The ESR1-CCDC170 Gene Fusion as a Diagnostic Biomarker for Breast Cancer

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Technology description

Publications: Recurrent ESR1-CCDC170 rearrangements in an aggressive subset of oestrogen receptor-positive breast cancers. Veeraraghavan J, Tan Y, Cao XX, Kim JA, Wang X, Chamness GC, Maiti SN, Cooper LJ, Edwards DP, Contreras A, Hilsenbeck SG, Chang EC, Schiff R, Wang XS. Nat Commun. 2014 Aug 7;5:4577. (http://www.ncbi.nlm.nih.gov/pubmed/25099679)

Estrogen receptor positive (ER+) tumors that account for 80% of breast cancer can be classified into luminal A and B subtypes. In contrast to the hormone-sensitive A subtype that can be treated with endocrine therapy alone, the luminal B subtype confers more aggressive phenotype and requires more robust treatment strategy (i.e., endocrine therapy combined with chemotherapy); however, clinically it is difficult to clearly define the two subtypes due to the lack of reliable and accurate surrogate biomarkers. Current available classification methods, like PAM50 gene expression profile or Ki67 index, are limited by controversial performance, or the need of a somewhat arbitrary cut-off score, and the patients, especially those who are on the borderline, may be misclassified and thus may not receive the appropriate treatment. Therefore, it poses an urgent yet unmet healthcare need to discover the underlying genetic aberrations and develop a more reliable genetic marker to define these luminal B tumors. Dr. Xiaosong Wang and his team have identified recurrent rearrangements between the estrogen receptor gene ESR1 and its neighbor CCDC170, resulting in a gene fusion that preferentially presents in luminal B breast tumors. They further verified the presence of ESR1-CCDC170 fusions in at least three breast cancer cell lines and about 8% of the luminal B tumor samples analyzed in the study. ESR1-CCDC170 endows more aggressive phenotypes in vitro and in vivo, reflecting the more aggressive phenotype of the luminal B subtype in patients. When introduced into ER+ breast cancer cells, the ESR1-CCDC170 fusion led to markedly increased cell motility and anchorage-independent growth, reduced endocrine sensitivity, and enhanced xenograft tumor formation. The presence of ESR1-CCDC170 gene fusion can be reliably detected by analyzing the RNA fusion transcript resulted from genomic rearrangements, such as RT-PCR or probe-based platforms. Alternatively, the DNA genomic fusion may be detected by appropriate DNA microarrays or NGS technologies. Available clinical and experimental data suggests that breast cancer patients bearing this fusion, indicating a luminal B subtype, may benefit from combined endocrine therapy and chemotherapy, but not likely from endocrine therapy alone.

Advantages

- Novel diagnostic/prognostic marker: genetically define a subset of luminal B breast cancers by using widely adopted nucleic acid analysis technologies to detect the said gene fusion. - A "yes or no" genetic marker: the ESR1-CCDC170 gene fusion detection test will yield a clear "yes or no" result, eliminating the need of any empirical threshold or cut-off scores. - Personalized medicine: Detection of the ESR1-CCDC170 gene fusion can be used as an independent or companion diagnostic to screen for patients who are likely to develop endocrine resistance and require enhanced treatment strategy such as chemotherapy.

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