Abstract:

The thesis The analysis of genetic factors of breast cancer by NGS deals with the current serious problematics of breast cancer from the perspective of genetic predisposition. Breast cancer is one of the most common tumors in women. Every year more than 7000 women are diagnosed with this disease and the mortality rate in the Czech Republic is nearly 2000 cases. Of the total number of patients diagnosed with breast cancer, approximately ten percent of patients have congenital mutations in one of the predisposing genes that cause a significantly increased risk of developing a cancer. More than half of these mutations occur in germline mutations of the **BRCA1** or **BRCA2** genes, others include a number of other genes, eg **tp53**, **CDH1**, **PTEN**, **STK11**, **ATM**, **PALB2**, **CHEK2**. Early diagnosis and identification of persons with increased risk of developing breast cancer is of key importance for their inclusion in preventive programs. Therefore, the thesis aims to testing genes that can cause a breast cancer.

In the thesis, 219 known and candidate predisposition genes were analyzed in a group of 263 non-selected breast cancer patients using a targeted panel NGS, the Illumina platform. Selected identified suspect variants were further confirmed by Sanger sequencing. The aim of this work was also a mutational analysis of an extended set of 1033 patients with breast cancer for **CYP1A2** and **CYP3A5** genes, both cases targeted to exon 2 with the High Resolution Melting (HRM) method.

Although there was a higher incidence of clinically relevant pathogenic mutations in the set of women meeting the indication criteria for genetic testing of tumor predisposition (21/89, 23.6%), a non-negligible group of women was found in the group of women with breast cancer not meeting the valid indication criteria (14 / 174, 8.1%) who confirmed a clear inherited cause of their disease. Most damaging mutations were found in the major **BRCA1** and **BRCA2** predisposition genes, but also in the genes with middle penetration, such as **CHEK2**, **PALB2**. Based on the results obtained, genes suitable for further analyzes were also selected for which association with hereditary breast cancer is not quite obvious. In order to refine the results, it will be necessary to extend the investigated file. Due to unavailability of other family members with disease, segregation analyses were not performed. The results of HRM analysis and subsequent statistical evaluation suggest that mutations in the **CYP3A5** gene do not increase the risk of developing breast cancer and, on the contrary, have a rather protective nature. Based on Fisher's exact assay, the **CYP1A2** gene would be evaluated as a
suitable candidate gene for association with breast cancer. However, both hypotheses will need to be verified on an extended set of patients and (if clinical data of other family members are available) to perform segregation analyzes.

**Key words:** breast carcinoma, breast cancer, heredity, NGS, gene mutation