

Summary:

Breast cancer (BC) is the most frequent cancer type in female population of Europe. Approximately 5 – 10 % accounts for its hereditary form which is characterized by high penetrance, early onset, risen recurrence risk and development of other cancers. Mutational analyses of high risk patients identify a predisposing mutation in one of the most studied genes (*BRCA1*, *BRCA2*, *TP53*, *ATM*, *CHEK2*, *NBS1*, *PALB2*) only in less than one third of tested breast cancer patients.

Lately, with the use of new methods of next-generation sequencing, a number of other susceptibility or candidate genes were characterized, but the incidence of their pathogenic alteration is often geographically different. A notable proportion of high risk patients from families with hereditary BC can represent carriers of population-specific, or private mutations. Most of the to date identified BC susceptibility genes codes for proteins involved in DNA repair, especially repair of double strand break DNA repair. Nevertheless the mutation analysis was conducted only on a small fraction of these DNA repair genes. We can expect that in the group of yet nontested genes coding for DNA repair proteins a rare, but clinically important genetic alterations predisposing to BC in affected families can be discovered.

This work describes a comprehensive analysis of BC susceptibility genes in Czech high-risk BC patients negatively tested for mutations in *BRCA1/BRCA2/PALB2* genes and identifies some truncating variant in 32% of analyzed patients and 9% of all patients were carriers of a truncating variant in the genes that are analyzed in the current clinical NGS panel for the BC risk prediction. Results also show an overrepresentation of the *FANCL* variant c.1096_1099dupATTA in high-risk patients, indicating that *FANCL* (or rather this variant alone) may represent a novel BC susceptibility allele, whose importance needs to be further clarified by larger studies. We have also performed an analysis of potentially pathogenic variants for hereditary breast cancer in *ERCC2* gene within an international collaboration study which outpointed an important aspect of analyses of cancer-predisposing genes from the point of population- and region-specific evaluation of genetic background. Interestingly, in other analyzed genes, truncating mutations in the group of cytochrome p450 genes coding the enzymes of steroid hormones metabolism in 5% of BC patients were identified. Therefore, this functional group may contribute to the explanation of so far undisclosed missing heritability in some high-risk BC patients; however, further studies will be necessary to confirm this hypothesis.