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Single nucleotide polymorphisms in genes connected with chromosomal instability and their relation to breast cancer risk, tumour characteristics and survival
- A search for breast cancer specific prognostic markers -

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The presented case-control study was performed on a Swedish study population and focused on the effects of putative functional and regulatory relevant SNPs in candidate genes with a strong probability to be involved in BC development.
We investigated the effects of SNPs in genes related to chromosomal instability and their contribution to BC susceptibility, tumour characteristics and survival with the aim to identify possible clinical markers.
Taken together, we investigated 64 SNPs, with the potential to affect protein expression or protein function, in nine telomere associated genes, six polymerase and polymerase associated genes and 16 genes underexpressed in chromosomal unstable BC. The SNPs were genotyped in a large Swedish case control population and additionally for selected SNPs in a Polish case control population with familial and early onset cases.
As chromosomal instability is a hallmark of many cancers and has been reported to predict the clinical outcome of the disease, SNPs selected in candidate genes with a possible role in chromosomal instability represent valuable targets for an association with BC risk, tumour characteristics and survival.
SNPs in the two telomere associated genes, *TERF2* and *TNKS2* as well as the polymerase encoding gene *REV3L* and the polymerase associated gene *MAD2L2,* were associated with BC risk. SNPs in the genes *TERF2* and *TNKS2* were additionally associated with tumour characteristics at the time of diagnosis. One SNP in a further telomere associated gene, *TNKS* as well as two SNPs in the polymerase associated gene *REV1* and SNPs in the two genes *CCL18* and *ASAH1,* which were underexpressed in chromosomal unstable BC were associated with tumour characteristics at the time of diagnosis.

Three SNPs were identified as possible independent clinical markers for the prognosis of the disease as they were associated with the survival of the patient. These were rs11153292 in the intronic region of the *REV3L* gene encoding for the catalytic subunit of Polymerase Zeta and the SNPs rs1044243 (nsSNP) and rs1157 (3`UTR) in the *ALCAM* gene which is underexpressed in chromosomal unstable BC and encodes for a glycoprotein of the immunoglobulin superfamily of adhesion molecules.

Altogether, Polymerase Zeta with its catalytic subunit *REV3L* and the two supporting subunits *MAD2L2* and *REV1* could be identified as an enzyme that plays a significant role in BC development and progression.

Only limited explanation of the effect of the SNPs on expression status or protein configuration could be provided. Some of the SNPs were tagSNPs capturing intronic SNPs for which no information about the functional relevance was available. For other SNPs in the promoter, 3`UTR or exon region of the gene publicly available prediction tools were used to predict the effect of a specific SNP. However, these prediction tools are limited and consist of estimations.

None of the SNPs that were associated with BC risk was associated with tumour characteristics or survival; indicating these SNPs only have an influence on the principal risk to get BC but not on the outcome of the disease and vice versa. None of the associations significantly observed in the Swedish study population were replicated in the Polish study population at a statistically significant level which may indicate the existence of different mechanisms regarding sporadic and familial/early onset BC.

In conclusion, we showed that SNPs in genes related to chromosomal instability can contribute to the inter-individual variability in susceptibility to BC and the prognosis of the disease and can therefore act as potential markers for the outcome of the disease.