MyD88 gene polymorphisms and their associations with tumour pathomorphological characteristics and progression of disease in patients with gynaecological malignancies

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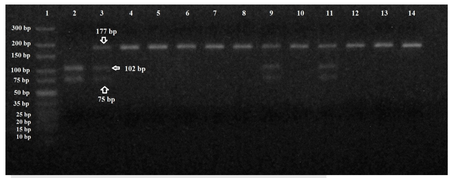
Objective

Myeloid differentiation primary response 88 (MyD88) is a protein that, in humans, is encoded by the *MYD88* gene. Signals from outside the cell are received by a group of proteins and the MyD88 functions as a connecting link that transmits the signals further towards proteins within the cell, this includes the signals coming from toll-like receptors (TLRs). TLRs signaling pathways are divided into MyD88-dependent pathways and MyD88-independent pathways. Ultimately, these signaling pathways lead to the expression of different molecules such as cytokines and different inflammatory factors which are essential for the proper immune response enabling natural cellular defences. It has been established that the TLR-MyD88 signaling pathway is involved in the pathogenesis of gynaecologic cancers caused by Human Papillomavirus (HPV) infections. Different single nucleotide polymorphisms (SNPs) of the *MYD88* gene have been identified. Some SNPs have been associated with increased susceptibility to different cancers and other diseases. However, the distribution of the SNPs of the *MYD88* gene and their effect, if any, in different gynaecological cancers and in tumor pathomorphological characteristics is poorly understood. Gynaecologic cancer is one of the major causes of global cancer deaths among women.

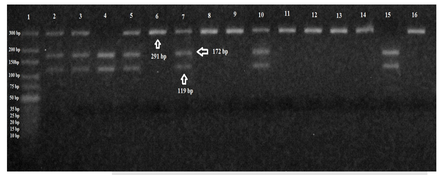
In this study we aim to investigate the link between *MYD88* polymorphisms and tumor pathomorphological characteristics, progression-free survival (PFS) and overall survival (OS) in a group of patients with cervical and uterine cancers in order to further extend our knowledge in processes which may play a crucial role in earlier diagnosis and more selective treatment plans that will improve the overall management of these conditions.

Methods

- This study included 121 women with cervical and uterine cancer.
- For SNP analysis genomic DNA was extracted from peripheral blood leukocytes.
- MyD88 rs6853 and rs7744 SNPs were analyzed by the polymerase chain reaction-restriction fragment polymorphism (PCR-RFLP) assay.
- The statistical analysis was performed using SPSS. The associations between the genotypes and alleles with tumor characteristics were assessed using Pearson's Chi-square or Fisher's Exact tests. Univariate and multivariate analysis to present odds ratios with 95% confidence intervals (CIs) and p-values were calculated with logistic regression. Differences in PFS and OS were assessed using hazard ratios (HRs) from univariate and multivariate Cox proportionate hazard models. p-value of <0.05 was considered statistically significant for all analysis.



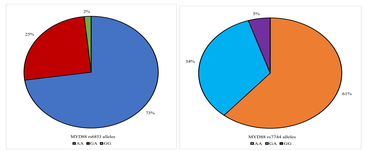
•Figure. 1. **The electropherogram of *MYD88* rs6853 polymorphism PCR-RFLP analysis**
•**Lane 1:** GeneRuler Ultra Low Range DNA Ladder (Thermo Fisher Scientific Baltics, Lithuania); Lane 2: GG genotype (102 and 75 bp fragments), Lane 4 – 8, 10, 12 –14: AA genotype (177 bp fragment); Lane 3,9,11: GA genotype (177, 102 and 75 bp fragments). The DNA ladders were used for approximate sizing of DNA fragments.



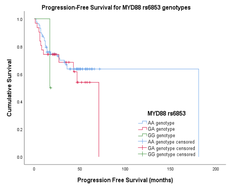
•Figure 2. **The electropherogram of *MYD88* rs7744 polymorphism PCR-RFLP analysis**
•**Lane 1:** GeneRuler Ultra Low Range DNA Ladder (Thermo Fisher Scientific Baltics, Lithuania); Lane 4, 15: GG genotype (172 and 119 bp fragments), Lane 6, 8, 9, 11 – 14, 16: AA genotype (291 bp fragment); Lane 2, 3, 5, 7, 10: GA genotype (291, 172 and 119 bp fragments). The DNA ladders were used for approximate sizing of DNA fragments.

Results

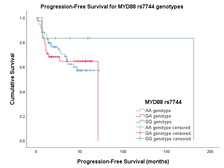
- 91 (75.2%) with cervical cancer and 30 (24.8%) with uterine cancer patients were involved in this study (mean (+/- SD age, 62.6 (+/- 12.5).
- Histopathology types of squamose cell carcinoma majority were in patients with cervical cancer (91.2%), and adenocarcinoma majority were in cases of uterine cancer (90%).
- The distribution of genotypes was as follows: MYD88 rs6853 AA-72.7%, GA-25.6%, GG-1.7%, 119 (98.3%) patients were A allele carriers and 33 patients (27.3%) were G allele carriers.
- For MYD88 rs7744 the distribution was AA-61.2% GA-33.9% GG-5%, 115 (95%) patients were A allele carriers, 48 (39.7%) patients were G allele carriers.
- The distribution of genotypes was according to the Hardy-Weinberg equilibrium.
- The AA genotype of MYD88 rs6853 was associated with a reduced risk of higher-grade (G3) cancer compared to the GA genotype (OR = 0.400, 95% CI 0.169-0.948, p-value = 0.037) in multivariate analysis following the adjustment for age at diagnosis, cancer type, lymph node status and cancer stage.
- MYD88 rs6853 polymorphism did not show any significant association with the course of the disease.
- In case of MyD88 rs7744 SNP, no significant link between tumor phenotype and patient PFS or OS was detected.



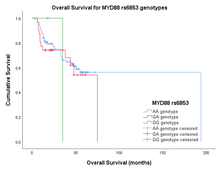
•Figure 3. *MYD88* rs6853 and rs7744 genotype distribution



•Figure 4. Kaplan-Meier curve showing PFS for *MYD88* rs6853 genotypes. Log Rank, p-value = 0.629



•Figure 5. Kaplan-Meier curve showing PFS for *MYD88* rs7744 genotypes. Log Rank, p-value = 0.551



•Figure 6. Kaplan-Meier curve showing OS for *MYD88* rs6853 genotypes. Log Rank, p-value = 0.741
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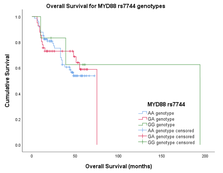

•Figure 7. Kaplan-Meier curve showing PFS for *MYD88* rs7744 genotypes. Log Rank, p-value = 0.777

Conclusions

Our study suggests that MYD88 rs6853 polymorphism has an impact on tumor differentiation grade. For more precise analysis further investigation on larger sample size should be conducted.

Key words

Gynaecological cancer, SNPs, MYD88, associations