Interaction of Werner and Bloom syndrome genes with p53 in familial breast cancer.

Abstract:
Mutations of the human RecQ helicase genes WRN and BLM lead to rare autosomal recessive disorders, Werner and Bloom syndromes, which are associated with premature ageing and cancer predisposition. We tested the hypothesis whether three polymorphic, non-conservative amino acid exchanges in WRN and BLM act as low-penetrance familial breast cancer risk factors. Moreover, we examined the putative impact of p53 MspI 1798G>A, which is completely linked to p53PIN3, a 16 bp insertion/duplication that has been associated with reduced p53 expression, on familial breast cancer risk. Genotyping analyses, performed on 816 BRCA1/2 mutation-negative German familial breast cancer patients and 1012 German controls, revealed a significant association of the WRN Cys1367Arg polymorphism with familial breast cancer (OR = 1.28, 95% CI 1.06-1.54) and high-risk familial breast cancer (OR = 1.32, 95% CI 1.06-1.65). The analysis of p53 MspI 1798G>A, which is completely linked to p53PIN3, showed a significantly increased familial breast cancer risk for carriers of the 16 bp insertion/duplication, following a recessive mode (OR = 2.15, 95% CI = 1.12-4.11). WRN Cys1367Arg, located in the C-terminus, the binding site of p53, is predicted to be damaging. The joint effect of WRN Cys1367Arg and
p53 MspI resulted in an increased breast cancer risk compared to the single polymorphisms (OR = 3.39, 95% CI 1.19-9.71). In conclusion, our study indicates the importance of inherited variants in the WRN and p53 genes for familial breast cancer susceptibility.