Polymorphisms in *MDM4* Gene: Effects on Clinicopathological Characteristics in Breast Cancer Patients

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Objective

Breast cancer is one of the most common malignancy among women. The main clinical parameters (tumor size, status of estrogen, progesterone, HER2 receptors, lymph node involvement, tumor histological grade, etc.) are indicators routinely used in clinical practice to assess the prognosis of the disease and to select treatment methods. Genetic factors also play a substantial role in breast cancer. The evidence suggests that the MDM family may be related to breast development, function and protection from cancer. The elevated level of the MDM family member MDM4 is associated with various human cancer types (including breast cancer). This suggests that single nucleotide polymorphisms (SNPs) in the *MDM4* gene may have functional implications for breast cancer morphology. However, the effect of SNPs in *MDM4* gene has not been sufficiently studied yet.

The aim of the current study was to evaluate the influence of polymorphisms in *MDM4* gene on the clinical and morphological characteristics of breast cancer.

Methods

A total of 100 patients (with mean age of 42 years) with breast cancer were enrolled in the study. For SNP analysis genomic DNA was extracted from peripheral blood leukocytes.

SNPs (rs1380576 and rs4245739) in *MDM4* gene were analyzed by the polymerase chain reaction-restriction fragment polymorphism (PCR-RFLP) assay (Figs. 1 and 2).

All clinical and tumor pathomorphological data of the patients were obtained from the medical records by the oncologists. Informed consent was obtained from every participant. Study data included the age at diagnosis, pathological tumor size (pT), status of pathological lymph node involvement, status of estrogen, progesterone and human epidermal growth factor receptor 2 (HER2), intrinsic subtype (luminal A, luminal B, HER2 or triple negative), tumor grade (G1 and G2, G3), progress, metastasis and death.

The associations between SNPs and clinical characteristics of the patients were evaluated. Statistical data analysis was performed using SPSS.

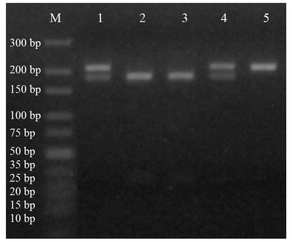
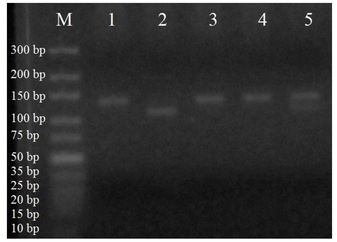


Figure 1. PCR-RFLP products of MDM4 rs1380576. Lane M - DNA molecular marker GeneRuler Ultra Low Range DNA Ladder; lanes 1 and 4 indicate GC genotype (195, 172 and 23 bp fragments); lanes 2 and 3 show CC genotype (172 and 23 bp fragments); lane 5 demonstrates GG genotype (195 bp fragment)

Figure 2. PCR-RFLP products of MDM4 rs4245739. Lane M - DNA molecular marker GeneRuler Ultra Low Range DNA Ladder; lanes 1 and 3-4 indicate AA genotype (134 bp fragment); lane 5 shows AC genotype (134, 110 and 24 bp fragments); lane 2 demonstrates CC genotype (110 and 24 bp fragments)



Results

In our study we investigated *MDM4* rs1380576 and rs4245739 polymorphisms in 100 Lithuanian breast cancer patients (Tables 1 and 2). The results of analysis showed some significant associations between rs1380576 and rs4245739 polymorphisms, located in *MDM4*, and tumor features. Our data indicated that compared to GG genotype, *MDM4* rs1380576 CC genotype showed 3.97-fold increased chance for developing estrogen-positive breast cancer (95 % CI 1.016-15.520, p=0.047). In addition, compared with the GG genotype, the CC was significantly associated with increased chances of positive progesterone receptor status (OR=12.150, 95 % CI 1.416-104.252, p=0.023). It was found that carriers of rs1380576 CC genotype had higher probability for developing luminal A subtype (CC versus GG OR=5.635, 95 % CI 1.082-29.337, p=0.040). Moreover, an increased chance for developing estrogen-positive breast cancer was significantly associated with rs4245739 AA genotype, compared to CC (OR=5.739, 95 % CI 1.027-32.065, p=0.047).

Table 1. Allele and genotype distribution of MDM4 polymorphisms in the study group

Polymorphism	Allele frequency		Genotype frequency		
MDM4 rs1380576 NG_029367.1:g.7772G>C	G - 0.24	C - 0.76	GG - 0.10	GC - 0.28	CC - 0.62
MDM4 rs4245739 NG_029367.1:g.38336C>A	C - 0.20	A - 0.80	CC - 0.07	AC - 0.26	AA - 0.67

Table 2. The clinicopathological characteristics of the study group

Characteristics	Subgroups and frequencies (%)
Age	30-40 years – 35 %, 41-50 years – 65 %
Pathological tumor size (pT)	T1 – 68 %, T2 – 32 %
Pathological lymph node involvement (N)	N0 – 55 %, N1 – 45 %
Estrogen receptor (ER)	ER negative – 43 %, ER positive – 57 %
Progesterone receptor (PR)	PR negative – 52 %, PR positive – 48 %
Human epidermal growth factor receptor 2 (HER2)	HER2 negative – 78 %, HER2 positive – 22 %
Intrinsic subtype	Luminal A – 51 %, Luminal B – 13 %, HER2 overexpression – 9 %, Triple negative – 27 %
Tumor grade (G)	G1 and G2 – 71 %, G3 – 29 %
Progress	absent – 69 %, present – 31 %
Metastasis	absent – 74 %, present – 26 %
Death	absent – 78 %, present – 22 %

T1 – >1 mm but ≤5 mm, T2 – >5 mm but ≤10 mm across, N0 – negative lymph node involvement, N1 – positive lymph node involvement, G1 – well differentiated (low grade), G2 – moderately differentiated (intermediate grade), G3 – poorly differentiated

Conclusions

The study suggests that there is correlation between *MDM4* genetic polymorphisms and breast cancer morphology. SNPs in the *MDM4* (rs1380576, rs4245739) may have the potential to operate as markers contributing to the assessment of breast cancer clinical characteristics.

Key words

breast cancer, SNPs, *MDM4*, associations