

HIGH-RISK BREAST CANCER: FROM BIOLOGY TO PERSONALIZED THERAPEUTIC STRATEGIES

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, torsdagen den 16 januari 2014 kl. 9.00

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Avhandlingen är baserad på följande delarbeten:

- I. **Parris T.Z.**, Danielsson A., Nemes S., Kovács A., Delle U., Fallenius G., Möllerström E., Karlsson P., and Helou K. Clinical implications of gene dosage and gene expression patterns in diploid breast carcinoma. *Clinical Cancer Research*. 2010 Aug 1;16(15):3860-74.
- II. **Parris T.Z.**, Kovács A., Aziz L., Hajizadeh S., Nemes S., Semaan M., Forssell-Aronsson E., Karlsson P., and Helou K. Additive effect of the AZGP1, PIP, S100A8, and UBE2C molecular biomarkers improves outcome prediction in breast carcinoma. *International Journal of Cancer*. 2013 *in press*.
- III. **Parris T.Z.***, Aziz L.*, Kovács A., Hajizadeh S., Nemes S., Semaan M., Karlsson P., and Helou K. Clinical relevance of breast cancer-related genes as potential biomarkers for oral squamous cell carcinoma. *Submitted*.
- IV. **Parris T.Z.**, Kovács A., Hajizadeh S., Nemes S., Semaan M., Karlsson P., and Helou K. Functional significance of *WHSC1L1* gene amplification and/or over-expression in breast carcinoma. *Manuscript*.



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Abstract

Adjuvant treatment regimens for breast cancer are primarily based on patient- and tumor-related factors, e.g. patient menopausal status, tumor stage and histological grade, and the status of molecular tumor markers (HER2/*neu* and the estrogen receptor). Despite improvements in survival rates, about 20% of patients experience recurrence within five years of initial therapy. There is therefore a need to improve patient risk assessment and to personalize therapy according to a combination of patient-specific clinicopathological features and tumor characteristics. This doctoral thesis is a multidisciplinary effort between molecular biologists, clinicians, and pathologists to identify potential therapeutic targets for high-risk breast carcinoma.

This work exploits common knowledge that the accumulation of deleterious genetic and epigenetic modulators contribute to breast cancer risk for recurrence and death by deregulating key cellular processes within a specific tumor. In the first work, we found that tumors from high-risk breast cancer patients were genetically unstable, containing a 2-fold increase in genetic alterations, an overrepresentation of alterations on chromosomes 3, 18, and 20, and the recurrent deregulation of a 13-marker transcriptome signature associated with significantly shorter disease-specific survival rates (*AZGP1*, *CBX2*, *DNALI1*, *LOC389033*, *NME5*, *PIP*, *S100A8*, *SCUBE2*, *SERPINA11*, *STC2*, *STK32B*, *SUSD3*, and *UBE2C*). Second, subsequent validation of the 13-marker signature demonstrated the importance of not only performing external validation in independent breast cancer microarray datasets, but also to assess the biological and clinical relevance of individual markers at the protein level because of frequent poor mRNA-protein correlation. It was shown that breast cancer outcome prediction was improved significantly by combining a four-marker immunohistochemical panel (*AZGP1*, *PIP*, *S100A8*, *UBE2C*) together with established clinicopathological features. Third, we showed that several putative markers previously identified by us may not only be useful for breast cancer prognostication, but may also be clinically relevant in oral squamous cell carcinoma, a cancer form bearing biological similarities to breast carcinoma. Lastly, we found that the 8p11-p12 genomic region is a hotspot for DNA amplification in breast cancer, where the *WHSC1L1* gene may be one of several genes located in region with oncogenic potential and a substantial contributor to the aggressive breast cancer phenotype.

Taken together, these findings further emphasize the importance of complementing established clinicopathological features with tumor-specific molecular markers to improve breast cancer risk assessment and develop more individualized treatment regimens.

Keywords: breast cancer, outcome prediction, molecular biomarker, 8p11-p12 amplification

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