	Not reported in literature	1 (3.3%)
4	c.1676A>G	p.Gln559Arg	Missense	152451	-	-	-	Not reported in literature	5 (16.6%)
5	c.2014G>C	p.Glu672Gln	Missense	45532440	-	Polymorph.	Neutral	Benign in ClinVar miner	2 (6.6%)
7	c.2706T>C	p.Asp902Asp	Synonymous	-	-	-	-	Benign in ClinVar miner	1 (3.3%)
7	c.2737C>A	p.His913Asn	Missense	-	Tolerated	Disease Causing	Deleterious	Not reported in literature	1 (3.3%)
8	c.2773G>C	p.Val925Leu	Missense	180177125	Deleterious	Disease Causing	Neutral	Not reported in literature	3 (10%)
9	c.2840T>G	p.Leu947Trp	Missense	-	-	Disease Causing	Deleterious	VUS in ClinVar miner	3 (10%)

Table 3 The alterations in the *PALB2* gene found only in the group of healthy control

Exon of <i>PALB2</i>	Nucleotide change	Protein change	Variant type	rs number	SIFT	Mutation taster	Polyphen	ClinVar Miner/Literature	Frequency n (%)
2	c.211+7C>G	-	-	-	-	-	-	Not reported in literature	2/30 (6.6%)
4	c.388C>T	p. His130Tyr	Missense	-	Tolerated	Polymorph.	Neutral	Not reported in literature	1/30 (3.3%)
4	c.1304T>A	p. Val435Asp	Missense	-	Deleterious	Polymorph	Deleterious	Not reported in literature	1/30 (3.3%)
4	c.1485A>T	p. Glu495Asp	Missense	-	Tolerated	Polymorph	Neutral	Not reported in literature	1/30 (3.3%)
5	c.1807C>G	p. Leu603Val	Missense	-	Tolerated	Polymorph	Neutral	Not reported in literature	1/30 (3.3%)
5	c.2280T>G	p. Leu760Leu	Synonymous	-	-	-	Neutral	Not reported in literature	1/30 (3.3%)
5	c.2299G>A	p.Val767Ile	Missense	-	Tolerated	Polymorph	Neutral	Not reported in literature	1/30 (3.3%)
5	c.2441A>T	p.Glu814Val	Missense	-	Deleterious	Polymorph	Deleterious	Not reported in literature	1/30 (3.3%)
11	c.3114-51A>T	-	-	249936	-	-	-	Likely benign	1/30 (3.3%)
12	c.3300T>G	p.Thr1100Thr	Synonymous	45516100	-	-	Neutral	Benign in ClinVar miner	3/30 (10%)

fective in the formation of protein complex having a role in DNA repair and in the accurately functioning.

The alterations of c.559C>G, c.604C>G, c.611C>G, c.1005T>A, c.1027C>A, c.1368G>T, c.1391G>A, c.1464C>T, and c.1676A>G were recently detected in 19 patients (63%) out of 30 in the region including the domain three named as Chromatin-Association Motive (ChAM) located in the center of PALB2 protein, and reported to have a role in the chromatin localization of PALB2. Among these alterations, c.1676A>G alteration was also found with no *rs152451*, which was previously reported in the literature. This alteration was detected in five (17%) out of 30 patients and in four (13%) individuals in the control group. Four patients were detected to have an alteration in heterozygous formation, and one patient was detected to have an alteration in homozygous formation. The investigation of the clinical features of five patients having c.1676A>G alteration showed that tumor had distant organ metastasis, and all patients were smokers longer than 20 years. One patient was detected to have a pancreas cancer history in his father in whom homozygous c.1676A>G alteration was found. Therefore, particularly, the homozygous formation of the alteration was suggested to be important in the etiology and in the inheritance of the familial pancreas cancer. The importance of alteration could be detected with studies with a larger pancreatic cancer cohort and with a population-based group of healthy controls in the future.

All the alterations detected in our study were separately evaluated in the SIFT, Mutation Taster, and Polyphen algorithms that were developed to clarify the differences caused in the protein structures and to identify how they affected the protein function. These three algorithms, named as SIFT, Mutation Taster, and Polyphen, are used in the identification of the pathogenicity of scientifically genetic alteration. The conditions where the two of these algorithms give results in the same direction are regarded valid. Considering this, the only alteration reported as “deleterious” was c.29G>T in all three algorithms in our study. The alterations regarded as “deleterious” in two out of three algorithms were the alterations c.2737C>A; c.2773G>C; and c.2840T>G.

The alterations of c.29G>T, c.2737C>A, c.2773G>C, and c.2840T>G detected in the patient group, and were calculated as “deleterious” in at least two algorithms could not be shown in any cases in the control group. The results suggested that these alterations might be important in the pancreas cancer pathogenesis. In addition, c.1676A>G alteration was observed in 17% of the patient group and in 13% of the healthy individuals in our study group. The c.1676A>G alteration was detected

in heterozygous formation except for one patient with pancreas cancer syndrome in the patient group. The heterozygous formation of this alteration was reported as “pathogenic” in accordance with the ClinVar data bank. However, the detection of the homozygous formation of c.1676A>G alteration in a patient with a family history of pancreas cancer in our study group suggested that the homozygous alteration might be important for the pancreas cancer pathogenesis, and was a topic to be investigated. In addition, the condition in the patient in whom the homozygous c.1676A>G alteration was detected in the first-degree relative demonstrated a similar condition to *SMAD4/DPC4* gene which is known to be effective in the pancreas cancer etiology, and which showed a homozygous mutation in 50% of the patients with pancreas cancer. The detection of the heterozygous formation of this alteration in the same ratio in both control, and patient groups, and detection of homozygous formation particularly in a patient with a family history of pancreas cancer in the first degree relative suggested that the homozygous formation of that region might be important in the pancreas cancer etiology similar to the homozygous form of the *SMAD4/DPC4* gene. The investigation of this condition, particularly in pancreas cancer tissue samples in future studies, will provide information about this alteration.

Conclusion

It was found that the alterations which were c.29G>T, c.2737C>A, c.2773G>C, and c.2840T>G were only detected in the patient group, and that another alteration which was c.1676A>G was observed as a homozygous formation in one patient with familial pancreatic cancer syndrome. Therefore, it is suggested that these alterations might be important in the pathogenesis, and inheritance of pancreas cancer and also should be investigated in the larger population of patients.

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Conflict of Interest: The authors declare that they have no competing interests.

Ethics Committee Approval: The material collection processes of all patients and controls were approved by the Istanbul University Ethics Board (protocol number: 2014/1961).

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