Group: Molecular Genetics of Breast Cancer (H0602)

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Molecular Genetics of Breast Cancer

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Breast cancer is the most common malignancy among women. In developed countries approximately one in ten women will be diagnosed with breast cancer. Whereas the vast majority of breast cancer cases are sporadic and not attributable to inherited traits, about 5% are due to an inherited predisposition, largely manifested as site-specific hereditary breast cancer or the breast-ovarian cancer syndrome. The aim of our research is the identification of genetic and environmental factors involved in the pathogenesis of hereditary and sporadic breast and ovarian cancer. The identification of such factors and their genetic alterations will lead to a better understanding of the development and progression of this disease and will improve early detection.

1. Molecular analysis of hereditary breast cancer

Two genes responsible for inherited predisposition to breast and ovarian cancer, BRCA1 (BReast CAncer gene 1) on chromosome 17q and BRCA2 (BReast CAncer gene 2) on chromosome 13q have recently been identified by positional cloning strategies. The proportion of breast and/or ovarian cancer families attributable to germline mutations of these genes varies widely among various populations.

1.1 Germline mutations of the BRCA1, BRCA2 and TP53 genes

In Germany, 16% of the breast and/or ovarian cancer families have been shown to be due to BRCA1 germline mutations. To evaluate the prevalence of BRCA2 and TP53 germline mutations in hereditary breast and/or ovarian cancer families of German origin, we have undertaken a systematic search for germline mutations in both genes in a series of BRCA1-negative breast/ovarian cancer families. All families contained at least three breast or ovarian cancer cases. Genomic DNA samples from patients’ lymphocytes were screened for mutations using a combination of single strand conformational polymorphism analysis (SSCP), and the protein truncation test (PTT) for the exon 11, followed by DNA sequencing analysis as directed by abnormalities in these two tests. We identified several disease associated novel BRCA2 germline mutations including missense, frameshift, and nonsense mutations and two intronic germline mutations in the TP53 gene in 12% and 8% of the cancer families, respectively. These findings show that BRCA2 and TP53 are implicated in a small fraction of German breast and/or ovarian cancer families supporting the notion that additional susceptibility gene(s) appear to be important in Germany.

The mutation spectrum of BRCA1 mainly involves small base pair changes, mostly leading to premature termination of translation. Methods used to screen for BRCA1 mutations focused mainly on PCR-based assays on genomic DNA, which do not allow the detection of large DNA rearrangements. This may explain why only a few large rearrangements and hundreds of small insertions, deletions, and point mutations have been described. Recently, a large rearrangement, a 6-kb duplication of exon 13, which creates a frameshift in the coding sequence, has been identified in the BRCA1 gene. This mutation was found in three, unrelated U.S. families of European ancestry and in one Portuguese family.

To estimate the frequency and geographic diversity of carriers of this duplication, a collaborative international screening study was performed including 3580 unrelated individuals with a family history of the disease and 934 early-onset breast and/or ovarian cancer cases. Eleven additional families carrying this mutation were identified in Australia, Belgium, Canada, United States and Great Britain. Haplotype analyses revealed that they are likely to derive from a common ancestor, possibly of northern British origin. These results demonstrated that it is strongly advisable, for laboratories carrying out screening in either English-speaking countries or in countries with historical links with Britain, to include within their BRCA1 screening protocols the PCR chain reaction-based assay as described by us [1].

1.2 BRCA1 mutation status as prognostic parameter

It is unclear whether the prognosis of hereditary breast cancers differs from that of sporadic cases. Pathological features suggested that there may be underlying differences in hereditary breast cancers compared to sporadic cases. Further information on the biological differences may be revealed by survival studies.

Therefore we investigated overall and disease-free survival for German hereditary breast cancer patients. Our results showed that German breast cancer patients from hereditary breast and/or ovarian cancer families with a BRCA1 mutation had a significantly earlier age of diagnosis and more frequently developed contralateral breast cancer than breast cancer patients from families that did not harbor a BRCA1 mutation. BRCA1-associated tumors more frequently were of larger size and higher grade of...
malignancy than non-BRCA1-associated tumors. Furthermore, patients harboring BRCA1 mutations had an impaired disease-free survival at 10 years. However, this prognostic impact of the BRCA1 mutation status was lost after stratification for age and in multivariate analysis. These results suggested that the worse prognosis of BRCA1 mutation carriers may be due to their younger age at diagnosis [2]. Thus, BRCA1 mutation status does not appear to be an independent prognostic factor.

1.3 Cancer risks associated with BRCA2 mutations

Carriers of BRCA2 germline mutations are at high risk of breast and ovarian cancers, but the risks of other cancers in mutation carriers are uncertain.

To provide a more comprehensive assessment of the cancer risks of BRCA2 mutation carriers we have studied in collaboration with the Breast Cancer Linkage Consortium these risks in 173 BRCA2-positive breast-ovarian cancer families identified in 20 centers in Europe and North America. Our results showed that there is evidence for an increased risk of several other cancers including prostate cancer, pancreatic cancer, gall bladder and bile duct cancer, stomach cancer and malignant melanoma. Further, women who had already developed breast cancer have increased cumulative risks of a second, contralateral breast cancer and of ovarian cancer [3]. The determination of these cancer risks is important for genetic counseling and clinical management of BRCA2 mutation carriers.

1.4 Breast cancer and predictive factors: Association with genetic polymorphisms and expression of human xenobiotic and drug metabolizing enzymes

Known risk factors for breast cancer involve reproductive, hormonal, nutritional, genetic and environmental factors, however their molecular basis and possible interplay are not well understood. We hypothesize that low penetrant susceptibility genes may act in concert to give rise to breast cancer rather than mutations of a single highly penetrant gene. Xenobiotic enzymes may be likely candidates since they are key players in metabolism and detoxification of endogenous and exogenous compounds. Such enzymes are frequently polymorphic with respect to gene structure and phenotype and thus may provide the basis for interindividual differences in cancer susceptibility.

We are involved in establishing a case control study of women with breast cancer and healthy controls in order to compare frequencies of constitutional genotypes of potentially relevant polymorphic enzymes, i. e. phase I and phase II enzymes, enzymes of the reactive oxygen metabolism and others as well as growth factors and signal transducers. Their role in breast tumorigenesis will be evaluated in light of specific exposures related to reproductive history, life style and occupational history inquired by questionnaire. Within two years we aim to recruit 600 to 800 patients. With histologically confirmed diagnosis of breast cancer and women without cancer. Cases and controls will be from relevant hospitals of a defined geographic region of about one million inhabitants in Germany. Patients will be followed-up for the clinical course of disease and survival under systemic therapies. According to our working hypothesis there may be differences in breast cancer risk among carriers of certain constitutional genotypes or patterns of genotypes of xenobiotic enzymes or related factors in relationship to endogenous and/or exogenous exposures. Likewise genotypes may govern response or resistance to systemic breast cancer therapy in patients.

Publications (* = external co-author)