High Risk breast cancer genes at 8q22-24 and their role in over 5000 patients evaluated with the MammaPrint risk of recurrence assay

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Background

Previous studies have shown that CCNE2 expression is higher in patients’ cancers resistant to CDK4/6 inhibitors (1). Increased expression of CCNE2, MTDH, or TSPYL5, genes contained within MammaPrint (MP), a 70-gene risk of distant recurrence signature, has also been implicated in breast oncogenesis, poor prognosis, and chemoresistance (2-4). These genes are located on chromosome region 8q22.1, one of the most recurrently amplified regions out of all MP genes in breast cancers (BC) (5). MTC, located within close proximity on 8q22.1, is overexpressed in 40% of all BC. Here we examined the expression of CCNE2, MTDH, and TSPYL5 in relation to MP risk and the 80-gene molecular subtype signature, BluePrint (BP), and their correlation with expression in early stage BC patients.

Methods

CCNE2, MTDH, TSPYL5, and MYC mRNA expression was measured in 5022 BC samples sent to Agenda (Irvine, CA) for MP and BP testing, which included FFPE microarray full-transcriptome data. Intensities were Lowess normalized and KEGG transformed. MP was used to stratify patients into Ultra Low Risk (UL), Low Risk (LR), High Risk (HR), and Ultra High Risk (UH). LR and HR are similar to MP High 1 (MPH1) and MP High 2 (MPH2) reported in the I-SPY2 trial, which have demonstrated the ability for these groups to predict chemo-sensitivity with Risk (%). Increased expression of MYC, located within close proximity on 8q24.21, is overexpressed in 40% of all BC. These data may be clinically relevant for stratifying patients in ongoing clinical trials evaluating response and resistance to targeted therapies in early stage BC.

Results

The expression of CCNE2, MTDH, and TSPYL5 was significantly higher in MP HR patients compared to LR patients and significantly higher in HR patients compared to MP HR patients (Figure 1). Additionally, CCNE2 and MTDH expression was elevated in LR compared to UL patients. In contrast, there was no difference in MYC expression between HR versus LR or UH versus HR (Figure 1).

The expression of CCNE2, MTDH, and TSPYL5 was the highest expressed in Basal type tumors, 83% of which were UH, followed by Luminal B type tumors while expression of these genes was lowest in Luminal A type tumors (Figure 3). MYC was significantly higher expressed in Basal type tumors but overall exhibited a smaller magnitude of differential expression across BP subtypes compared to CCNE2.1 genes.

The expression of CCNE2, MTDH, and TSPYL5 significantly correlated with each other (Figure 3). The highest correlations were observed between MTDH and CCNE2 and MTDH and TSPYL5. There was no association between the expression of CCNE2 and MYC in any MP risk subgroup (Figure 3).

In 84% (866) of the 1036 BC TCGA samples, the 8q22.1 genes were detected on the same DNA segment, of which 57% (496) were determined to have an “amplification” and 43% (370) with “no amplification”. The 8q22.1 amplified regions out of all MP genes in breast cancers (BC) (5).

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Figure 1. 8q22-24 gene expression in MP risk groups

Figure 2. 8q22-24 gene expression among BP subtypes

Figure 3. Gene expression correlation

Figure 4. 8q22-24 copy number amplification and gene expression in TCGA samples

CCNE2, MTDH, and TSPYL5, genes contained within the MammaPrint assay, have similar expression patterns and when overexpressed represent a subgroup of high risk breast tumors.

The data may be clinically relevant for stratifying patients in ongoing clinical trials evaluating response and resistance to targeted therapies in early stage BC.

References

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