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Computational identification of genetic patterns and essential risk factors associated with clinical heterogeneity of aggressiveness of breast cancer

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Despite the improvements in detection and treatment of breast cancer, about 40% of patients still succumb to disease. The search of novel genetic patterns related to clinical heterogeneity of breast cancer and essential molecular tumor markers able to unambiguously identify low- and high-aggressive tumor types are important. Recent studies using DNA microarrays in combined with advanced data mining tools and clinical data indicate that such clinical heterogeneity may be reclassified at the molecular level. Indeed, gene expression patterns or signatures underlying specific biological properties and pathways of cancer cells have been proposed and established prognostic markers. In this work we demonstrate that advanced computational analysis of microarray data from large and independent cohorts of patients analyzed in combination with treatment follow-up data allows provide a more objective and clinically valuable measure of post-surgery tumor relapse in patients with apparently localized breast cancer and of tumor grades. Our combined approach reveals several low-dimension gene expression signatures (contained from 5 to 7 genes only) which can accurately distinguish between low(G1)- and high(G3)- grade tumors. More importantly, these signatures are able to subdivide the intermediate-grade tumors (G2) into two novel subtypes (G1-like and G3-like) with biological properties and survival outcomes highly similar to those with G1 and G3 histology, respectively. These genetic signatures enable reclassify the patients in two groups, with ~90% and ~50% five-year survival rates, and establish strong associate our genetic grade signatures with 5 subtypes of the 456-gene "intrinsic molecular signature" (Sorlie et al., 2003) of breast cancer. Our genetic grade signatures show the potential to be developed into powerful and objective new prognostic factors, which could be used to improve therapeutic planning up to 50% of breast cancer patients.