

MISSENSE MUTATIONS OF NBS1 AND THE RISK OF BREAST AND PROSTATE CANCERS.

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The DNA damage signaling pathway plays a crucial role in the maintenance of the integrity of the genome in response to DNA damage and has been implicated in the pathogenesis of prostate cancer. Individuals with an inherited recessive clinical syndrome, such as Nijmegen breakage syndrome (NBS), which is characterized by spontaneous chromosomal instability carry a homozygous mutation in the NBN (NBS1) gene. The product of the gene is a part of the BRCA1-associated genome surveillance complex, which is responsible for DNA damage repair. A 5-bp deletion in exon 6 of *NBS1* (657del5) is a founder mutation present in the majority of NBS patients from Eastern Europe. The 657del5 allele (in heterozygous state) is present with a frequency of 0,6% in the Polish population. Recent studies suggested that heterozygous carriers of the 657del5 truncating mutation exhibit increased susceptibility to prostate and breast cancer, but missense variants of NBS1 have not been studied in this regard.

In order to investigate whether missense mutations of NBS1 predispose to prostate cancer and breast cancer, we assayed for the presence of three missense variants of NBS1 (Ile171Val, Arg215Trp, Glu185Gln) in 5097 men with prostate cancer, 1090 women with breast cancer and 4208 cancer-free controls using TaqMan-PCR. Genotyping call rate exceeded 98% for all variants in both cases and controls. We saw a higher frequency of Arg215Trp missense mutation in women with unselected breast cancer (0.6%) than in controls (0.6% vs 0.3%; OR = 2.5, p = 0.1). Also, the Arg215Trp variant was more frequent in women with familial breast cancer than in controls (0.8% vs 0.3%; OR=3.1, p = 0.3). The frequencies of Ile171Val, Arg215Trp and Glu185Gln variants were similar in prostate cancer cases and controls (OR between 0.9 and 1.1). The frequencies of Ile171Val and Glu185Gln variants were almost identical in breast cancer cases and controls (OR = 1.0).

This is the first large study to investigate the role of three missense mutations of NBS1 in genetic susceptibility to both prostate and breast cancer. Our results suggest that Arg215Trp missense mutation of NBS1 may be associated with two to three fold increased risk of breast cancer, but further studies are needed in this regard.