The *APOBEC3B* deletion – analysis of its role in familial breast cancer predisposition and determination of its consequences on mRNA level

The vast majority of cancer cases is sporadic and predominantly results from various environmental factors and lifestyle. However, a small portion of some cancer types (mainly breast and/or ovarian cancer and colorectal cancer) is inherited and clusters in families. About five to ten percent of breast cancer cases occur in a familial setting. Hereditary breast cancer, on average, is diagnosed at a young age and/or co-occurs with ovarian cancer. Besides the *BRCA1*/*BRCA2* genes and several genetic factors associated with hereditary syndromes increasing risk of breast and/or ovarian cancer, a considerable fraction (~50%) of genetic factors associated with familial aggregation of breast cancer is still unknown. The *APOBEC3B* gene is among candidate genes, potentially associated with breast cancer predisposition. *APOBEC3B* is involved in various essential cellular processes and is responsible for induction of specific somatic hypermutation patterns, so called "*kataegis*", in cancer genomes (primarily breast cancer). In the framework of our preliminary research, we revealed that approximately 10% of Poles/Europeans inherit at least one chromosome with deletion of the *APOBEC3B* gene (instead of 2 copies of the gene, they possess one or even zero copies of *APOBEC3B*). The objective of the proposed project is to determine the role of the *APOBEC3B* deletion in breast cancer susceptibility and to define its consequences on mRNA level.

The proposed project encompasses two major research aims. In the framework of the first aim, an analysis of the *APOBEC3B* deletion association with breast cancer risk will be conducted with the use of 3000 DNA samples from women with unselected breast cancer and 3000 adjusted controls. In the framework of the second aim, we will perform analysis of the relation between *APOBEC3B* genotype and alteration of the expression level of *APOBEC3B* and functionally related *APOBEC3A*. Additionally, we will define the structure of fusion mRNA that is transcribed from the allele with *APOBEC3B* deletion, which presence determines generation of hybrid APOBEC3A/APOBEC3B transcript (APOBEC3A with 3'UTR of APOBEC3B).

The results that will be obtained in the proposed project will expand knowledge on genetic factors associated with hereditary breast cancer. If the breast cancer risk conferred by the presence of homozygous *APOBEC3B* deletion reaches the adequate level, the inclusion of *APOBEC3B* testing into genetic diagnostics could be a far-reaching consequence of the proposed project.
Moreover, the obtained results will also add up to the knowledge of the function of the *APOBEC3B* gene. Verification of the relation between the *APOBEC3B* genotype and the expression of *APOBEC3B* and *APOBEC3A*, as well as determination of the structure of the hybrid transcript, will provide new valuable insights into molecular mechanism of activity of the *APOBEC3B* and *APOBEC3A* genes that encode proteins responsible for various vital cellular functions as well as are involved in progression of several cancer types and are potentially associated with predisposition to various human diseases, including breast cancer.