The presence of A5935G, G5949A, G6081A, G6267A, T9540C mutations in *MT-CO1* and *MT-CO3* genes and other variants of *MT-CO1* and *MT-CO3* gene fragments in the study population diagnosed with endometrial cancer

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ABSTRACT

Objectives: The specific purpose of this study was the assessment of A5935G, G5949A, G6081A, G6267A mutations in *MT-CO1* and T9540C in *MT-CO3*, and alterations detected during the analysis of *MT-CO* gene fragments in subject and control groups. A secondary aim was to assess the relationship between *MT-CO1* and *MT-CO3* gene alterations and endometrial cancer incidence and evaluation of the prognostic value of *MT-CO1* and *MT-CO3* gene alterations.

Material and methods: In this study, we investigated A5935G, G5949A, G6081A, G6267A mutations in *MT-CO1* and T9540C in *MT-CO3*, and alterations detected during the analysis of *MT-CO* gene fragments in formalin-fixed, paraffin-embedded endometrial and benign endometrial hyperplasia of a cohort of 125 subjects.

Results: The T9540C mutation in *MT-CO3* was detected in one patient from the subject group. None of the remaining mutations were detected. The research showed that the presence of alterations in *MT-CO1* and *MT-CO3* typical of other types of cancer is not a risk factor for endometrial cancer.

Analysis of *MT-CO1* and *MT-CO3* gene fragments revealed 10 alterations (6 and 4 respectively). The alterations detected were identified in 10% of the tested group and 8% of the control group.

Conclusions: The research showed that the presence of alterations in *MT-CO1* (A5935G, G5949A, G6081A, G6267A) typical of other types of cancer is not a risk factor for endometrial cancer. Three new alterations detected in this study (A6052G, A9545G, G9575A) were described for the first time.

Key words: mtDNA mutations, alterations in *MT-CO1*, alterations in *MT-CO3*, endometrial cancer

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INTRODUCTION

In recent years, there has been a rise in the number of reported mtDNA mutations predisposing to neoplasm growth. There are few studies concerning *MT-CO* genes mutations on endometrial cancer development. Thus, the present study is an attempt to complete the knowledge concerning the meaning of mtDNA disorders in endometrial cancer development.

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We would like to focus on A5935G, G5949A, G6081A, G6267A mutations in *MT-CO1* and T9540C in *MT-CO3* presence and other variants of *MT-CO1* and *MT-CO3* gene fragments in the study population. The mutations selected for this research occur in prostate, breast, pancreatic cancer, colorectal cancer as well as ulcerative colitis [1, 2].

Alterations of *MT-CO* can lead to dysfunction of mitochondrial respiratory chain complex IV, which leads to changes in cellular metabolism, resulting in modifications to the cell's susceptibility to cancerous transformation [3–5].

A5935G, G5949A, G6081A, G6267A are nonsynonymous mutations which stem from transition (A-G or G-A) and change the amino acid in protein product of *MT-CO1*.

The A5935G mutation exchanges asparagine for serine at position 11 in cytochrome c oxidase's first subunit, resulting in protein function impairment. Substitution of an asparagine radical for a serine radical prevents the formation of multiple hydric bonds, which may disrupt protein tertiary structure. In addition, the alteration can destabilize transmembrane protein (conduit D) structure, which serves as a pathway for proton transfer in oxygen reduction [1, 6, 7].

Another G5949A mutation, detected in prostate cancer, triggers premature formation of STOP codon in *MT-CO1*, which results in a shorter polypeptide length of 15 amino acids, instead of 513 amino acids. The shorter polypeptide product is highly unstable and quickly breaks down. In effect, this mutation decreases COX1 and COX2 levels. The unstable protein structure and its decreased concentration impairs the assembly process of oxidative phosphorylation IV subunit [1, 7, 8].

The G6081A mutation introduces alanine radical instead of threonine into the 60th position on cytochrome c oxidase. In most Eukaryotes, 60th position of polypeptide contains amino acids with a small molecular weight such as alanine or glycine. A replacement of alanine with threonine with its branched lateral chain in the 60th position and close proximity to heme group iron stabilizer histidine can disrupt protein helix structure. Polypeptide secondary structure dysfunction can affect electron transfer via α heme [7, 9, 10].

The 6267G>A change prompts the replacement of alanine radical with threonine at 122th locus of the polypeptide. Similarly to A5935G and G6081A mutations, alanine radical in this locus is highly evolutionarily preserved. According to the authors, cells with G6267A mutation have restricted growth on culture medium without glucose. It can suggest respiratory chain failure due to this mutation [2, 7].

The T9540C mutation is a T=>C transition, characteristic of oxidative stress damage [11]. This mutation causes a change in mRNA codon from UUA to CUA, which does not, however, lead to a change of amino acids in the protein chain. It is therefore a silent mutation [12].

MATERIAL AND METHODS

Material for the trial included:
— formalin-fixed, *paraffin*-embedded (FFPE) endometrial cancer (*adenocarcinoma endometrioides*) samples collected during abdominal hysterectomy and stored at Clinical Pathomorphology Department in "Polish Mother's Memorial Hospital" Research Institute in Lodz. Tested samples were taken from 100 European women operated on for endometrial cancer of varying stages according to the FIGO cancer staging system and malignancy grading in the Department of Gynecology ICZMP in Lodz from 2007 to 2014 (subject group);
— formalin-fixed, *paraffin*-embedded (FFPE) histopathological specimens of benign endometrial hyperplasia stored at Clinical Pathomorphology Department. The samples were collected from 25 patients diagnosed with abnormal vaginal bleeding who underwent dilation and curettage (D & C) at the Department of Gynecology from 2011 to 2012 (control group).

Ethical aspect

The study was approved by the local ethic committee of „Polish Mother's Memorial Hospital" Research Institute (ethical agreement 3/2011).

DNA isolation

Genomic and mitochondrial DNA were extracted from formalin-fixed, *paraffin*-embedded (FFPE) endometrial cancer and benign endometrial hyperplasia samples by using the *QIAamp DNA FFPE Tissue Kit* (Qiagen, Germany) in accordance with the manufacturer's protocol (purified DNA is free of proteins, nucleases, and other impurities).

The concentration (A260) and purity (A260/A280 ratio) of isolated DNA were determined by using a PicoDrop — spectrophotometer (Picodrop Limited, United Kingdom). The extracted pure DNA was used in amplification reactions or stored at −20°C.

Polymerase chain reaction amplification

The purified DNA was used as a template for PCR amplification. The reaction mixture in 20 μL volume contained 50 ng of DNA, 1UTaq DNA polymerase (Promega, USA), 1.5 mM $MgCl_2$, 0.25 mM each of dATP, dCTP, dGTP, and dTTP, and 0.5μM of the primers.

Amplification was performed with a thermal cycler, Gene-Amp PCR System 9700 (Applied Biosystems, USA).

The following *COX1* and *COX3* — specific sets of primers were used:

COX1
For: *5´-GAAAATCACCTCGGAGCTGG-3´*
Rev: 5´-GATGGTTAGGTCTACGGAGG-3

COX3

For: 5´-GGCCTTCGATACGGGATAAT-3´
Rev: 5´-ATGGTGAGCTCAGGTGATTG-3´

Thermal cycling conditions for PCR reactions included an initial denaturation step at 95°C for 5 minutes followed by 30 cycles of a denaturation step at 95°C for 30 seconds, a primer annealing step at 60°C for 30 seconds, an extension step at 72°C for 30 seconds, and a final step at 72°C for 7 minutes.

Microchip electrophoresis of DNA fragments

The PCR amplification products were separated and analyzed on the automated microchip electrophoresis system MCE-202 MultiNa (Shimadzu, Japan) using the DNA-1000 kit according to the manufacturer's protocol. A SYBR Gold fluorescent dye for DNA staining (Invitrogen, USA) and PhiX174 DNA/Hae III Markers (Promega, USA) were used to determine the size of the PCR products.

Sequencing

Amplification products were purified using MiniElute PCR Purification Kit (Qiagen, Germany). The sequencing reactions were run using a Big Dye® Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, USA) on the GeneAmp PCR System 9700 using standard sequencing protocols. Sequence analysis was performed by using the same primers as previously used in preamplification step.

The PCR products were purified to eliminate unincorporated primers and dNTPs using BigDye XTerminator Purification Kit and then subjected to separation by the 3130xl GeneGenetic Analyzer (Applied Biosystems).

The DNA sequences were analyzed using DNA Baser Sequence Assembler.

Statistical analysis

STATISTICA 10.0 (StatSoft, Inc., USA) and Excel MS Office 2013 (Microsoft Corporation, USA) software was used in the course of the research to process and analyze the data.

RESULTS

The T9540C mutation in *MT-CO3* was detected in one patient from the subject group.

None of the remaining mutations (A5935G, G5949A, G6081A, G6267A into *MT-CO1*) were detected in either patient group.

Analysis of *MT-CO1* and *MT-CO3* gene fragments revealed 8 alterations (5 and 3 respectively). The alterations detected in 9% of the study group and 8% of the control group. The most common alterations included: A6047G with an incidence of 2/100 (2%) in the study group and 1/25 (4%) in the control group and T5999C with an incidence

Table 1. Detected variants of *MT-CO1* and *MT-CO3* in the study and control group

Cigarette smoking	0	1	3	0	0	0	0	0	0	0	0
Concomitant diseases	HA	Nephrolithiasis, depression	HA, stroke	Diabetes mellitus, HA	Absence	HA, stroke	HA	HA, hyperthyroidism	HA	HA	HA
Number of deliveries	3	2	3	4	1	1	1	0	1	2	1
Last menstrual period (age)	54	54	50	48	46	54	51	58	52	51	51
First menstrual period (age)	n/a	n/a	11	14	n/a	14	14	n/a	n/a	n/a	13
BMI [kg/m²]	34.9	27.1	30.3	21.8	21.6	29.7	28.5	40.6	40.1	30.9	31.7
Adjuvant therapy	0	0	1	0	1	0	0	1	1	n/r	n/r
FIGO	IA	IA	IB	IVA	IB	IA	II	IA	II	n/r	n/r
Grading	G2	G1	n/a	G2	G1	G1	G1	G1	G2	n/r	n/r
Age at the time of diagnosis/curettage	58	61	75	75	46	54	57	69	63	51	51
Gene name	MT-CO3	MT-CO3	MT-CO1	MT-CO1	MT-CO1	MT-CO1	MT-CO3	MT-CO3	MT-CO1	MT-CO1	MT-CO1
Nucleotide position number	G9477A,	G9477A	T6152C	A6047G, T5999C	T6152C	G5913A	G9575A	T9540C, A9545G	T5999C, A6047G	A6047G, T5999C	A6052G

of 2/100 (2%) in the study group and 1/25 (4%). T6152C, G9477A mutations were also detected in the study group, each with an incidence of 2/100 (2%).

The remaining variants G5913A, G9575A, A9545G occurred in 1% (1/100) of the study group while A6052G was found in 4% (1/25) of the control group.

As the above data demonstrates, only 2 *MT-CO* gene variants were detected in both the study and control group. Given their low incidence testing for these mutations seems to be unwarranted.

In the study group *MT-CO1* and *MT-CO3* gene variants were detected, whereas in the control group only alterations in *MT-CO1* were observed.

Table 1 shows a summary of *MT-CO1* and *MT-CO3* genes mutations including medical history data from patients in the study and control groups.

Due to the rarity of the aforesaid alterations statistical analysis could not be performed as it would be unreliable.

Among the detected mutations are those observed in prostate cancer, pancreatic cancer, glioblastoma multiforme, hydatidiform mole, ovarian and thyroid cancers, head and neck cancers (Table 2). The remaining 3 alterations were described for the first time in this study (Table 3).

Three of the detected variants are transitions (A-G or G-A) leading to amino acid change in the protein product of *MT-CO1* and *MT-CO3*. The effect of the amino acid change on polypeptide structure and function was analyzed based on UniProt database [19].

The G5913A mutation substitutes asparagine radical for aspartate into the 4th locus of COX1 subunit. Amino acids presented in the 4th locus are different for Eukaryote species. As the data in the chart implies, the sequence containing the mutation is not evolutionarily preserved. Therefore it seems safe to assume that the amino acid change does not affect polypeptide properties.

The A6052G mutation, which causes substitution of asparagine with serine in the 50th locus of cytochrome c oxidase's first subunit, is highly evolutionarily modified. Poor evolutionary variability of a given sequence may suggest that amino acid substitution does not alter protein structure or function.

Also the G9477A mutation causing the substitution of valine with isoleucine at locus 91 does not change the phenotype. One of the human variants of polypeptide first subunit of cytochrome c oxidase is the occurence of isoleucine at locus 91. Isoleucine located at locus 91 occurs in 17.5% of the European and 6.7% of the African population [19]. The remaining *MT-CO1* and *MT-CO3* gene variants detected in this study do not cause any amino acid change.

Table 2. Detected variants in *MT-CO1* and *MT-CO3* in study population observed in other neoplasms

References	[13, 14]	[15]	[13, 14]	[1, 16]	[17, 18]
Type of cancer	Glioblastoma multiforme, pancreatic cancer	Head and neck squamous cell carcinoma	Glioblastoma multiforme, pancreatic cancer	Prostate cancer, hydatidiform mole	Thyroid and ovarian cancers
Amino acid change	Leu 48 Leu	Val 83 Val	Ala 32 Ala	Asp 4 Asn	Val 91 Ile
Altered codon sense mtDNA strand	CTG	GTC	GCC	AAC	ATT
Codon sense mtDNA strand	CTA	GTT	GCT	GAC	GTT
Gene name	*MT-CO1*	*MT-CO1*	*MT-CO1*	*MT-CO1*	*MT-CO3*
Substitution	A-G	T-C	T-C	G-A	G-A
Nucleotide position number	6047	6152	5999	5913	9477

A — adenine, C — cytosine, G — guanine, T — thymine, Leu — leucine, Val — valine, Ala — alanine, Asp — asparagine, Asn — aspartate, Ile — isoleucine

Table 3. Variants of *MT-CO1* and *MT-CO3* identified in the study population but absent from the available literature

Nucleotide position number	Substitution	Gene name	Codon sense mtDNA strand	Modified codon sense mtDNA strand	Amino acid change
6052	A-G	*MT-CO1*	AAC	AGC	Asn 50 Ser
9545	A-G	*MT-CO3*	GGA	GGG	Gly 113 Gly
9575	G-A	*MT-CO3*	CCG	CCA	Pro 123 Pro

Leu — leucine, Asn — aspartate, Gly — glycine, Pro — prolin

DISCUSSION

In recent years, there has been a rise in the number of reported congenital and somatic mutations as well as mtDNA polymorphisms predisposing to neoplasm growth. Among the mutations tested in the subject population the T9540C mutation in *MT-CO3* was detected in one of the patients diagnosed with endometrial cancer. Due to the mutation's sporadic occurrence, 1/100 patients, the case is statistically irrelevant and does not qualify for further statistical analysis.

The T9540C reported in breast cancer is a germline mutation, i.e. one present in both cancerous and healthy cells of the same individual. Germline mutations are transmitted from one generation to the next [20]. Likewise, in case of ovarian cancer, investigators determined the T9540C variant to be a germline mutation based on tumor and healthy cell samples taken from sons of mothers diagnosed with ovarian cancer [21]. The T9540C mutation also occurs in ulcerative colitis, chronic inflammatory disease predisposing to colorectal cancer [22].

Analysis of *MT-CO1* and *MT-CO3* gene fragments for other changes revealed: variants in *MT-CO1* (A6047G, T6152C, T5999C, G5913A, A6052G) and in *MT-CO3* (G9477A, A9545G, G9575A).

Among the detected mutations are those observed in other neoplasms: prostate cancer and hydatidiform mole (G5913A) [1, 16], pancreatic tumor and glioblastoma multiforme (A6047G, T5999C) [13, 14], ovarian and thyroid cancers (G9477A) [17, 18], head and neck squamous cell carcinoma (T6152C) [15]. The remaining 3 alterations (A6052G, A9545G, G9575A) were described in this study for the first time.

The G5913A mutation desribed by Petros at al. [1] is a transition (G>A) which causes substitution of aspartate with asparagine at 4th locus of COX1 product. The locus where amino acid substitution occurred is highly evolutionarily modified. It is therefore improbable that the changed amino acid affects the polypeptide's phenotype [1, 7]. The same mutation occurs in hydatidiform mole, a disease which predisposes to choriocarcinoma [16].

Researchers have suggested a relationship between A6047G and T5999C mutations occuring in glioblastoma multiforme and oxidative stress in cancerous cells. They suspect there is a correlation between the transition and both respiratory chain failure and an increased concentration of reactive oxygen species [13, 23–26]. Investigators of mtDNA variants in pancreatic cancer have inferred a similar conclusion [14].

In the course of study on somatic mutations in human thyroid cancer, where 68 patients were enrolled, *MT-CO1* and *MT-CO3* gene mutations were detected in 9 patients. The G9477A mutation occured in tumoral and adjacent healthy tissue samples from 3 patients. Scientists demonstrated a prevalence of variants of genes encoding complex IV in malignant tumors compared with benign neoplasms [17]. The G9477A mutation, also described in ovarian cancer, increases the risk of its incidence by 1.27 times [18]. Another T6152C mutation was first described in head and neck squamous cell carcinomas. Researchers focused mainly on the analysis of D-loop vatiants, but did not imply any statistically significant relationship between detected alterations and head and neck cancers as the tested variants were too rare [15].

The variants of *MT-CO1* and *MT-CO3* described in this study for the first time are also transitions. One of them, namely A6052G, introduces serine instead of asparagine into the 50th locus of COX1 subunit. The sequence where the amino acid change occurred is not evolutionarily preserved. Given the low evolutionary diversity of the studied sequence it seems safe to assume that amino acid substitution does not affect polypeptide structure or function [19]. The two remaining variants detected in this study do not trigger any amino acid change in the protein product.

Due to the limited reports on *MT-CO1* and *MT-CO3* gene mutations in endometrial cancer, selected mutations and variants detected in endometrial cancer patients and the study group during *MT-CO* gene fragments testing were subject to further analysis.

It was a rather difficult task since compared with the variants in hypervariable D-loop region these mutations occur only in a small portion of the studied neoplasms. Petros et al. [1] studied mutations in *MT-CO1* occuring in only 11–12% of the population with prostate cancer and in < 2% of the control group. Among the 17 patients diagnosed with glioblastoma multiforme only one carried an *MT-CO1* gene mutation, the remaining alterations were mostly located in D-loop [13]. Similarly, out of 68 thyroid cancer patients *MT-CO1* and *MT-CO3* gene mutations were detected in 9 cases [17]. Nevertheless, the influence of mtDNA mutations encoding respiratory chain subunits impairs energy and metabolic processes in cells, and affects the function of tissues and thus the whole body. The importance of this question prompted us to study *MT-CO1* and *MT-CO3* gene mutations in endometrial cancer.

CONCLUSIONS

The analysis performed indicates none of the remaining *MT-CO1* mutations (A5935G, G5949A, G6081A, G6267A) occur in endometrial cancer.

Three new alterations detected in this study (A6052G, A9545G, G9575A) were described for the first time.

Authors' contribution

Kinga Księżakowska-Łakoma — concept and design of study, collection of material, analysis and interpretation of data; Dominika Kulczycka-Wojdala — performing laboratory

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