Description for the general public (in english)

Epigenetic alterations, including methylation of DNA, are one of the most common molecular mechanism which play a role in cancer development. Methylation of *BRCA1* gene which can be detected in peripheral blood correlates with increased risk of breast cancer. However, the underlying mechanism causing this phenomenon is not completely understood. In the present study we will investigate molecular mechanism which leads to constitutional *BRCA1* methylation associated with breast cancer development. In order to achieve this aim we will investigate germline variants located in promoter region of *BRCA1* gene and perform genome-wide methylation analysis.

To identify germline alterations associated with *BRCA1* constitutional methylation quantitative determination of *BRCA1* methylation status by pyrosequencing and determination of BRCA1 protein expression in breast cancer tumor tissue by immunohistochemistry in 100 breast cancer cases will be performed, followed by genotyping of selected variants in a group of 2000 breast cancer cases and 2000 healthy controls to estimate their possible association with breast cancer risk. Genome-wide methylation analysis will be performed in 10 breast cancer patients and 10 healthy controls with detected constitutional *BRCA1* methylation using Infinium MethylationEPIC Kit (Illumina) encompassing over 800 000 CpG sites across the genome.

Although of many studies performed in the last twenty years, epigenetics is still not fully understood area, especially in the context of origination mechanisms. Thus, it is worth to extend the studies to new populations in order to confirm current knowledge or to find new information which can help with understanding the mechanisms of gene methylation. Identification of new germline variants in *BRCA1* gene we will allow to investigate a genetic cause of constitutional methylation leading to breast cancer and explain the indirect way of inheritance of constitutional methylation through the inheritance of identified genetic variants. Analysis of methylation along the whole genome in breast cancer patients and healthy controls with detected constitutional *BRCA1* methylation allows us to find out whether *BRCA1* methylation is an isolated phenomenon or is a part of some specific pattern being a consequence of disrupted methylation processes affected other genes. Obtained results can also indicate regions/genes which may be associated with breast cancer development, similarly to *BRCA1* gene.