2. Summary
Background: A greatly increased risk for development of hereditary breast cancer is associated with germline mutations in several susceptibility genes. In this study we analyzed large genomic rearrangements (LGRs) in BRCA1/2 genes and we also focused on the role of CHEK2 and TP53 in tumorigenesis.
Methods: A series of 586 high risk patients with breast/ovarian cancer that had previously been tested negatively for small mutations in BRCA1/2 was screened for LGRs by MLPA, LR-PCR and sequencing. Chromosome 17-specific aCGH was used to locate deletion breakpoints in regions flanking the BRCA1 gene. MLPA-analysis was also used to detect two frequently occurring mutations in CHEK2 (c.1100delC and a deletion of 5395 bp). The coding region of the TP53 gene was analyzed by sequencing.
Results: We identified 9 different LGRs in the BRCA1 gene in 16 patients. Five alterations (deletion of exons 1-17, 5-10, 13-19, 18-22 and 21-24) were novel. Deletions of exons 1-17, 5-14 and 21-22 were identified repeatedly, and represented population specific (founder) mutations. LGRs accounted for 12.1% (16/132) of all detected pathogenic BRCA1 mutations. No LGRs were found in the BRCA2 gene. Pathogenic mutations in other tested genes were less frequent; 2 were detected in TP53 and 9 in CHEK2.
Conclusions: In our population, LGRs represent substantial proportion of pathogenic mutations in BRCA1. Our results indicate that screening for LGRs in BRCA1 should include patiens from high-risk families as well as patients with non-familial cancer; in particular cases with early-onset breast cancer. Testing of CHEK2 for the two recurrent mutations seems to be also relevant in our population; analysis of TP53 may be restricted to cases of early onset breast cancer.