

Clinical significance of germline variants in *BRCA1/2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes and their association with prostate cancer risk in Polish men.

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Background/Objectives: Currently, prostate cancer (PC) is the most common medical problem endangering men's health and life worldwide. We tested the association of detected germline variants in *BRCA1/2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* with PC risk and estimated their impact on the clinical course of the disease, including overall survival time (OS) for Polish men with localized prostate cancer qualified for radical prostatectomy (RP).

Materials/Methods: DNA of 97 prostate cancer patients, from each age group and with different stages of the disease. The control group consisted of 100 male volunteers without PC, age-matched to the study group. Next Generation Sequencing (NGS), and Sanger sequencing were used for variants detection in both groups.

Results: In 17/97 (17,5%) patients, 21 rare germline variants of *BRCA2*, *ATM*, *MSH2*, *MSH6*, and *PMS2* genes were detected. No variant was detected in *BRCA1*, and *MLH1*. Among the detected variants, there were 4 pathogenic, 1 likely pathogenic, 10 variants of uncertain significance (VUS), 4 likely benign, and 2 benign. The *BRCA2* c.8010G>C (VUS) and *ATM* c.8947dup (pathogenic) were newly identified variants. In the carrier of the *BRCA2* c.6393_6396del pathogenic variant, PC was diagnosed at 64 years of age and at the T3 stage. The patient survived 48 months after prostate cancer diagnosis (the date of biopsy). In the carrier of the *ATM* c.8947dup pathogenic variant, prostate cancer was diagnosed at 49 years of age. The carrier originated from a family fulfilling Hereditary Prostate Cancer (HPC) criteria.

Conclusions: Carrier status of the *BRCA2* c.6393_6396del pathogenic variant could be associated with a high Gleason Score, advanced TNM stage, and shorter overall survival, whereas carrier status of the *ATM* c.8947dup could be linked to early-onset prostate cancer (<50) and the hereditary form of the disease in patients with localized prostate cancer undergoing radical prostatectomy. However, this assumption requires thorough studies on the larger groups of patients. Additionally, our findings suggest that multi-organ cancer aggregation within families, including prostate cancer clustering among close relatives, as well as early age at cancer onset, should be considered by clinicians as important indicators for patients' referral to molecular testing.