

Clinical significance of germline variants in *ASXL1*, *CHD1*, *IDH1*, *SETD2* and *TET2* epigenetic genes and their association with prostate cancer risk in Polish men – preliminary results.

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Introduction: The epigenetic variants are present in all human cancers and associated with genetic alterations to drive a cancer phenotype. Thus, we searched for germinal variants in *ASXL1*, *CHD1*, *IDH1*, *SETD2* and *TET2* epigenetic genes in Polish prostate cancer patients and controls and analyzed the impact of them on disease clinical course, including overall survival time.

Material: The material of investigation was DNA from 97 men with prostate cancer (PC) from all over Poland and DNA from 100 men - volunteers, healthy at the time of the study. The median age of patients at PC diagnosis was $60,4 \pm 6,3$ years (45-76). The mean age of controls was 59.9 ± 6.6 and matched the PC group (46 to 74).

Methods: NGS and Sanger sequencing.

Results: 16 variants of *ASXL1*, *CHD1*, *IDH1*, *SETD2* and *TET2* epigenetic genes were detected in 14 PC patients. There were 9 missense variants (1 in *ASXL1*, 2 in *CHD1*, 1 in *IDH1*, 3 in *SETD2* and 2 in *TET2*), 1 duplication of *ASXL1* and 6 silent variants (2 in *CHD1* and 4 in *TET2*). All detected variants are localized in coding sequences of genes. Bioinformatic analysis of all variants was performed using Franklin or VarSome databases. Among detected variants, there were: 1 pathogenic, 1 likely pathogenic, 9 variants of uncertain significance (VUS), 1 likely benign and 4 benign. Two PC patients were carriers of two variants in different genes. The first of them was a carrier of *ASXL1* c.1934dupG pathogenic variant and *TET2* c.2370G>A variant of uncertain significance. The second was a carrier of *CHD1* c.2321A>T and *TET2* c.972A>G benign variants. 10 prostate cancer patients were carriers of pathogenic, likely pathogenic or VUS (P, LP or VUS) variants. 8 of 10 (80%) P, LP or VUS carriers and 54 of 87 (62,1%) non-carriers of investigated genes had at least one relative with cancer, including breast, uterus, stomach, colon, ovary, lung, larynx, kidney, liver, bladder, pancreas, lip, nose, blood, bone, duodenal cancers, glioblastoma and chronic lymphocytic leukemia (OR=2.4, p=0.3). 4 out of 10 P, LP or VUS carriers originated from families fulfilling HPC criteria and 6 out of 10 from families without HPC (PC frequency: 19,1% vs 7.9%, OR=2.75, p=0.14, trend). For the survival analysis, the patients were followed from the date of biopsy (confirmation of prostate cancer) until death, or in living patients, five-year survival was analyzed. 9 P, LP or VUS carriers diagnosed with PC between 2005 and 2007 survived five years from the date of biopsy and 1 carrier with PC diagnosed in 2019 is still living.

Comment: We found germline variants in each of the tested genes, but only 1 of them was pathogenic (*ASXL1* c.1934dupG) and 1 was likely pathogenic (*TET2* c.2218C>T). The frequency of both was 2,1% in the tested group and they were not detected in healthy men (p = 0.3). Noteworthy is a high OR (5.26) of disease occurrence in these patients. Additionally, the 9 variants of uncertain significance in *ASXL1* (c.3623C>T), *CHD1* (c.4949C>T, c.3723A>G, c.1434C>T), *IDH1* (c.565A>G), *SETD2* (c.3383C>G) and *TET2* (c.3930G>A, c.2370G>A, c.4161C>T) genes were detected. The presence of P, LP or VUS may be associated with hereditary prostate cancer, but this observation should be confirmed on larger PC groups. Due to the detection in Polish prostate cancer patients of a large number of epigenetic genes germline variants, including pathogenic, likely pathogenic and variants of uncertain clinical significance, there is a need to perform next investigations in this area and focus mainly on germline variants of genes involved in epigenetic processes.