Prostate cancer is one of the most prevalent cancers among men in Poland and elsewhere. Genetic susceptibility plays an important role in the etiology of the disease. A recent study of 49 000 Nordic twin pairs suggests that the heritability of prostate cancer is as high as 58%. However, genetic background of prostate cancer remains elusive, and only a few prostate cancer genes were identified including BRCA2, HOX13, NBS1 and CHEK2, which are responsible for minority of cases with prostate cancer.

Because of the unique structure of its population, Poland is now a leader in the genetic epidemiology of cancer. To date, founder alleles have been found in three different prostate cancer genes (NBS1 (one allele), CHEK2 (three truncating mutations) and HOXB13 (one allele). In total, one of these alleles is present in 2 percent of the Polish population. These three genes account for approximately 10% of Polish families with hereditary prostate cancer (HPC) – it is expected that additional, unknown mutations/genes are responsible for the other 90% of HPC families.

The main objective of the current project is to identify new prostate cancer susceptibility genes in founder population of Poland. We will assay coding regions of 20 000 genes using whole-exome sequencing (WES) on 300 Polish men with prostate cancer from HPC families. We expect to find about 20-30 potentially deleterious (protein truncating) mutations in each men, including recurrent mutations that are present in two or more cases among 300 men screened by WES.
Then, we will select ten most frequent recurrent mutations in genes which are functionally related to cancer pathogenesis. We will study these specific gene mutations in a large case-control study of 5000 men with unselected prostate cancer and 5000 controls using real-time PCR and TaqMan probes (validation phase).

Recently we provided evidence for the utility from using a homogeneous ethnic population in the search for new cancer genes by WES. With the support of the National Science Center (finished project NCN-2011/03/B/NZ2/01510, PI - C. Cybulski) we have identified a new breast cancer susceptibility gene RECQL by whole-exome approach (Cybulski et al. Nature Genetics 2015). A key finding in that study was the identification of a recurrent/founder mutation of RECQL that allowed us to investigate its association in a large series of cases and controls in the validation phase.

Poland is a 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 prostate and/or breast cancer in Poland are represented by one or a few founder alleles. Therefore in our study we are looking for recurrent founder mutations not genes *per se.*

Previous studies of genetic background of prostate cancer in Poland population were restricted to analysis of selected mutations in candidate genes. In this project, for the first time, we will screen the entire coding sequence of 20 000 genes in 300 men with prostate cancer from Polish HPC families. This is the first such comprehensive attempt to detect all mutations in known and novel genes for prostate cancer in our population. Identification of new genes for prostate cancer may enable development of new genetic test to identify men at high (or moderate risk) of prostate cancer. In future, this will in turn enable individualized management of these high-risk men (mutation carriers) including targeted screening, early detection and treatment of prostate cancers. In particular, it will be of interest to study usefulness of targeted prostate cancer screening using prostate specific antigen (PSA) in carriers of novel mutations in future clinical trials. It is also possible that prostate cancers that develop in the mutation carriers may have specific clinical characteristics, i.e. more aggressive clinical behavior (such as BRCA2 mutation associated prostate cancers) and may respond to specific treatments (i.e. chemotherapy).

Our research may generate further insights into the relevant pathways for inherited cancer susceptibility, will enable future collaboration with researchers to verify our findings, and 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 prostate cancer susceptibility genes using whole genome approaches.