identified. This pathogenic mutation, that had previously been shown to cause A-T in the homozygous state, was found in breast and ovarian cancer family (with one case of leukemia) in a patient with bilateral BC at the ages of 53 and 60 and ovarian cancer at the age of 61. Product of alternative splicing with deleted exon 36, which leads to a shift of the ATM reading frame, was the second identified sequence variant. To date, the mechanism for generation of this splice variant is not known.

Conclusions: Examination of a larger group of patients is currently under investigation to determine the incidence of ATM mutations in risk families and to test the hypothesis that mutations responsible for A-T cause in heterozygotes an elevated risk for breast cancer.

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p53 codon 72 and p21 codon 31 polymorphisms and susceptibility to breast cancer in the Turkish and Greek populations

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Background: The tumour suppressor gene TP53 and its downstream effector p21 are thought to play major roles in the development of breast cancer. Polymorphisms in TP53 are considered candidate risk factors because of the crucial role played by this gene in the maintenance of genomic integrity following genotoxic insult. p53 codon 72 polymorphism appears to be significantly associated with several cancers including that of the breast. Independent studies also provided evidence that the Arg and Pro alleles at codon 72 are structurally and functionally distinct and therefore may influence cancer risk or treatment. p21 cyclin dependent kinase inhibitor mutations proved to be extremely rare in a variety of cancer types investigated. Polymorphic variants of p53 at codon 72, and p21 at codon 31, have been found to be associated with cancer susceptibility, but few studies have investigated their effect on breast cancer risk. In this study, we aimed to investigate any possible association between increased susceptibility to breast cancer and p21 codon 31 and/or p53 codon 72 polymorphisms in the Turkish and Greek populations.

Materials and methods: In total, 478 breast cancer patients with breast cancer and 382 age-matched controls were genotyped by PCR-based restriction endonuclease digestion. The Minitab 13.1 software program was used for statistical analysis of the data. Binary logistic regression analysis was performed for odds ratio and 95% confidence interval calculations. Adjusted odds ratio calculations were carried out with the SPSS software program.

Results: The p53 Arg72 Arg inheritance was found to be significantly associated with breast cancer susceptibility in the Turkish (OR = 2.16; 95%CI = 1.08–4.31) as well as in the combined Greek-Turkish populations (OR = 2.35; 95%CI = 1.25–4.41). This association was further exacerbated with increased BMI (OR = 3.86; 95%CI = 1.12–13.26) in the Turkish population. p21 codon 31 was not associated with breast cancer susceptibility in either population. Most notably, combination of the two high-risk genotypes, p53 Arg72Arg and p21 Arg31Arg or Ser31Arg increases the risk to 2.66-fold (95%CI = 1.06–6.66).

Conclusion: These results let us to conclude that there is a strong association between the p53 Arg72Arg genotype and breast cancer risk in the Turkish and Greek populations and that the combination of the high-risk allelic variants of both p53 and its downstream effector protein p21 may have a role in breast cancer development.

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Silencing of LASP-1 influences zyxin localization, inhibits proliferation and reduces migration in breast cancer cells

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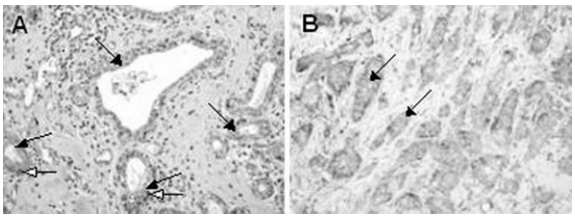
LIM and SH3 protein 1 (LASP-1), initially identified from human breast cancer, is a specific focal adhesion protein involved in cell migration. LASP-1 is an actin binding protein, which also interacts with the proline-rich domains of zyxin, a scaffolding protein required for cell movement and gene transcription.

In the present work we analyzed the effect of LASP-1 on different human breast cancer cell lines using the powerful small interfering RNA technique (siRNA) to silence protein expression in a sequence specific manner. Transfection with LASP-1 specific siRNA resulted in a reduced protein level of LASP-1 in BT-20 and MCF-7 cell lines. The siRNA-treated cells were arrested in G2/M phase of cell cycle and proliferation of the tumor cells was suppressed by 30–50% corresponding to around 50% of the cells being transfected successfully as seen by immunofluorescence. Tumor cells transfected with LASP-1 si-RNA showed a 50% reduced migration compared to control cells transfected with scrambled si-RNA. Overexpression of LASP-1 in non-tumor PTK-2 cells, which don't express endogenous LASP-1, resulted in a significant increase in cell motility. LASP silencing is accompanied with a reduced binding of the of LASP-1 binding partner zyxin to focal contacts without changes in actin stress fibre organisation as observed in immunfluorescence experiments.

The data provide evidence for an essential role of LASP-1 in tumor cell growth and migration, possibly through influencing the localization of zyxin.



Immunohistochemical staining of normal and cancerous breast tissue samples.

A): Normal breast tissue with two ducti in the centre and the acini at the left and right sides. LASP is positive in the myoepithelial cells (white head arrow) surrounding the LASP-negative luminal epithelia cells (black arrow). *B):* In breast cancer all cancer cells are intensively stained positive for LASP (arrows). Magnification × 400.

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Expression of the growth factor receptors HER2 and EGFR in primary tumors and in brain metastases of breast cancers

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Background: The EGFR-related growth factor receptors play an important role in breast cancer. Both HER2 and EGFR are targets for specific therapeutic interventions such as tyrosineinhibitors or Tratuzumab. Because of the unsatisfactory therapeutic results with brain metastases it is necessary to understand the expression of these growth factor receptors both in the primary tumor and in the brain metastases derived from them.

Material and methods: The expression of EGFR and HER2 in both the primary tumor and the derived brain metastases was investigated by means of immunohistochemistry. Further, the HER2 gene amplification was determined by fluorescence in situ hybridization (FISH).

Results: Immunohistologically 11 (37.9%) of the 29 primary tumors showed a clear positive (3+), 2 (6.9%) a medium-grade (2+), and 3 (10.3%) a weak (1+) HER2 expression. 13 patients (44.8%) showed no HER2 expression. Amplification of the HER2 gene was observed in all 2+ and 3+ cases. There was no amplification in the 1+ cases. Only one of the negative cases had a moderate amplification (5–10 gene copies). A total of 13 patients (45%) were evaluated as positive concerning a Trastuzumab-therapy. 28 (96.6%) of the 29 patients in this study showed the same HER2 expression both in the primary tumor and in the brain metastases. In only one patient the primary tumor revealed an overexpression of HER2, while the brain metastasis was HER2-negative. Only 2 of the 29 patients (7%) showed a clear EGFR expression in the primary tumor. In 28 of the 29 patients (96.6%) the expression pattern of EGFR in the primary tumor corresponded to that of the brain metastases. In only one patient who was EGFR-negative in the primary tumor, did the brain metastasis show a clear EGFR expression.

Conclusion: In the course of the development of a cerebral metastasis there is no essential change in the expression patterns for HER2 and EGFR between the primary tumor and the brain metastases. The expression patterns in the primary tumors are representative of the corresponding brain metastases. The failure of HER2 target therapy in cases of brain metastasis derived from HER2-positive tumors can not be attributed to a putative loss of the receptor.