

Mitochondria-related TFAM gene variants and their effects on patients with cervical cancer

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Abstract. Cervical cancer is the fourth most common type of cancer in women worldwide, with high incidence and mortality rates, particularly in developing countries. There are human papillomavirus vaccines and cytological screening programs available; however, there are no molecular markers that would aid the prognosis of the course of the disease or prediction of the outcomes of the patients. The aim of the present study was to investigate the associations between single nucleotide polymorphisms (SNPs) of the mitochondrial transcription factor A (*TFAM*) gene (rs11006132, rs11006129, rs1937, rs16912174, rs16912202 and rs3900887), and the clinical parameters and tumor phenotype of patients with cervical cancer. DNA isolated from patients with cervical cancer (n=172) was used for genotyping using Real-Time PCR using TaqMan probes. It was revealed that the *TFAM* rs3900887 TT and AT genotypes were associated with a lower risk of developing larger tumors. The results showed an association between the rs3900887 SNP and tumor phenotype, indicating *TFAM* rs3900887 as a potential biomarker for tumor size in cervical cancer.

Introduction

Cervical cancer is frequently diagnosed in women and, with a 6.5% incidence rate, ranks as the fourth most common type of cancer globally. Furthermore, it also ranks fourth in mortality statistics, with a rate of 7.7% (1). Cervical cancer incidence and mortality rates are higher in developing than in developed countries. The vast majority of the highest cervical cancer rates are observed in countries in sub-Saharan Africa, Melanesia, South America and South-Eastern Asia (1). Previous studies have demonstrated that cervical cancer is a disease caused by multiple interacting factors, and thus, human papillomavirus (HPV) is

a necessary but not sufficient cause of cervical cancer occurrence (2). Infections, such as human immunodeficiency virus, and environmental factors, such as smoking or long-term use of oral contraceptives, are important co-factors (3). Cervical cancer is considered highly preventable, and HPV vaccination and screening programs are widely used for preventative purposes (4,5). Countries that successfully implement these measures have lower cervical cancer rates. For example, in the United States, cervical cancer incidence rates declined 1.9% per year between 2007 and 2012 (6). However, numerous lower-income countries have not fulfilled mass screening programs, and the cervical cancer incidence and mortality rates remain high (7). Therefore, to reduce the gap between developing and developed countries, and help diagnose cervical cancer during the early stages, predict the course of the disease and predict the outcome, more accessible screening options are required.

Mitochondria are essential and complex organelles involved in cellular processes, such as energy generation through oxidative phosphorylation, apoptosis and metabolism. Therefore, mitochondria are considered to serve an essential role in carcinogenesis (8). Mitochondrial transcription factor A (*TFAM*) is a nuclear-encoded protein, which serves an important role in mitochondria, since it is required for the transcription and replication of mitochondrial DNA (9,10). *TFAM* expression has been reported to be altered and associated with breast and lung cancer (11-13), and polymorphisms in the *TFAM* gene have been reported to be associated with prostate (14), colorectal (15), breast (16), uterine, ovary and cervical cancer (17). Numerous studies have investigated the associations between various single nucleotide polymorphisms (SNPs) and the risk of cervical cancer; however, there are not enough studies analyzing mitochondria-related SNPs and the associations with the clinical/pathological characteristics of the patients or the morphological characteristics of their tumors (18). In the present study, genotyping analysis was used to investigate *TFAM* SNP distribution in a cervical cancer cohort, and to explore their potential as biomarkers for the tumor phenotype or outcomes of patients.

Materials and methods

Study subjects. The study population consisted of 172 female patients who were diagnosed with cervical cancer. All patients were Lithuanians with a median age of 56 years (age range, 22-83 years). Patients were included in the present study if they

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matched all of the following criteria: Cervical cancer was diagnosed as a primary disease, the patient signed a consent form, a blood sample was taken at the time of the diagnosis and clinical information was available. In our previous study, the same patient group was analyzed focusing on the polymorphisms of a different gene (DNA polymerase γ , catalytic subunit) and their associations with cervical cancer (18). The research was conducted at the Institute of Oncology, Lithuanian University of Health Sciences (Kaunas, Lithuania) between 2015 January and 2021 May. The present study was performed in accordance to the guidelines of the Declaration of Helsinki (19) and was approved by the Kaunas Regional Biomedical Research Ethics Committee (approval nos. BE-2-10 and P1-BE-2-10/2014; Kaunas, Lithuania). Clinical data were gathered retrospectively from medical records.

Tumor grading. At present no particular grading system has achieved universal acceptance, and grading of cervical carcinomas remains of uncertain clinical value. In the present study histopathological grading (G) was based on the degree of cell and tissue atypia and mitotic activity. The definitions of the G categories apply to all carcinomas, these are: GX, grade of differentiation cannot be assessed; G1, well differentiated; G2, moderately differentiated; and G3, poorly differentiated or undifferentiated (20).

Genotyping. DNA was isolated from EDTA-preserved peripheral blood using a GeneJet Genomic DNA purification kit (cat. no. K0721; Thermo Fisher Scientific, Inc.). SNPs (rs11006132, rs11006129, rs1937, rs16912174, rs16912202 and rs3900887) in the *TFAM* gene were determined using TaqMan probe SNP Genotyping assays (cat. no. 4351379; Thermo Fisher Scientific, Inc.) and a QuantStudio 3 Real-Time PCR system (cat. no. A28137; Thermo Fisher Scientific, Inc.). The reaction mixture contained 15 ng purified DNA sample, 6.125 μ l TaqMan Universal MasterMix (cat. no. 4304437; Thermo Fisher Scientific, Inc.), 0.625 μ l TaqMan SNP Genotyping assay and nuclease-free water to reach a total volume of 12 μ l. Nuclease-free water was used as a no-template control for every plate. The standard genotyping PCR program: Pre-read step at 60°C for 30 sec, 95°C for 10 min; followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min; with a final post-read step at 60°C for 30 sec, was used to determine the genotype, and this relied on VIC and FAM fluorescence intensity.

Statistical analysis. Associations between all *TFAM* polymorphisms included in the present study (rs11006132, rs11006129, rs1937, rs16912174, rs16912202 and rs3900887) and clinical data, pathological tumor size (T), tumor differentiation grade (G), lymph node status (N), distant metastasis (M), histological tumor type, progression and death, were analyzed. Additionally, patients were divided into two groups according to median age at diagnosis (<56 and \geq 56 years old) and pathological tumor size [small tumors (T1 + T2; n=110) and larger tumors (T3 + T4; n=62)]. Furthermore, patients were divided into groups based on tumor differentiation grade; the first group included patients with well-differentiated and moderately differentiated tumors (G1 + G2), and the second group included patients with poorly differentiated tumors (G3).

SPSS version 22 software (IBM Corp.) was used for association analysis. Associations between genotype and clinical data were evaluated using a Pearson's χ^2 test (rs11006132,

Table I. Demographic and clinicopathological characteristics of the patients.

| Characteristics | Frequency, n (%) |
|-----------------------|------------------|
| Stage | |
| I | 16 (9.3) |
| II | 60 (34.9) |
| III | 83 (48.3) |
| IV | 13 (7.6) |
| Tumor size | |
| T1 | 26 (15.1) |
| T2 | 84 (48.8) |
| T3 | 55 (32) |
| T4 | 7 (4.1) |
| Lymph node status | |
| Negative | 95 (55.2) |
| Positive | 77 (44.8) |
| Distant metastasis | |
| Absent | 162 (94.2) |
| Present | 10 (5.8) |
| Differentiation grade | |
| G1 | 13 (7.6) |
| G2 | 113 (65.7) |
| G3 | 44 (25.6) |
| Missing ^a | 2 (1.2) |
| Survival status | |
| Alive | 132 (76.7) |
| Deceased | 40 (23.3) |
| Fact of progression | |
| Absent | 123 (71.5) |
| Present | 49 (28.5) |

^a2 data points missing due to lack of patients' clinical information.

rs11006129, rs1937 and rs3900887) or Fisher's Exact (rs16912174 and rs16912202) tests and binary logistic regression. Univariate logistic regression analysis adjusted for age at diagnosis (Model A) and multivariate logistic regression analysis with additional confounding factor N (Model B), were used. Survival analysis was performed using Kaplan-Meier analysis and the difference between survival curves was analyzed using a log-rank test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Distribution of clinical characteristics. The present study included 172 patients with cervical cancer with a median age of 56 years (age range, 22-83 years). The majority of the patients had squamous cell carcinoma (n=157), whereas adenocarcinoma (n=9) or mucinous adenocarcinoma (n=6) were less frequent. The tumor differentiation grade was mostly G2 (n=113). The majority of the patients did not have distant metastasis (n=162) or affected regional lymph nodes (n=95). Additional information on the clinical characteristics are provided in Table I.

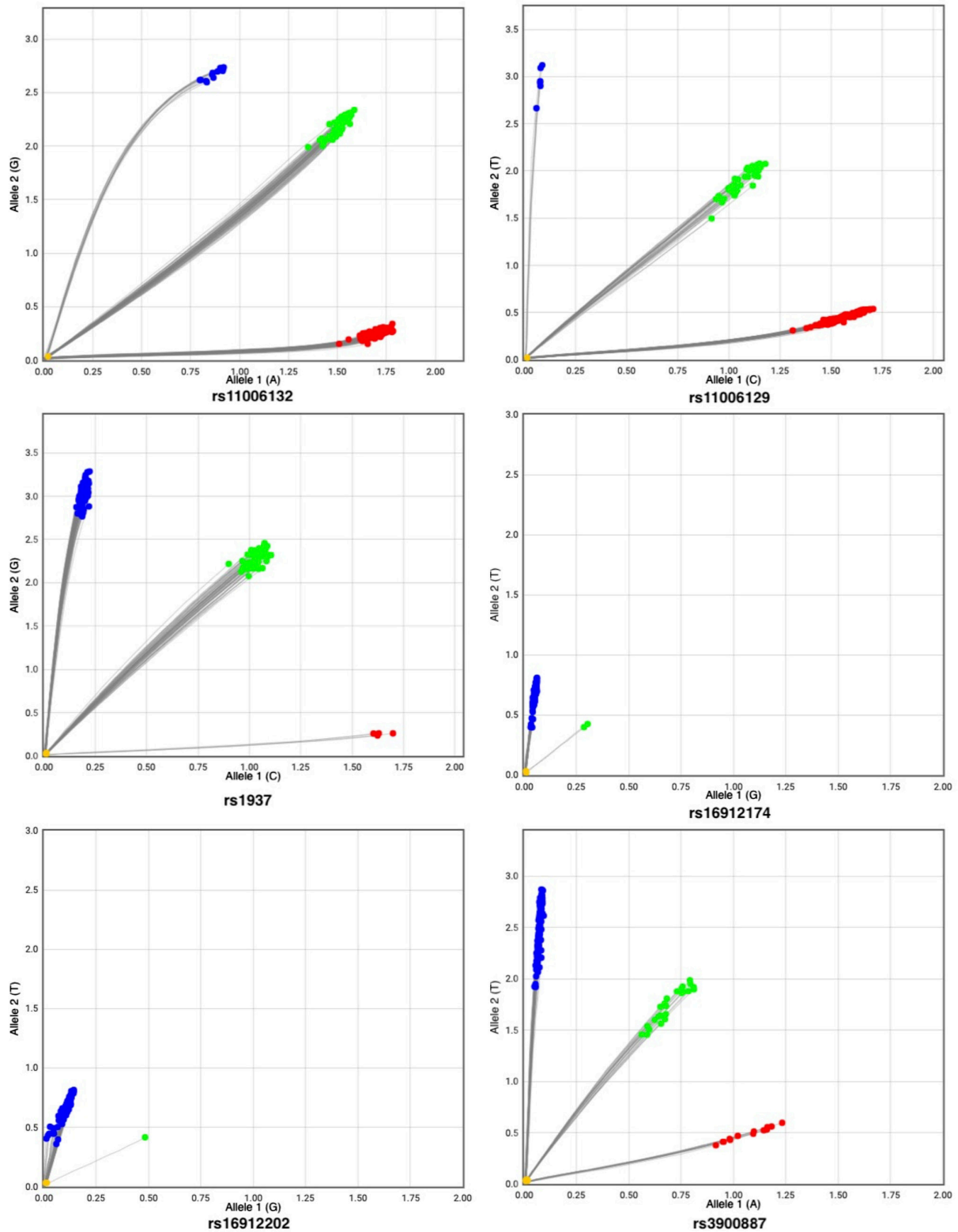


Figure 1. Distribution of *TFAM* genotypes. Allelic discrimination plots representing the *TFAM* rs11006132, rs11006129, rs1937, rs16912174, rs16912202, rs3900887 genotypes in the cervical cancer cohort. The x-axis represents Allele 1 labeled with VIC dye, and the y-axis represents Allele 2 labeled with FAM dye. The colored dots represent different genotypes called according to VIC and FAM fluorescence intensities. Red dots represents the homozygous Allele 1 genotype, blue dots represents the homozygous Allele 2 genotype, and the green dots represents the heterozygous genotype. The no-template control is marked as a yellow dot at the bottom left corner of the plot. *TFAM*, *TFAM*, mitochondrial transcription factor A.

Distribution of genotypes. The distributions of all genotypes in the present cohort were estimated using the Hardy-Weinberg equilibrium (HWE), and it was revealed that rs11006132, rs11006129, rs1937, rs16912174 and rs16912202 SNPs were

in HWE, whereas rs3900887 was not. There were 13 missing data points from rs3900887 genotyping due to amplification failure. The distribution of *TFAM* genotypes is shown in Fig. 1 and Table II.

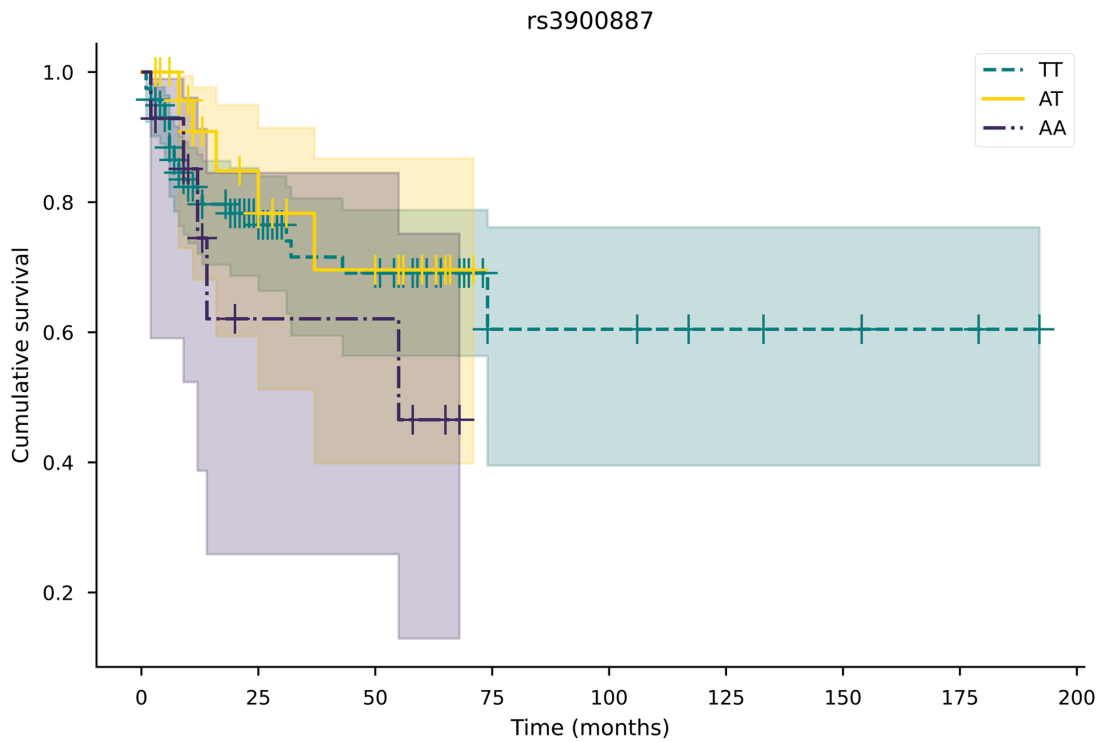


Figure 2. Overall survival of the patients with cervical cancer with different *TFAM* rs3900887 genotypes. Kaplan-Meier survival curves for overall survival comparing different *TFAM* rs3900887 genotypes: TT vs. AT ($P=0.548$), TT vs. AA ($P=0.357$) and AT vs. AA ($P=0.195$) in the cervical cancer cohort. The x-axis represents the overall survival of the patients in months, and the y-axis represents cumulative survival. Vertical lines indicate censored cases. The different colors represent different genotypes; the shadow of the same color represents the respective 95% confidence interval.

Table II. Genotype and allele frequencies of the analyzed *TFAM* polymorphisms in the study population.

| <i>TFAM</i> | Patient count | Genotype, frequency | Allele, frequency |
|-------------|---------------|---------------------|-------------------|
| rs11006132 | 90 | AA, 0.52 | A, 0.72 |
| | 68 | AG, 0.4 | G, 0.28 |
| | 14 | GG, 0.08 | |
| rs11006129 | 130 | CC, 0.76 | C, 0.86 |
| | 36 | CT, 0.21 | T, 0.14 |
| | 6 | TT, 0.03 | |
| rs1937 | 115 | GG, 0.67 | G, 0.82 |
| | 53 | CG, 0.31 | C, 0.18 |
| | 4 | CC, 0.02 | |
| rs16912174 | 170 | TT, 0.99 | T, 0.99 |
| | 2 | GT, 0.01 | G, 0.01 |
| rs16912202 | 171 | TT, 0.99 | T, 1.00 |
| | 1 | GT, 0.01 | G, 0.00 |
| rs3900887 | 118 | TT, 0.74 | T, 0.83 |
| | 27 | AT, 0.17 | A, 0.17 |
| | 14 | AA, 0.09 | |

TFAM, mitochondrial transcription factor A.

Association analysis. Associations between *TFAM* polymorphisms and clinical data were evaluated using Pearson's χ^2 or Fisher's exact tests and are presented in Table III.

The present study revealed that rs3900887 was associated with grouped tumor size T1 + T2 vs. T3 + T4 ($P=0.006$). However, no associations with age group ($P=0.905$), lymph node status ($P=0.468$), distant metastasis ($P=0.166$), differentiation grade ($P=0.898$), adenocarcinoma ($P=0.376$), squamous cell carcinoma ($P=0.480$), stage ($P=0.065$), progression ($P=0.258$) or death ($P=0.457$) were observed. To further evaluate the associations amongst rs3900887 and clinical data, logistic regression analysis was performed. It was revealed that rs3900887 remained significantly associated with grouped tumor size in logistic regression analysis of genotype and allele models. Patients with the rs3900887 TT [odds ratio (OR)=0.328; 95% CI, 0.127-0.849; $P=0.022$] or AT (OR=0.091; 95% CI, 0.023-0.367; $P=0.001$) genotypes were less likely to have larger tumors than those with the AA genotype. Univariate and multivariate logistic regression analyses are presented in Table IV.

No statistically significant associations of rs11006132, rs11006129, rs1937, rs16912174 and rs16912202 with clinical data were observed.

Survival analysis. Kaplan-Meier survival analysis was used to determine the association between rs3900887 and overall survival; however, it was not statistically significant: TT vs. AT ($P=0.548$), TT vs. AA ($P=0.357$), AT vs. AA ($P=0.195$). The Kaplan-Meier survival plot is shown in Fig. 2.

Discussion

Despite extensive prevention and vaccination programs, cervical cancer remains the fourth most common cancer in

Table III. Associations between mitochondrial transcription factor A polymorphisms and clinical data.

| Variable | rs11006132 | rs11006129 | rs1937 | rs16912174 | rs16912202 | rs3900887 |
|--|------------|------------|--------|------------|------------|-----------|
| T (T1 + T2 vs. T3 + T4) | 0.789 | 0.105 | 0.309 | 0.408 | 0.640 | 0.006 |
| N (negative vs. positive) | 0.979 | 0.893 | 0.954 | 0.696 | 0.448 | 0.468 |
| M (negative vs. positive) | 0.427 | 0.382 | 0.211 | 0.887 | 0.058 | 0.166 |
| Differentiation grade (G1 + G2 vs. G3) | 0.417 | 0.910 | 0.439 | 0.452 | 0.741 | 0.898 |
| Stage (I + II vs. III + IV) | 0.775 | 0.225 | 0.966 | 0.690 | 0.558 | 0.065 |
| Survival status (alive vs. deceased) | 0.565 | 0.833 | 0.661 | 0.588 | 0.767 | 0.457 |
| Fact of progression | 0.310 | 0.209 | 0.986 | 0.510 | 0.715 | 0.258 |
| Age group (<56 vs. ≥56) | 0.249 | 0.546 | 0.605 | 0.254 | 0.494 | 0.905 |
| Adenocarcinoma | 0.472 | 0.150 | 0.734 | 0.898 | 0.948 | 0.376 |
| Squamous cell carcinoma | 0.328 | 0.615 | 0.812 | 0.833 | 0.913 | 0.480 |

T, pathological tumor size; N, lymph node status; M, distant metastasis.

Table IV. Univariate and multivariate logistic regression analysis of the associations of mitochondrial transcription factor A rs3900887 genotypes, alleles and clinical data with potential confounding factors.

| Single nucleotide polymorphism | Parameter | Covariates | Model A | | | Model B | | |
|--------------------------------|----------------------------------|---|------------|-------------------------|--------------------|------------|-------------------------|----------------------|
| | | | Odds ratio | 95% confidence interval | P-value | Odds ratio | 95% confidence interval | P-value |
| rs3900887 | Tumor size (T1 + T2 vs. T3 + T4) | TT vs. AA | 0.328 | 0.127-0.849 | 0.022 ^a | 0.350 | 0.097-1.261 | 0.108 |
| | | AT vs. AA | 0.091 | 0.023-0.367 | 0.001 ^b | 0.093 | 0.018-0.490 | 0.005 ^b |
| | | Age | 1.011 | 0.996-1.028 | 0.156 | 1.038 | 1.008-1.070 | 0.013 ^a |
| | | Lymph node status (negative vs. positive) | - | - | - | 7.242 | 3.199-16.395 | <0.0001 ^c |
| rs3900887 T allele | Tumor size (T1 + T2 vs. T3 + T4) | Carrier vs. non-carrier | 0.277 | 0.109-0.709 | 0.007 ^b | 0.286 | 0.080-1.020 | 0.054 |
| | | Age | 1.011 | 0.995-1.027 | 0.168 | 1.037 | 1.007-1.068 | 0.014 ^a |
| | | Lymph node status (negative vs. positive) | - | - | - | 7.105 | 3.195-15.799 | <0.0001 ^c |

^aP<0.05, ^bP<0.01, ^cP<0.001.

women globally and has the fourth highest mortality rate amongst all types of cancer (1). In more developed countries with better established screening and vaccination programs, the incidence rates of cervical cancer have been declining each year (6); however, it is considerably more common in developing countries (1).

Mitochondria are organelles responsible for energy generation, apoptosis and metabolism, and serve an essential role in cancer development (8). The *TFAM* gene encodes mitochondrial transcription factor, a protein encoded in nuclear DNA that is responsible for the transcription and translation of mitochondrial DNA (9,10). Research has revealed that SNPs in the *TFAM* gene are associated with various types of cancer (14-16), including cervical cancer (17). Numerous studies have assessed the association between the risk of developing cervical cancer and SNPs; however, few studies have investigated the possible

associations between SNPs and clinical and morphological cervical tumor characteristics. In the present study, the associations of the rs11006132, rs11006129, rs1937, rs16912174, rs16912202 and rs3900887 polymorphisms in the *TFAM* gene with cervical tumor clinical and morphological characteristics, including tumor histological type, stage, size, differentiation grade, regional lymph node involvement, distant metastases, progression and survival status, were analyzed.

It was revealed that the *TFAM* rs3900887 polymorphism was associated with tumor characteristics. Logistic regression analysis indicated that patients with TT and TA genotypes had a lower risk of possessing larger tumors than patients with the AA genotype. rs3900887 is located in an intron of the *TFAM* gene and it may affect splicing. However, it is also reported to be benign by VarSome (21) and Franklin (22) databases. The imum allele frequency (MAF) of this gene in

the 1,000 Genome project was 0.11, and a similar MAF (0.17) was calculated in the present study. Our previous study identified several associations between this polymorphism and morphological characteristics of breast cancer. It was revealed that TT and TA genotypes were associated with an increased risk of positive lymph nodes, and TT genotype carriers also had an increased risk of positive estrogen receptors (ER) and lymphatic invasion compared with patients with the AA genotype (16). Additionally, there has been only one study investigating associations between this polymorphism and late-onset Alzheimer's disease, in which no significant associations were observed (23). Our recent study revealed significant associations between this SNP and tumor size, which remained significant after multivariate analysis. The results may indicate the role of the rs3900887 SNP in cervical tumor development, and thus, more in-depth studies are required to confirm its role in cervical tumor development.

Other SNPs in the present study (rs11006132, rs11006129, rs1937, rs16912174 and rs16912202) exhibited no significant associations with cervical tumor morphological parameters. The rs11006132 SNP is located in the 3' untranslated region of the gene. Our previous study indicated no associations between this SNP and morphological characteristics of breast cancer (16). There was also no observed association with aggressive prostate cancer (14). However, researchers have found a link between this SNP and the age at onset of Huntington's disease (24). rs11006129 is located in an intron of the gene. Our previous study demonstrated an association between this SNP and breast cancer. It was revealed that T allele carriers were less likely to be predisposed to ER-positive tumors and carriers of the C allele were less likely to develop tumors with vascular invasion than non-carriers of the respective allele (16). To the best of our knowledge, no other studies have investigated this SNP to date. rs1937 is a missense variant of the *TFAM* gene. Our previous study found no significant associations between this SNP and breast tumor parameters (16). Other studies have investigated the association between the rs1937 and early-onset myocardial infarction (25), late-onset Alzheimer's disease (26) and aggressive prostate cancer (14); however, no significant results were determined. One study has reported a link between the rs1937 polymorphism and cervical cancer development in women (27). The rs16912174 SNP is located in the 5' untranslated region of the gene. Our previous study revealed no significant association between this polymorphism and breast cancer (16). The rs16912202 polymorphism is located in the 3' untranslated region of the gene (c.*3236T>G) and, therefore, it may interfere with mRNA stability or translation. Our previous study did not find any significant associations between this SNP and morphological characteristics of breast cancer (16). To the best of our knowledge, no other studies have been performed for this SNP in cervical cancer to date.

Despite the limitations of the present study, including the small sample size and small number of SNPs, it was possible to detect significant association, suggesting that the *TFAM* gene may serve a role in cervical cancer development. In this study the individual SNPs were analyzed as a pilot study to understand the impact of *TFAM* SNPs on cervical cancer. In future studies, larger cohorts will be employed to investigate the mitochondria-related SNPs in other genes, examining grouped SNPs and haplotypes, and their impact on cervical

cancer. Additional studies should be performed on broader and more ethnically diverse cohorts of patients with cervical cancer to verify these results.

In conclusion, the results of the present study suggest that mitochondrial transcription factor A, encoded by the nuclear *TFAM* gene, is important in cervical cancer, and the rs3900887 SNP may serve as a potential biomarker of tumor size.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

IG, RU and EJ conceived the study. IG and JC developed the methodology. IG and JC performed the formal analysis. JC performed the experiments. RU, EZ, AI, LP and EJ curated the data. IG, RU and JC prepared the original draft of the manuscript. EZ, AI, LP and EJ reviewed and edited the manuscript. IG prepared the tables. RU and EJ supervised the study. All authors have read and approved the final manuscript. JC and IG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was performed in accordance with the guidelines of the Declaration of Helsinki and approved by the Kaunas Regional Biomedical Research Ethics Committee (approval nos. BE-2-10 and P1-BE-2-10/2014). Informed written consent was obtained from all subjects involved in the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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