The main objective of the current grant *"Identification of new breast cancer susceptibility genes by whole-exome sequencing in the genetically homogeneous Polish population"* is to identify new breast cancer susceptibility genes in founder population of Poland. Our preliminary work clearly shows that Poland is a relatively homogeneous country from a genetic perspective and that the background genetic variation is expected to be much less than that seen in western European countries or in North America. To date, all genes which predispose to breast cancer in Poland (BRCA1, CHEK2, NBS1, PALB2 and RECQL) are represented by one or a few founder alleles. Of the current common breast cancer alleles in the world, approximately one-half have been identified through Polish studies (see Narod SA, Genetic variants associated with breast cancer risk, Lancet Oncology, May 2011). Therefore in our study we are looking for founder mutations not genes *per se.*
An approximately 50% of families with strong aggregation of breast cancer (HBC families) are negative for mutations in known susceptibility genes. Our research hypothesis assumes that a proportion of HBC families in our genetically homogeneous population (in which no known mutations/genes were detected) is caused by rare founder mutations in several different highly penetrant genes, such as the RECQL gene (Cybulski et al., Nature Genetics, 2015).

The current submission is a critical continuation of our ongoing research program in which we intend to identify the genetic basis for breast cancer in the Polish population. With the support of the National Science Center (finised project NCN-2011/03/B/NZ2/01510, PI C. Cybulski) we performed whole-exome sequencing (WES) of above 20 000 genes in 144 women with breast cancer from Polish HBC families. In that study we have identified a new breast cancer susceptibility gene RECQL (Cybulski et al. Nature Genetics 2015). Of note, in our previous grant we did not find any founder mutation in RECQL gene among the 144 patients studied by WES in the discovery phase, but when we sequenced this gene in additional 475 cases, we found a recurrent founder mutation of RECQL that allowed us to investigate its association in a relatively large series of cases and controls in the validation phase.
The lesson we learned from our experience in our previous study is that since we are probably dealing with very rare mutations even in founder populations, and therefore we need a larger sample sizes (probably 400-500 cases) for the discovery phase to capture those rare founder mutations.

Therefore, in this project we would like to repeat the scheme that led us to discovery of RECQL gene:
1) whole-exome sequencing of 528 women with breast cancer from HBC families (144 from the previous project and 384 from this new proposal) to detect founder mutations - discovery phase.
2) investigation of the relationship of these founder mutations with breast cancer risk in association study of at least 10 000 women with unselected breast cancer and 5000 controls from Poland using real-time PCR and TaqMan probes – verification phase.

We believe that we have an opportunity to identify new generation of high penetrance genes for breast cancer because of: 1) the structure of the Polish population (genetically homogeneous population, so we are looking for founder alleles, not genes per se); 2) registry of DNA samples from over 2000 women with breast cancer from HBC families, 15 000 women with unselected breast cancer, and 5000 healthy women (controls) which has been collected in the Department of Genetics and Pathology for about 20 years; 3) the possibility of fast verification of our results in a genetically homogenous group of French-Canadians (collaboration with - Dr. MR Akbari, Prof. SA Narod from Canada, that already led to the identification of new breast cancer susceptibility gene (RECQL) and publication of this finding in Nature Genetics in 2015.

Our research will enable to identify new determinants (inherited mutations) of breast cancer, the most common malignant tumor in women. Identification of new cancer predisposing genes may generate further insights into the relevant pathways for inherited cancer susceptibility. It is possible that new cancer gene may represent a novel pathway. Moreover this study will enable future characterization of clinical characteristics of breast cancers in mutation-positive cases; collaboration with researchers in Poland and elsewhere to verify our findings, collaboration with researchers in Poland and worldwide to look for similar mutations in these genes in other populations. The results of this study will inform other researchers in Poland and around the world about the potential utility and benefit achieved from using a homogeneous ethnic population in the search for new genes using whole genome approaches.