VARIETY MUTATIONS IN THE GENES OF HEREDITARY TUMOR SYNDROMES IN PANCREATIC CANCER

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Abstract. Pancreatic cancer (PC) is one of the most aggressive malignant neoplasms. Next-generation sequencing (NGS) was performed in 223 patients from Nizhny Novgorod with morphologically verified pancreatic cancer (PC) treated at the Oncological Dispensary of the Nizhny Novgorod Region in 2021-2022. The patients were conditionally divided into two subgroups: The first subgroup (184 patients) underwent PCR testing at the Nizhny Novgorod Regional Oncology Dispensary and then next-generation sequencing (NGS) of the coding regions of the BRCA1/2 genes at the National Medical Research Centre of Radiology of the Ministry of Health of the Russian Federation. The second subgroup (39 patients) underwent NGS of the coding regions of cancer-associated genes at the Centre for Personalised Medicine of the Moscow Clinical Scientific and Practical Centre named after A.S. Loginov. Germline mutations in the BRCA1/2 genes were detected in 6 patients with pancreatic cancer (3.3 ± 1.3%), including one case in the BRCA1 gene and 5 in the BRCA2 gene. Various pathogenic mutations in genes (ATM, FANCC, POLE, NBN, BLM, SMARCA4, MUTYH, FANCG) associated with different oncological syndromes were found in 9 patients (23.1 ± 1.2%). The high prevalence rates of different pathogenic variants in PC patients, regardless of age and family history of oncology, indicate the need for medical genetic counselling followed by NGS. The detection of germline mutations in genes of hereditary tumour syndromes in PC patients will help to identify high-risk groups for tumor development in relatives and enable early diagnosis.

Keywords: pancreatic cancer, hereditary tumor syndromes, molecular genetic diagnosis, next-generation sequencing, BRCA1/2.

List of Abbreviations

PC – Pancreatic cancer

DNA – Deoxyribonucleic acid

PMR – Primary multiple cancer

NRAS/KRAS – Proto-oncogenes, members of the Ras protein family

BRAF – MAP3K family threonine protein kinase

BRCA1/BRCA2 – breast cancer 1/breast cancer 2

ATM – a serine/threonine protein kinase that is recruited and activated by DNA double-strand breaks

PALB2 – Partner and Localizer of BRCA2

RAD50 – DNA repair protein RAD50

POLE – Alytic subunit of DNA polymerase epsilon

NBN – Gene encodes the protein nibrin, which is involved in the regulation of the cell cycle and repair of double-stranded DNA breaks.

BLM – Gene encodes a protein of the RecQ-helicase family

SMARCA4 – BRG1 transcriptional activator, also known as ATP-dependent chromatin remodeler SMARCA4

MUTYH – Muty DNA glycosylase

MLH1, MSH2, MSH6, PMS2 – proteins of the DNA repair system

FANCC – Fanconi anemia group C protein

FANCG – Fanconi anemia group G protein

SMAD4 – SMAD Family Member 4

CDKN2A – cyclin-dependent kinase inhibitor 2A

TP53 – transcription factor regulating cell cycle

SMARCB1 – gene encoding the matrix-associated actin-dependent chromatin regulator protein SWI/SWF, subfamily B, type 1

STK11 – Tumor suppressor gene encoding serine/threonine kinase 11

pMMR – surplus of mismatch repair proteins

NGS – Next Generation Sequencing

wt – "wild" type of genes

EDTA – Ethylenediaminetetraacetic acid

Introduction

Pancreatic cancer (PC) is one of the most aggressive malignant neoplasms with survival rates that have hardly changed in the last 30 years. According to various authors, the 5-year overall survival rate is between 5% (Vietri *et al*., 2022; Dal *et al*., 2023) and 9% (Wieme *et al*., 2021), and the 10-year survival rate is less than 1 % (Dal *et al*., 2023). The incidence of pancreatic cancer has increased significantly in the last ten years (2011-2021), by 25.94% in men and 36.13% in women (Kaprin, 2022). Exocrine tumors account for over 90% of PC cases, especially ductal adenocarcinoma.

The development of malignant neoplasms in pancreatic cancer is multifactorial and requires further research. One of the most common factors is an unhealthy lifestyle, including excessive alcohol consumption and smoking. Most cases of pancreatic cancer are sporadic, but 5 to 10% of cases are associated with a hereditary predisposition (Pilarski *et al*., 2019; Popova, 2020; Vietri *et al.*, 2022). According to several authors, pathogenic mutations with high penetrance in the BRCA1 (Brose *et al*., 2002) and BRCA2 (Goggins *et al*., 1996; Kashintsev *et al*., 2013) genes play an important role in the development of hereditary PC. These are mostly heterozygous mutations in the germline. In addition, recent compelling data indicate an increased risk of developing PC in carriers of germline mutations in genes such as ATM (Roberts *et al*., 2012), PALB2 (Jones *et al*., 2009), RAD50 (Wang *et al*., 2008), MLH1 (Vietri *et al.*, 2022), MSH2, MSH6, PMS2, FANCC and FANCG (Wang *et al*., 2005; Van Der Heijden *et al*., 2012), SMAD4, CDKN2A (Ghiorzo *et al*., 2012), TP53 and STK11. Pathogenic variants in these genes have a different geographical prevalence (Golan *et al.*, 2020; Murali *et al.*, 2021). According to European authors (Pilarski *et al*., 2019; Wieme *et al*., 2021; Vietri *et al*., 2022), the frequency of mutations in the BRCA1/2 genes is between 3 and 17%, while domestic data report frequencies of 5% to 10% (Kashintsev *et al.*, 2013; Abramov *et al.*, 2021). It is important to note that the information on the frequency and spectrum of pathogenic mutations in genes associated with hereditary tumor syndromes in PC in the Russian Federation is limited and does not fully reflect the actual situation. The aim of this study is to determine the prevalence of clinically significant mutations in genes of hereditary tumour syndromes in patients with pancreatic cancer (PC) in Nizhny Novgorod.

Materials and Methods

The study involved 223 patients aged between 35 and 84 years (average age at onset of PC disease – 61.8 years) with morphologically confirmed PC who were undergoing treatment at the Nizhny Novgorod Oncology Dispensary (NOKOD) between 2021 and 2022. All participating patients provided written informed consent. Data on oncological diseases in the personal and family history of the subjects were collected prospectively. DNA extracted from peripheral blood lymphocytes collected in EDTA vials (4 ml) was used as material for the study. All samples were anonymized and no confidential data were included in this study.

The study included analysis of BRCA1/2 genes and other genes by using real-time PCR and NGS (next-generation sequencing) to identify germline mutations. The design of the molecular genetic study is shown in Figure 1.

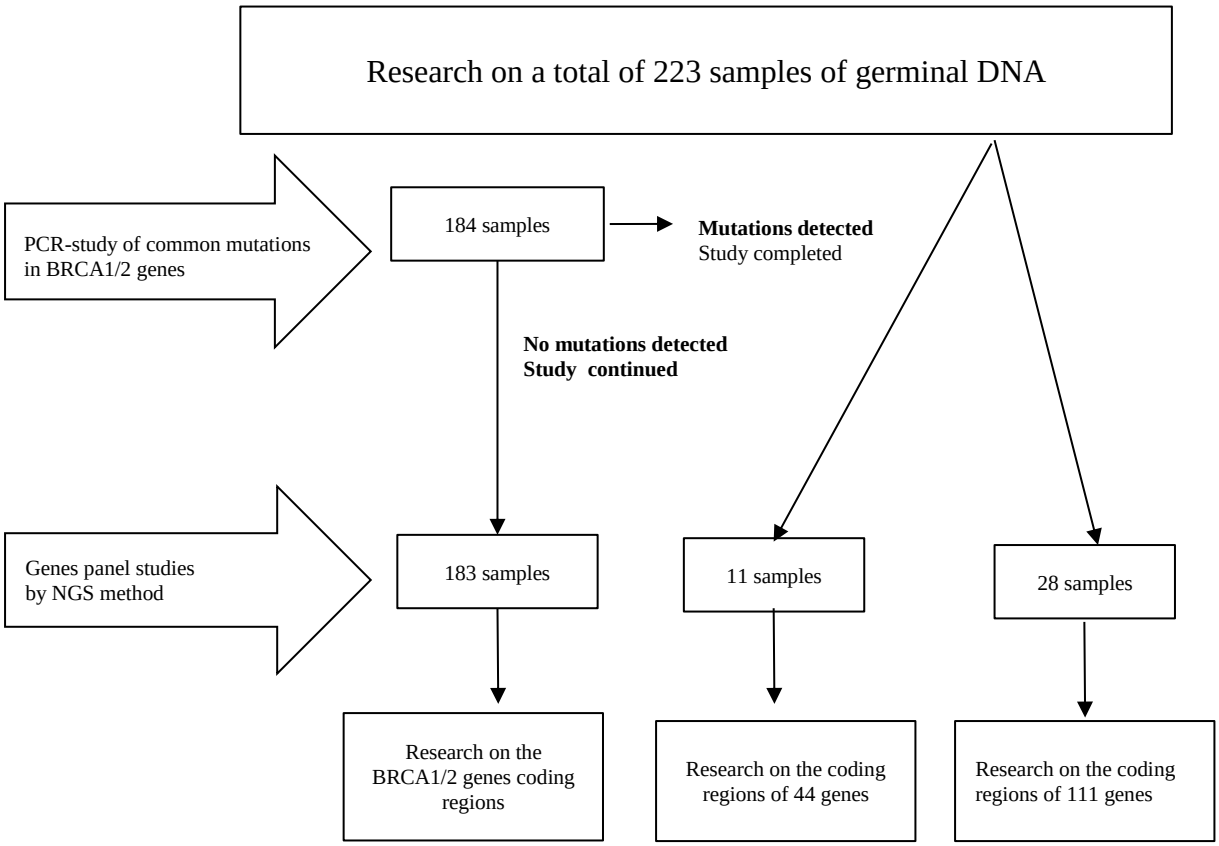

Fig. 1. Design of molecular genetic study

For the first group of 184 patients, a PCR test for «common» mutations was performed at NOKOD using the «OncoGenetics BRCA» kit (DNA Technology LLC) in accordance with the manufacturer's instructions. In the Department of Molecular Biology Research «National Medical Research Center of Radiology» of the Ministry of Health of the Russian Federation, the «coding regions of the BRCA1 and BRCA2 genes were examined for the 183 patients without «common» mutations using the targeted paired-end sequencing method on MGISEQ G400 technology and using a Roche multiplex panel. Bioinformatic data processing was performed using programs for demultiplexing and mapping (BOWTIE2 v 2.2.5), variant calling (GATK 3.8-0), annotation (SNPEff 4.3T Annovar 2017J) and other tools. The pathogenicity assessment was performed in accordance with the recommendations of ACMG (Richards *et al.*, 2015) and the Medical Genetic Science Center (Ryzhkova *et al.*, 2018).

For the second group of 39 patients, NGS-test was carried out, on the coding and adjacent intronic regions of 44 and 111 oncology-associated genes, including BRCA1/2 genes, at the Centre for Personalised Medicine of the State Budgetary Healthcare Institution, «Moscow Clinical Scientific and Practical Center named after A.S Loginov» of the Moscow Department of Health. The study was conducted using the paired-end sequencing method on an Illumina MiSeq sequencer.For sample preparation, a hybridization-based selective enrichment of DNA fragments associated with the coding regions of genes was performed, custom probe panels, in particular the KAPA HYPER probes (Roche), were used according to the manufacturer's protocol. Bioinformatic data processing was performed according to the previously described protocol (Bilyalov *et al.*, 2022).

Statistical processing and data analysis were conducted using methods of variational statistics, including the calculation of the mean, the

standard error of the mean (m) and the determination of the significance level (*Student's t-test*). The difference between the compared values at a confidence level of 95% and 99% was considered statistically reliable, i.e., $p < 0.05$ and $p < 0.001$. The statistical analysis was performed using generally accepted algorithms in Microsoft Office (Excel), the statistical software package Statz, Statistica 6.0, Biostat.

Results

In the first subgroup, a «founder» variant c.5266dupC (5382insC) in the BRCA1 gene was detected by PCR in one patient (1/184; 0.5%), and this sample was subsequently excluded from further testing. Using NGS, aberrations in the BRCA2 gene were identified in 5/183 probands (3.3%). In total, germline mutations in the BRCA1/2 genes were found in 6/184 (3.3%) patients, including 1 (1/183; 0.5%) male and 5 (5/183; 2.7%) female (Table 1).

In the second subgroup, which was examined using custom gene panels, no clinically significant variants were identified in the BRCA1/2 genes. Thus, in the overall group, the frequency of carriers of clinically significant nucleotide sequence variants in the BRCA1/2 genes was 2.7% (6/223), of which a proportion of «common» mutations was 0.4% (1/223) and unique variants in the BRCA2 gene was 5/223 (2.24%). The pathogenic variants in the BRCA2 gene were more frequently frameshift mutations (3/5; 60.0%), one of which, c.8158del, had not previously been registered in international population frequency databases. In addition, we identified a splice site mutation, c.7007+1G > C (n = 1; 20.0%), and a previously unregistered point substitution, c.8158del, leading to premature termination of protein synthesis (n = 1; 20.0%). The mean age of BRCA1/2-associated pancreatic cancer was 54 ± 10.3 years, and ranged from 47 to 67 years. Of the 223 patients, 186 (83.4%) had tumors located in the head of the pancreas and histologically represented by moderately differentiated ductal adenocarcinoma G2.

When the second group was examined using targeted gene panels, 9 of 39 probands (23.1%) were found to carry heterozygous pathogenic and likely pathogenic variants in the following genes: ATM (n = 1), FANCC (n = 2), POLE (n = 1), NBN (n = 1), BLM (n = 1), SMARCA4 (n=1), MUTYH (n = 1) (Table 2). In 7 of 9 patients, the tumour was located in the head of the pancreas.

In one patient, a synonymous variant of p.Cys167= was detected at a splice site in the SMARCB1 gene and characterized as a mutation of unclear clinical significance. In 4 out are 10 cases, genetic aberrations, are nucleotide substitutions that lead to the occurrence of premature stop codons. All patients with these different genetic alterations denied a significant history of cancer in their family.

Genetic aberrations found in Nizhny Novgorod patients with pancreatic cancer are presented in Figure 2.

Discussion

As indicated in the literatures, the frequency of BRCA1/2 germline mutations in pancreatic cancer varies between 2% and 8% (Kashintsev *et al*., 2013; Golan *et al.,* 2020; Pokataev *et al.,* 2018; Yashin *et al.,* 2018; Vietri *et al*., 2022). According to the results of our study, the frequency of detection of pathogenic mutations in the BRCA1/2 genes in pancreatic cancer patients in Nizhny Novgorod was 2.7%. Despite the low prevalence of these mutations, interest in their detection has increased significantly in recent years. This is due to their predictive significance for the efficacy of treatment with PARP inhibitors and platinum derivatives, as well as their prognostic significance and the identification of high-risk groups for the development of malignant neoplasms in relatives of patients with pancreatic cancer (Goggins *et al.,* 1996; Brose *et al.,* 2002; Lowery *et al.,* 2011; Tsukanov *et al.,* 2014; Holter *et al.,* 2015; Baranova *et al.,* 2020; Bykova *et al.,* 2020; Murali *et al.,* 2021).

It should be noted that the PCR panel with 8 common mutations does not reflect the actual distribution of mutations in the BRCA1/2 genes in the population of pancreatic cancer patients in Nizhny Novgorod; only one patient was found to have the most common “founder” mu-

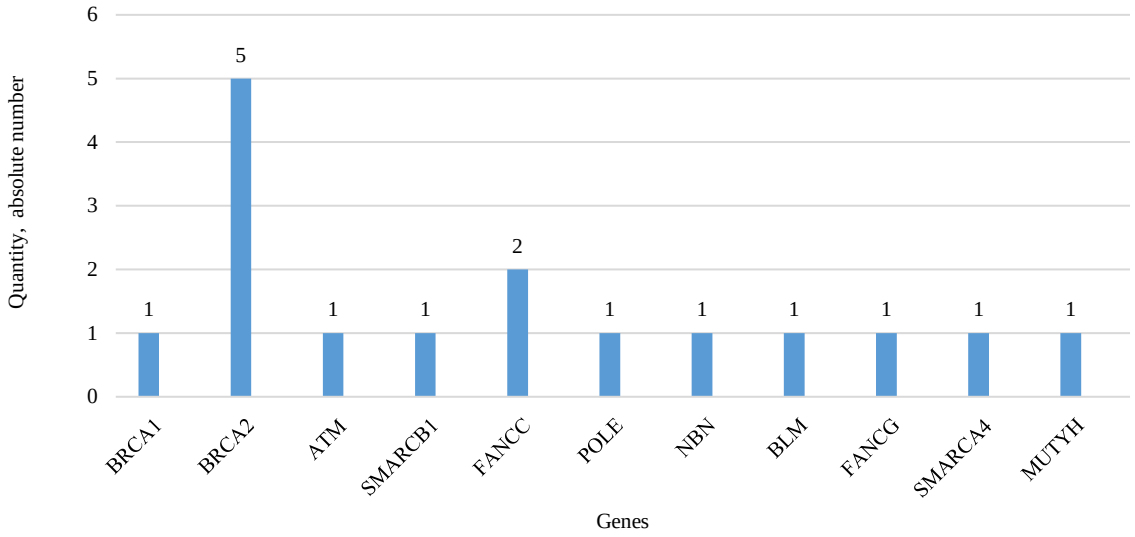

Fig. 2. Genetic aberrations in various genes in patients with pancreatic cancer

tation c.5266dupC in the BRCA1 gene. This leads to the conclusion that performing a PCR test in patients with pancreatic cancer is not informative. The use of NGS (next-generation sequencing) is required for comprehensive detection of a broad spectrum of point mutations. It should also be borne in mind that around 1% of mutations in these genes are represented by large rearrangements, which require additional assessment of the gene structure using the MLPA (multiplex ligation-dependent probe amplification) method (Park *et al.*, 2017).

The results of our study indicate a higher frequency of mutations in the BRCA2 gene in pancreatic cancer, which is consistent with data from global literatures. It is worth noting that the only male carrier of a pathogenic mutation in the BRCA2 gene (Table 1) was treated for primary multiple cancers (PMC): Melanoma of the back skin pT1aN0M0 stage IA, excision in March 2021; ductal adenocarcinoma of the head of the pancreas, involving the uncinate process pT4N1M0 stage III, gastrojejunostomy on 9 August 2021. Somatic profiling of the melanoma revealed a «wild-type» status (wt) status for the BRAF and NRAS genes, and in the pancreatic cancer no mutations were found in the KRAS gene, and there were no signs of mismatch repair deficiency (pMMR). Cases of the combination of PMC (primary multiple cancers) are also described in the literatures: Melanoma + pancreatic cancer (PC) associated with the presence of pathogenic mutations in BRCA genes (Ibrahim *et al.*, 2018).

There are few studies to determine the spectrum of mutations in genes responsible for the development of various hereditary tumour syndromes in pancreatic cancer; the study was conducted for the first time in the Nizhny Novgorod region. Analysis of the results of NGS (next-generation sequencing) using custom gene panels in the second subgroup (n = 39) revealed the presence of clinically significant variants in genes with autosomal recessive inheritance patterns. In order to manifest a hereditary cancer syndrome, the mutations must be detected in a compound heterozygous or homozygous form. However, numerous literature sources show that carrying pathogenic germline mutations in genes such as ATM, FANCC, FANCG, POLE, NBN, BLM, SMARCA4 and MUTYH can be a risk factor for the development of various malignancies, including pancreatic cancer (Van Der Heijden *et al.*, 2003; Wang *et al.*, 2005; Ghiorzo *et al.*, 2012; Sokolenko *et al.*, 2012; Damiola *et al.*, 2014; Esteban-Jurado *et al.*, 2015; Hansen *et al.*, 2015; Sokolenko *et al.*, 2015; Lener *et al.*, 2016;Suspitsin *et al.*, 2017; Slavin *et al.*, 2018; Goggins *et al.*, 2020).

The data analysis revealed mutations in the FANCC gene in two cases and mutations in the FANCG gene in one case. As is known, patho genic germline variants in homozygous or com-

Table 1

Spectrum of pathogenic variants found in the *BRCA1/2* genes

№	Gender/ Age of malignancy onset	Exon	Gene Transcript (NCBI ID)	dbSNP	cDNA	Protein	Function
1	Female/59	20	*BRCA1* NM_007294.4	rs80357906	c.5266dupC	p.Gln1756ProfsTer74	Frameshift
2	Male/67	18	*BRCA2* NM_000059.4	–	c.8158del	p.Glu2720AsnfsTer13	Frameshift
3	Female/49	11	*BRCA2* NM_000059.3	rs397507663	c.3296C>A	p.Ser1099Ter	Stop codon
4	Female/62	11	*BRCA2* NM_000059.4	rs80359530	c.5722_572del	p.Leu1908fs	Frameshift mutation
5	Female/40	24	*BRCA2* NM_000059.3	rs397508041	c.9247delA	p.Lys3083fs	Frameshift mutation
6	Female/47	13	*BRCA2* NM_000059.4	rs397507891	c.7007+1G>C		Splice site mutation

Table 2

The spectrum of heterozygous variants in the hereditary cancer genes

№	Gender/ Age of	Gene	Transcript - NCBI ID	dbSNP	cDNA	Protein	Function	Clinical relevance
1	Male/52	*ATM*	NM_000051.4	rs587776547	c.2353del	p.Arg785ValfsTer3	Stop codon	Likely pathogenic
2	Male/67	*SMARCB1*	NM_003073.5	rs779221331	c.501C>T	p.Cys167=	Splice site mutation	VUS
3	Male/67	*FANCC*	NM_000136.3	rs774170058	c.455dup	p.Asn152LysfsTer9	Frameshift mutation	Pathogenic
4	Male/77	*POLE*	NM_006231.4	rs576578672	c.1108C>A	p.Pro370Thr	Missense mutation	Likely pathogenic
5	Female/51	*NBN*	NM_002485.5	rs587776650	c.657_661del	p.Lys219AsnfsTer16	Frameshift mutation	Pathogenic
6	Female/55	*FANCC*	NM_000136.3	rs774209201	c.844-1G>C		Stop codon	Pathogenic
7	Female/63	*BLM*	NM_001287247.2	rs200389141	c.1642C>T	p.Gln578Ter	Stop codon	Pathogenic
8	Female/65	*FANCG*	NM_004629.2	rs1563984976	c.1772del	p.Leu591ArgfsTer3	Frameshift mutation	Likely pathogenic
9	Female/67	*SMARCA4*	NM_001128849.3	rs1600335765	c.3277C>T	p.Arg1093Ter	Stop codon	Pathogenic
10	Female/73	*MUTYH*	NM_001128425.2	rs36053993	c.1103G>A	p.Gly368Asp	Missense mutation	Pathogenic

pound heterozygous form in these genes are the cause of Fanconi anaemia and are characterised by a predisposition to tumours (OMIM#227645; #614082). It is noteworthy that a 67-year-old patient with the c.455dup mutation in the FANCC gene had PMC: right kidney cancer cT1N0M0 stage I, kidney resection in 2020; pancreatic head cancer cT4N1M1 (hep, lym) stage IV. In the second patient, a carrier of the c.844-1G>C variant in the FANCC gene, pancreatic cancer manifested at the age of 55. The c.1772del variant in the FANCG gene, which had previously been discovered in a 65-year-old patient, was not described in international population frequency databases such as gnomAD Genomes according to the ACMG criteria (PVS1, PM2) and was assessed as likely pathogenic. In line with numerous studies, mutations in the genes of the Fanconi anaemia group are frequently found in cases of pancreatic cancer (Slavin *et al.,* 2018), but the risk of developing pancreatic cancer in such patients has not yet been investigated.

An interesting discovery was the c.2353del mutation in the ATM gene in a man who developed pancreatic cancer at the age of 52, which was previously characterised in ClinVar as a pathogenic or likely pathogenic variant. In the homozygous state, pathogenic mutations in the ATM gene lead to the development of ataxia-telangiectasia (OMIM#208900). According to some studies, pathogenic heterozygous variants in the ATM gene are considered moderately penetrant markers and have been discussed as a risk factor for the development of breast and pancreatic cancer (Goggins *et al.,* 2020; Vietri *et al.,* 2022).

Homozygous and compound heterozygous variants in the NBN gene lead to the development of Nijmegen syndrome and predisposition to immunological defects and tumor diseases (OMIM#251260). In our study, a c.657_661del variant in the NBN gene was identified in a 51-year-old patient with PC, which was previously described as a «founder» mutation and a risk factor for the development of breast cancer in women, colorectal cancer, melanoma and other diseases [34]. In view of the fact that the NBN gene, like the BRCA1/2 genes, is involved in the repair process of double-strand DNA breaks, the clinical significance of this mutation remains a subject of intensive research. In a study by Lener M.R. and co-authors, the carrier frequency of the c.657_661del variant in the NBN gene in the Polish population was 2.09%, and this variant was associated with a fourfold increased risk of pancreatic cancer. The authors consider it advisable to perform genotyping for the presence of this mutation in order to exclude high risk of pancreatic cancer (Lener *et al.,* 2016).

In another case, a pathogenic mutation of c.1642C> T in the BLM gene was detected in a 63-year-old woman with a pancreatic body tumour. This variant was previously described in individuals of Slavic origin with a carrier frequency of 0.2-0.6% (Sokolenko *et al.,* 2012). Furthermore, there have been reports of compound heterozygous and biallelic carriage of this variant in Bloom syndrome- a hereditary tumour syndrome with autosomal recessive inheritance (OMIM#210900). Previous studies have provided conflicting data on the effects of heterozygous BLM gene variants on the risk of developing colorectal cancer (De Voer *et al.,* 2015), and we found no publications on the association of increased risk of developing PC in mutation carriers.

We also identified mutations in the POLE and MUTYH genes, which are described as the cause of hereditary malignant colon tumors against the background of polyposis (Hansen *et al.,* 2015). Heterozygous germline mutations in the POLE gene have been described as a risk factor for the development of colon cancer, endometrial cancer (OMIM#615083), pancreatic cancer, ovarian cancer and small intestine cancer (Hansen *et al.,* 2015). The age of manifestation of prostate cancer in a patient carrier of the c.1108C >A mutation in the POLE gene examined by us was 77 years. In compliance with studies by Buchanan D.D. et al., the average age of manifestation of POLE-associated colorectal cancer is 50.2 years, the risk of its development is 21-28% before the age of 70 (Buchanan *et al.,* 2018), which explains the absence of malignant neoplasms of other localizations in the patient's history. However, isolated cases of PC associated with germline mutations in the POLE gene

have been described, indicating the need for further studies to assess the risk of POLE-related PC.

In the oldest patient (77 years old), the previously registered pathogenic missense mutation c.1103G>A was detected in the MUTYH gene. Inactivation of the second allele of this gene leads to the development of familial adenomatous polyposis (FAP) type 2 syndrome (OMIM#608456), and in view of the absence of characteristic clinical signs in the patient, this variant is considered to have carrier status.

An interesting finding in our study was the pathogenic variant c.3277C> T in the 24th exon of the SMARCA4 gene in a heterozygous form in a 67-year-old patient. Pathogenic germline variants in this gene lead to the development of Coffin-Siris syndrome type 4 (OMIM#614609) and predisposition to rhabdoid tumors (OMIM#613325). The patient's phenotype was characterized by average height (163 cm), underweight (50 kg), developmental delay, moderate cognitive retardation, aplasia of the fifth fingernail, coarse facial features and strabismus. Characteristic facial features included a broad nasal bridge and a wide mouth with full, outturned lips. Secondary features that characterized the patient's phenotype were sparse scalp hair, a nodular goiter on the right side, hypoplasia of the left thyroid gland, and a non-neoplastic process in the pelvis in the form of serosometry. In accordance with the patient's statement, no clinical disorders similar to the patient's disease were found in her family history (her parents are not related). In addition, the patient was not married and had no children of her own. It is noteworthy that the tumor in this patient occupied the head and body of the pancreas and was represented by moderately differentiated ductal adenocarcinoma. According to literature, there have been more than 150 cases of Coffin-Siris syndrome described to date, and as many as 10% of them have heterozygous variations in the SMARCA4 gene. Truncating heterozygous mutations in this gene have been described in patients with various tumors, including small cell ovarian cancer and colorectal cancer (Sokolenko *et al.,* 2012; Esteban-Jurado *et al.,* 2015; Aref-Eshghi *et al.,* 2018). Inactivating somatic mutations in this gene and disruption of SMARCA4 protein expression have been described as markers of unfavorable prognosis in certain malignant neoplasms (Peng *et al.,* 2021). The SMARCA4 gene has been characterized as a tumor suppressor gene, but more recent reports have identified its oncogenic role (Kim *et al.,* 2021). Further research is therefore needed to determine the spectrum and degree of cancer risk in patients with Coffin-Siris syndrome.

Conclusion

Carrying out molecular genetic tests on genes associated with hereditary tumour syndromes allows the discovery of new additional therapeutic targets for the treatment of a disease as aggressive as pancreatic cancer. The genetic research results presented in this article indicate the widespread occurrence of germline mutations in pancreatic cancer patients. The use of broad molecular panels that include not only BRCA1 and BRCA2 genes expands our understanding of the prevalence of different pathogenic variants of hereditary tumour syndromes in the group of pancreatic cancer patients.

The analysis of rare clinical cases enables a deeper understanding of tumour biology. In addition, the identification of carriers of pathogenic mutations among healthy relatives of pancreatic cancer patients helps to form groups of individuals with a high oncological risk. The creation of an individual monitoring and screening programme for healthy carriers contributes to the early detection and prevention of neoplastic diseases. A personalised approach using molecular genetic methods is an important step towards reducing morbidity and improving survival rates of patients with various neoplastic diseases in Russia.

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