**Analysis of the role of *BARD1* gene in genetic predisposition to breast cancer - utilization of unique strategy of association analysis of founder mutations**

The predominant part of cancers is sporadic. Sporadic cancers are developed due to environmental exposures, lifestyle or multiple low risk genetic variants. However, a fraction of some cancers (especially breast, ovarian, and colorectal cancers) is inherited and occurs in the form of a familial aggregations, i.e. occurs in closely related individuals more frequently than it could be expected based on the frequency of the cancer in general population. Predominantly, familial aggregation of cancer cases is attributed to a loss-of-function mutation inactivating specific tumor suppressor gene, which general function is to maintain genomic integrity and to inhibit tumorigenic cell transformation.

It is estimated that five to ten percent of all breast cancer cases are inherited and consequently occur in familial setting. Familial breast cancer, on average, is diagnosed at a younger age and frequently co-occurs with ovarian cancer. Aside from *BRCA1/2* genes and other genetic factors associated with hereditary syndromes increasing risk of breast and/or ovarian cancer as well as several genes of moderate to low penetrance, a considerable fraction of breast and/or ovarian predisposing factors (~50%) still remains to be identified. It was observed that among the candidate breast and/or ovarian cancer susceptibility genes are those encoding proteins that interact with BRCA1/2 in different DNA damage response and tumor suppressor processes. One such gene is *BARD1* (BRCA1 associated RING domain 1), encoding a protein indispensable for BRCA1-mediated tumor suppression function. Initial studies of the *BARD1* gene in subjects with breast and/or ovarian cancer revealed the presence of various *BARD1* sequence variants, including deleterious and potentially deleterious mutations leading to premature termination of translation, disruption of protein structure/function, or alternative splicing. Despite these preliminary insights, none of the analyses performed so far provided unequivocal evidence for the role of *BARD1* as a breast cancer susceptibility gene.

Therefore, the goal of our project is to deliver clear, statistically supported proof for the role of *BARD1* in genetic predisposition to breast cancer. To this aim, in the framework of our project, we will perform a large scale case-control association study of the selected *BARD1* founder mutations recurrent in the Polish population with the risk of breast cancer (the comparison of a cumulative and an individual mutations frequency in the group of 7500 cases and 7500 controls). Additionally, we will prepare an open database of *BARD1* sequence variants (BARD1mut+) which are implicated in different types of cancer, especially breast and ovarian cancers. The BARD1mut+ database will assist in the interpretation of the function of individual mutations and will help to understand the role of *BARD1* in determination of the risk of different cancers, including breast cancer. Based on BARD1mut+ we will select additional mutations that are to be analyzed in case-control association study conducted within this project.

The positive verification of the hypothesis that *BARD1* mutations are responsible for substantial increase of breast cancer risk and thus account for familial aggregation of breast cancer, will give rationale for more extensive testing for *BARD1* mutations in families with breast cancer aggregation. Importantly, if breast cancer risk associated with *BARD1* mutations turn out to be considerably high, the inclusion of testing of the *BARD1* mutation into genetic diagnostics of breast cancer and other genetically associated cancers (i.e. ovarian and prostate cancers), will be a far-reaching consequence of the proposed project.