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Association between *SIRT1* rs3758391 genetic variant and susceptibility to pancreatic and gastric cancer

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Abstract

Background The *SIRT1* gene encodes a NAD^+-dependent deacetylase that regulates apoptosis, metabolism and genomic stability through interaction with p53 and other transcription factors. Functional single nucleotide polymorphisms within *SIRT1* may alter gene expression and affect cancer susceptibility. The rs3758391 and rs369274325 polymorphisms have been implicated in various malignancies; however, their role in pancreatic and gastric cancer remains unclear.

Methods This case-control study included 94 patients with pancreatic ductal adenocarcinoma (PDAC), 38 patients with gastric cancer (GC), and 74 healthy controls, all of Greek origin. Genomic DNA was extracted from peripheral blood samples. Genotyping was performed by RFLP-PCR for rs3758391 and tetra-primer ARMS-PCR for rs369274325. Genotype and allele frequencies were compared using χ^2 test and odds ratios (ORs) with 95% confidence intervals (CIs).

Results A significant association was identified between *SIRT1* rs3758391 and PDAC and GC susceptibility. The TT genotype was overrepresented among PDAC patients, while the TC genotype conferred a protective effect against both PDAC (P=0.0039; OR 0.35, 95%CI 0.17-0.62) and GC (P=0.0059; OR 0.26, 95%CI 0.10-0.66). The C allele was more frequent in healthy controls compared to PDAC patients (P<0.001; OR 0.39, 95%CI 0.25-0.62). No significant association was observed for rs369274325 in either cancer type or with clinicopathological parameters.

Conclusions This is the first study to evaluate *SIRT1* genetic variants in PDAC and GC. The rs3758391 polymorphism appears to influence susceptibility to both malignancies, potentially via altered p53-mediated regulation of *SIRT1*. These findings suggest *SIRT1* as a candidate biomarker for gastrointestinal cancer risk, meriting further validation in larger, ethnically diverse cohorts.

Keywords *SIRT1*, rs3758391, rs369274325, pancreatic ductal adenocarcinoma, gastric cancer

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Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing an immense burden on global health systems. According to projections by the American Cancer Society, approximately 2,041,910 new cancer cases and 618,120 cancer-related deaths are expected in the United States alone in 2025, reflecting the persistent and growing challenge of cancer control and prevention [1]. On a global scale, cancers of the digestive system represent a significant proportion of this burden. In 2022, the estimated worldwide incidence of digestive system malignancies reached 4,905,882 cases, accounting for a substantial share of the global cancer caseload. These cancers were also responsible for approximately 3,324,774 deaths, underscoring their lethality [2]. Among them, colorectal cancer was the most prevalent in both incidence and mortality, but other digestive tract cancers—including pancreatic and gastric cancers—contribute significantly to cancer-related deaths because of their aggressive nature and often late diagnosis [3].

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Conflict of Interest: None

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Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent form of pancreatic cancer, accounting for over 90% of pancreatic malignancies [4]. It is characterized by aggressive clinical behavior, poor prognosis and limited therapeutic options. Because of its deep anatomical location and nonspecific early symptoms, PDAC is typically diagnosed at an advanced stage, with fewer than 20% of patients eligible for surgical resection [5,6]. As a result, the 5-year survival rate remains low—currently estimated at approximately 13%—despite modest improvements in recent years. Globally, PDAC ranks as the 12th most common cancer, but the 7th leading cause of cancer-related mortality, with a rising incidence, particularly in high-income countries [7].

At a molecular level, PDAC exhibits a distinct set of somatic alterations. Over 90% of tumors harbor activating mutations in *KRAS*, often present in early precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN) [8]. As the disease progresses, additional mutations in *TP53*, *CDKN2A* and *SMAD4* contribute to tumor aggressiveness and resistance to therapy [9,10]. While *KRAS* remains a critical oncogenic driver, emerging evidence suggests a subset of PDACs may evolve independently of *KRAS* signaling, complicating targeted treatment approaches. In parallel, germline mutations in DNA repair genes (e.g., *BRCA1/2*, *PALB2*) have been identified in a proportion of cases, opening the door to targeted therapies such as PARP inhibitors and platinum-based chemotherapies [11].

Gastric cancer represents a major global health challenge, ranking as the fifth most common cancer and the fourth leading cause of cancer-related death worldwide. In 2020, over 1 million new cases and nearly 650,000 deaths were reported globally, with marked geographic and sex-based variations [12]. Its incidence is approximately twice as high in men as in women, and it is particularly prevalent in East Asia and Eastern Europe [2].

Gastric cancer is a heterogeneous disease that can be classified anatomically into cardia (upper stomach) and non-cardia (lower stomach) cancers, each with distinct epidemiological and etiological profiles [13]. Non-cardia gastric cancer is primarily linked to chronic *Helicobacter pylori* (*H. pylori*) infection, along with lifestyle factors such as alcohol consumption, tobacco use, and diets high in sodium or smoked foods. Cardia gastric cancer has a dual etiology, involving *H. pylori* infection as well as obesity and gastroesophageal reflux, which also contribute to gastroesophageal junction and distal esophageal adenocarcinomas [14].

At the molecular level, gastric tumors frequently harbor amplifications or mutations in genes encoding receptor tyrosine kinases (RTKs), including *EGFR*, *HER2* (*ERBB2*), and *FGFR2*, alongside alterations in *KRAS*, *NRAS* and *VEGFA* [15]. Comprehensive genomic studies, including those by The Cancer Genome Atlas (TCGA), have classified gastric cancers into 4 major molecular subtypes: chromosomal instability (CIN), microsatellite instability (MSI), Epstein-Barr virus (EBV) positive, and genomically stable (GS), each exhibiting distinct histopathological and immunological characteristics [16]. Notably, the CIN subtype is characterized by *TP53* mutations and focal amplifications of RTKs, while MSI and EBV-positive subtypes display high immunogenicity, suggesting potential responsiveness to immune checkpoint inhibitors. Although these classifications have deepened our understanding of gastric cancer biology, their clinical utility in prognosis and therapy selection is still under investigation [17,18]

Sirtuins constitute a family of NAD^+-dependent deacetylases and ADP-ribosyltransferases that are highly conserved across species, and play critical roles in cellular regulation, metabolism and aging [19]. Among them, *SIRT1*, primarily a nuclear deacetylase, regulates gene expression and protein function to control key processes, such as cell proliferation, differentiation, apoptosis, metabolism and genome stability. It shuttles between the nucleus and cytoplasm, enabling versatile cellular functions [20].

The role of *SIRT1* in cancer is complex and context-dependent, exhibiting both tumor-suppressive and oncogenic activities, depending on the tissue type and cellular environment [21]. This duality stems from its interaction with multiple substrates, including important tumor suppressors such as p53, FOXO and HIC1, influencing diverse pathways in tumorigenesis [22].

In pancreatic cancer, research on sirtuins, especially *SIRT1*, remains limited. However, *SIRT1* is frequently upregulated at both mRNA and protein levels in pancreatic cancer tissues. Functional studies reveal that *SIRT1* knockdown induces apoptosis, inhibits invasion and enhances chemosensitivity, suggesting it may promote tumor progression and represent a potential therapeutic target in pancreatic cancer [23].

On the other hand, *SIRT1* exhibits a dual role in gastric cancer, functioning as both tumor suppressor and promoter, depending on the cellular context. High levels of *SIRT1* expression have been found in some cases to be correlated with poor overall survival and lymph node metastasis, while other studies suggest that *SIRT1* can act as a tumor suppressor through ferroptosis regulation [24].

Despite significant efforts to uncover the genetic basis of PDAC and gastric cancer, no specialized biomarkers have yet been identified. This study aimed to investigate the potential association of 2 specific single nucleotide polymorphisms (SNPs) in the *SIRT1* gene, rs3758391 and rs369274325, with both pancreatic adenocarcinoma and gastric cancer in a Greek patient cohort.

The rs3758391 polymorphism, located in the promoter region of *SIRT1* at the p53-binding site, involves a C variant that disrupts p53 binding and alters *SIRT1* expression *in vitro*, suggesting a functional role in human disease [25]. Previous studies have implicated rs3758391 in various cancers, including urinary bladder cancer, diffuse large B-cell lymphoma and laryngeal squamous cell carcinoma [26-28]. The rs369274325 polymorphism has also been studied before in the same urinary bladder cancer cohort [26].

Patients and methods

Ninety-four patients with a diagnosis of PDAC and 38 patients with gastric cancer were included in the present

study. All the samples were recruited from the First Department of Propaedeutic Surgery, Hippocration General Hospital, Medical School, National and Kapodistrian University of Athens, Greece. A total of 74 sex- and age-matched healthy volunteers were used as the control group. Detailed characteristics and clinical features of patients and healthy volunteers are presented in Table 1.

DNA isolation and genotyping

Genomic DNA from peripheral blood samples of patients and healthy donors was extracted using the Nucleospin Blood Kit (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany). Two SNPs of *SIRT1* gene were investigated in this study: rs3758391 and rs369274325. The rs3758391 polymorphism was genotyped by restriction fragment length polymorphism- polymerase chain reaction (RFLP-PCR), using the primers Forward: 5'-ACGCAGGTAATTGATGCAGT-3', Reverse: 5'-CGTGAGCTATCTAGCCGTTT-3' (Eurofins Genomics AT GmbH, Vienna, Austria) and restriction enzyme *Nco*I (New England Biolabs, Ipswich, Massachusetts, USA). Genotypes were extracted after overnight incubation of PCR products with *Nco*I and digested products, and the respective genotypes are listed in Table 2. The rs369274325 polymorphism was genotyped using the tetra-primer amplification refractory mutation system (ARMS)-PCR. In this method 4 primers were used in total: 2 outer ones, which produced a control product, and 2 inner primers, each of them specific for the 2 alleles and produced allele-specific products. More specifically, the reaction was conducted using the primers F_o: 5'-TAGGTTCCATACCCCATGAAG-3', R_o: 5'-CATTACTCTTAGCTGCTTGGTC-3', F_I (G allele): 5'-GAATTGTGTCATAGGTTAGGAGG-3' and R_I (A allele): 5'-ACAGCAAAGTTTGGCATATTGAT-3' (Eurofins Genomics AT GmbH, Vienna, Austria). PCR products and the respective genotypes are listed in Table 2. The primers that were used for these 2 reactions are derived from previous studies. [26,27] To ensure genotyping accuracy, each PCR run included negative (no-template) controls, and a random subset of samples was re-genotyped in independent experiments with 100% concordance. All genotype distributions in the control group were tested for Hardy–Weinberg equilibrium.

Table 1 Demographic and clinicopathological characteristics of pancreatic cancer patients, gastric cancer patients and healthy individuals

Characteristics	Pancreatic ductal adenocarcinoma (94) n (%)	Gastric cancer (38) n (%)	Healthy individuals (74) n (%)
Sex			
Male	51 (54.25)	27 (71.05)	38 (51.35)
Female	43 (45.75)	11 (28.95)	36 (48.65)
Age (years, mean±SD)	63.17±15.39	61±11.13	56±17.03
Tumor location			
Head	87 (92.55)	N/A	N/A
Tail	5 (5.31)		
Vater	2 (2.12)		
Smoking			
Current	13 (13.83)	N/A	18 (24.33)
Ex-smoker	6 (6.39)		10 (13.51)
No	75 (79.78)		46 (62.16)
TNM Stage			
I	14	10	N/A
II	40	7	
III	37	12	
IV	3	9	
Lymph node metastasis			
Negative	N/A	11 (28.95)	N/A
Positive		27 (71.05)	
Other metastasis			
Negative	N/A	28 (73.68)	N/A
Positive		10 (26.32)	
Lauren classification			
Intestinal	N/A	17 (44.73)	N/A
Diffuse		21 (55.27)	
Tumor size (cm)			
≤5	N/A	17 (44.73)	N/A
>5		21 (55.27)	

N/A, nonapplicable; SD, standard deviation

Statistical analysis

Genotype frequencies were analyzed by the χ^2 test with Yate's correction, using S Plus (version 6.2 Insightful, Seattle, WA, USA) software. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using GraphPad (version 300, GraphPad Software, San Diego, CA, USA). All P-values are 2-sided. P-values <0.05 were considered significant.

Results

Genotype and allele distributions for rs3758391 and rs369274325 are listed in Tables 3 and 4, respectively. The rs3758391 T/T genotype was overrepresented in both PDAC and gastric cancer patients. Moreover, the T/C genotype appeared to exert a protective effect against both PDAC (P=0.0039; OR 0.3468, 95%CI 0.1742-0.6249) and gastric cancer (P=0.0059; OR 0.2554, 95%CI 0.0985-0.6617). The CC genotype was found to be overrepresented in healthy donors, and might also exert a protective role against PDAC (P=0.0015; OR 0.1815, 95%CI 0.0648-0.5080). At the allele level, the C allele was significantly overrepresented in healthy donors compared to PDAC patients (P<0.001; OR 0,3930, 95%CI 0.2472-0.6249), but not gastric cancer patients, because of the limited availability of samples (P=0.1539; OR 0.6497, 95%CI 0.3668-1.151). The genotyping of the rs369274325 polymorphism did not show any significant differences in genotype or allele

Table 2 Polymerase chain reaction primers and reaction conditions for the studied SNPs

SNP	Primers (5'-3')	Primers Tm	Restriction enzyme and products (bp)
rs3758391	F: ACGCAGGTAATTGATGCAGT R: CGTGAGCTATCTAGCCGTTT	56	*Nco*I T/T: 500 T/C: 500,280,220 C/C: 280,220
rs369274325	F_O : TAGGTTCCATACCCCATGAAG R_O: CATTACTCTTAGCTGCTTGGTC F_I (G allele): GAATTGTGTCATAGGTTAGGAGG R_I (A allele): ACAGCAAAGTTTGGCATATTGAT	56	GG: 381,229 GA: 381,229 ,152 AA: 381,152

SNP, single nucleotide polymorphism; bp, base pair

Table 3 *SIRT1* rs3758391 genotype and allele distributions among PDAC and GC patients and healthy individuals

Genotype	PDAC (94) n (%)	GC (38) n (%)	Healthy individuals (74) n (%)	PDAC P-value; OR (95%CI)	GC P-value; OR (95%CI)
T/T	54 (57.4)	20 (52.6)	21 (28.4)	>0.99	>0.99
T/C	33 (35.1)	9 (23.7)	38 (51.4)	0.0039; 0.3468 (0.1742-0,6249)	0.0059; 0.2554 (0.0986-0.6617)
C/C	7 (7.5)	9 (23.7)	15 (20.2)	0.0015; 0.1815 (0.0648-0.5080)	0.444; 0.63 (0.2252-1.763)
T	141 (76.6)	49 (64.5)	80 (54.1)	>0.99	>0.99
C	47 (23.4)	27 (35.5)	68 (45.9)	<0.001; 0.3930 (0.2472-0.6249)	0.1539; 0.6497 (0.3668-1.151)

PDAC, Pancreatic ductal adenocarcinoma; GC, gastric cancer; OR, odds ratio; CI, confidence interval

Table 4 *SIRT1* rs369274325 genotype and allele distributions among PDAC and GC patients and healthy individuals

Genotype	PDAC (94) n (%)	GC (38) n (%)	Healthy individuals (74) n (%)	PDAC P-value; OR (95%CI)	GC P-value; OR (95%CI)
G/G	74 (78.7)	27 (71)	62 (83.7)	>0.99	>0.99
G/A	20 (22.3)	11 (29)	12 (16.3)	0.4106; 1.523 (0.6779-3.423)	0.076; 2.48 (0.9531-6.453)
G	168 (89.3)	65 (82.9)	136 (91.9)	>0.99	>0.99
A	20 (10.7)	11 (17.1)	11 (8.1)	0.4356; 1.461 (0.6765-3.156)	0.0596; 2.532 (1.075-9.967)

PDAC, Pancreatic ductal adenocarcinoma; GC, gastric cancer; OR, odds ratio; CI, confidence interval

level between PDAC patients and healthy donors. In terms of gastric cancer, both GA genotype and A allele were found to be overrepresented in patients; however, the correlation between patients and controls did not reach statistical significance, possibly because of the limited number of samples. Given the very low reported allele frequency of rs369274325 in European populations, the observed genotype distribution should be interpreted with caution, and may reflect population-specific variation or methodological limitations inherent to PCR-based genotyping.

No significant association was observed between the rs3758391 or rs369274325 genotypes and clinicopathological characteristics, including tumor stage, grade and size, in either PDAC or gastric cancer patients.

Discussion

Despite considerable advances in elucidating the genetic landscape and molecular mechanisms of pancreatic and gastric cancers, the identification of reliable and specific biomarkers for these malignancies remains a major challenge. This gap is clinically significant, as early detection and risk stratification are crucial for improving patient outcomes, particularly in PDAC, which is typically diagnosed at advanced stages and carries a poor prognosis [5].

The present study represents the first genetic analysis investigating the potential association of *SIRT1* SNPs rs3758391 and rs369274325 with the risk of developing pancreatic and gastric cancer. We analyzed the genotype and allele distributions of these variants in a Greek PDAC and gastric cancer cohort. Although no previous studies have examined these associations in pancreatic or gastric cancer, our findings are consistent with reports concerning other malignancies, including bladder, breast, lymphoma and laryngeal cancers, where the T allele or TT genotype of rs3758391 has been linked to increased cancer susceptibility. Both SNPs have previously been evaluated in other malignancies and pancreas-associated disorders, but to our knowledge, not in PDAC or gastric cancer [26-29].

Our results revealed a strong association between the rs3758391 variant and PDAC. The T/T genotype was

significantly overrepresented in PDAC patients, whereas the heterozygous T/C genotype and the C allele appeared to confer a protective effect. These findings are in agreement with previous studies suggesting that rs3758391 plays a functional role in carcinogenesis. For example, Kan *et al* reported that the T allele increased susceptibility to diffuse large B-cell lymphoma [27]. Similarly, Rizk *et al* demonstrated a significant association between the TT genotype of rs3758391 and elevated breast cancer risk in Egyptian women [30]. Moreover, Shafieian *et al* found that the T allele of rs3758391 was significantly more frequent among urinary bladder cancer patients compared to healthy controls [26]. These findings collectively suggest that the T allele may confer increased cancer susceptibility across multiple tumor types.

In the gastric cancer group of our study, the rs3758391 TT genotype was also more frequent among patients than controls, while the TC genotype appeared protective. Although the association did not reach the same level of statistical significance as it did in PDAC, the trend aligns with earlier studies linking rs3758391 to digestive and epithelial cancers [27].

In contrast, the rs369274325 polymorphism did not show any statistically significant differences in genotype or allele frequencies between PDAC patients and healthy donors. For gastric cancer, both the GA genotype and A allele were somewhat more frequent among patients, but the difference did not reach statistical significance, probably because of the small sample size. This SNP was previously investigated in urinary bladder cancer cohorts. Shafieian *et al* reported a significant association of the GA genotype with bladder cancer in Iranian patients [26]. Conversely, a more recent study in a Turkish population by Bostancı *et al* found no significant association between rs369274325 and bladder cancer risk [31]. These discrepancies may reflect ethnic differences in allele frequencies or population-specific linkage disequilibrium patterns within the *SIRT1* locus.

Mechanistically, *SIRT1* encodes a NAD^+-dependent deacetylase involved in chromatin remodeling, DNA repair and the regulation of several transcription factors, including FOXO, PPARγ, NF-κB and p53 [22]. By deacetylating p53, *SIRT1* suppresses its transcriptional activity, thereby reducing apoptosis and promoting tumor cell survival [32]. The rs3758391 polymorphism is located within the promoter region of *SIRT1* at a p53-binding site [27]. Disruption of p53 binding by the C allele may reduce SIRT1-mediated deacetylation of p53, thereby preserving p53 tumor-suppressor activity and providing a plausible explanation for the observed protective effect of the C allele in both pancreatic and gastric cancer. The rs369274325 variant, located near the 5′ regulatory region of SIRT1 [26], might also influence gene expression, although our results did not confirm a significant effect. An important limitation of the present study concerns the analysis of the rare rs369274325 polymorphism. According to publicly available databases, this variant exhibits extremely low allele frequency in European populations. Although genotyping was performed using a previously published and widely applied ARMS-PCR protocol, the absence of sequencing-based validation represents a methodological limitation. Therefore, the findings related to rs369274325 should be interpreted cautiously and considered exploratory.

Although our study focused on *SIRT1* polymorphisms rather than its expression, the observed associations complement previous findings implicating *SIRT1* deregulation in pancreatic and gastric tumorigenesis. In pancreatic cancer, *SIRT1* overexpression enhances proliferation, invasion and chemoresistance, whereas its silencing induces apoptosis and sensitizes cells to therapy [33-35]. In gastric cancer, *SIRT1* exhibits context-dependent behavior: some studies report oncogenic functions, such as promoting cell survival through suppression of p53-mediated ferroptosis [36], while others describe tumor-suppressive effects linked to downregulation of NF-κB/Cyclin D1 or activation of AMPK/FOXO3 signaling [37,38]. It is therefore plausible that functional promoter variants such as rs3758391 may influence *SIRT1* transcription or activity, thereby contributing to the tissue-specific and context-dependent effects observed across different tumor types.

No significant associations were detected between either *SIRT1* polymorphism and clinicopathological parameters, such as tumor stage, grade, or lymph node involvement in PDAC or gastric cancer. This lack of association probably reflects the limited cohort size and the multifactorial nature of tumor progression. Accordingly, these results should be interpreted with caution, and warrant validation in larger, multicenter and ethnically diverse populations. Additionally, the relatively small sample size, particularly for gastric cancer, limits the statistical power of the study. A *post hoc* power analysis suggested that the study was adequately powered to detect moderate-to-large effect sizes for rs3758391, but may be underpowered to identify weaker associations, especially for rare variants. Larger, multicenter studies are therefore required to confirm these findings.

In conclusion, our study provides new evidence linking the *SIRT1* rs3758391 polymorphism with susceptibility to pancreatic and gastric cancers in a Greek population. The observed protective role of the C allele, along with similar findings from other studies, supports the hypothesis that rs3758391 influences *SIRT1* expression by modulating p53 binding. Larger multicenter studies, as well as functional assays, are required to validate these findings and clarify the mechanistic basis of *SIRT1*-mediated cancer susceptibility. Taken together, our findings suggest that *SIRT1* rs3758391 represents a promising candidate biomarker for susceptibility to pancreatic and gastric cancers; however, validation in larger cohorts using sequencing-confirmed genotyping approaches is required.

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Summary Box

What is already known:

- *SIRT1* is a NAD^+-dependent deacetylase that regulates apoptosis, metabolism, and genomic stability through modulation of p53 and other transcription factors
- Genetic polymorphisms in *SIRT1*, such as rs3758391, have been associated with susceptibility to various malignancies including bladder, breast and lymphoid cancers
- The functional rs3758391 variant, located at the p53-binding site in the *SIRT1* promoter, may alter p53–SIRT1 interactions, thereby affecting tumor suppressor activity
- No previous studies have examined the association of *SIRT1* gene variants with pancreatic ductal adenocarcinoma (PDAC) or gastric cancer

What the new findings are:

- The *SIRT1* rs3758391 TT genotype was significantly overrepresented among PDAC and gastric cancer patients, while the TC genotype and C allele conferred a protective effect
- The rs369274325 polymorphism showed no significant association with either PDAC or gastric cancer in this cohort
- No correlation was found between *SIRT1* genotypes and clinicopathological parameters such as tumor stage or grade
- These findings suggest that *SIRT1* rs3758391 may influence susceptibility to gastrointestinal cancers, potentially through modulation of p53-mediated transcriptional control, and highlight SIRT1 as a promising biomarker candidate for cancer risk assessment

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