Association of genetic variants in the Rho guanine nucleotide exchange factor AKAP13 with familial breast cancer.

The A-kinase anchor protein 13 (AKAP13, alias BRX and lbc) tethers cAMP-dependent protein kinase to its subcellular environment and catalyses Rho GTPases activity as a guanine nucleotide exchange factor. The crucial role of members of the Rho family of GTPases in carcinogenesis is well established and targeting Rho proteins with antineoplastic compounds has become a major effort in the fight against cancer. Thus, genetic alterations within the candidate cancer susceptibility gene AKAP13 would be expected to provoke a constitutive Rho signalling, thereby facilitating the development of cancer. Here, we analysed the potential impact of four polymorphic non-conservative amino acid exchanges (Arg494Trp, Lys526Gln, Asn1086Asp and Gly2461Ser) in AKAP13 on familial breast cancer. We performed a case-control study using genomic DNA of BRCA1/2 mutation-negative German female index patients from 601 unrelated families, among a subset of 356 high-risk families, and 1053 German female unrelated controls. The newfound Lys526Gln polymorphism revealed a significant association with familial breast cancer (OR = 1.58, 95% CI = 1.07-2.35) and an even stronger association with high-risk familial breast cancer (OR = 1.85, 95% CI = 1.19-2.88). Haplotype
analyses were in line with genotype results displaying a similar significance as analyses of individual polymorphisms. Due to the pivotal role of AKAP13 in the Rho GTPases signalling network, this variant might affect the susceptibility to other cancers as well.

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