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Pathogenic mosaic germline mutational landscape in breast cancer patients and pharmacogenomics

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Precision medicine aims to identify the right drug, for the right patient, at the right dose, at the right time, which is particularly important in cancer therapy. Problems such as the variability of treatment response and resistance to medication have been long-standing challenges in oncology, especially for development of new medications. Solid tumors, unlike hematologic malignancies or brain tumors, are remarkably diverse in their cellular origins and developmental timing. Precision medicine, also often called personalized medicine, has been defined as identifying the right drug, for the right patient, at the right dose, at the right time. This concept relies heavily on access to information on an individual's unique genetic characteristics to tailor therapy. Today, about 10% of labels for Food and Drug Administration (FDA)-approved drugs contain pharmacogenomic information. Precision medicine is not a new concept but the availability of large-scale human genome databases, the advent of powerful methods such as next-generation sequencing (NGS) and advancement of computational tools have created an opportunity for significant progress. Precision medicine is particularly important in oncology because along-standing problem is the variability of treatment response, especially in early stage clinical trials. In recent years, a huge number of germline mutational variants had been identified in breast cancer by nextgeneration sequencing technologies. Even though a considerable portion of them are variants with low variant allele fraction (< 30%), which could give rise to suspicion among us regarding whether they might be false or true, recent pioneering studies have begun to corroborate that a certain amount of them are true variants associated with mutational mosaicism. In this study, we present pathogenic mosaic germline mutational landscape in 490 breast cancer patients by carrying out targeted next-generational sequencing of 62 cancer-associated genes. We discovered 112 pathogenic, 37 likely pathogenic and 252 VUS mosaic germline mutations with variant allele fraction less than 30%. PRSS1 (97%), ATM (22%), PMS2 (11%), BARD1 (11%), PTEN (8%), BRCA2 (8%), BRCA1 (7%), APC (5%), MSH2 (5%) and NF1 (5%) mosaic mutations occurred in the top 10 biggest portions among the 490 patients, respectively. Gene pairs showing statistically significant mutual exclusivity in mutation carriers are PRSS1 and FANCC ($p < 0.01$), PRSS1 and PTEN ($P < 0.01$), and PRSS1 and ATM ($p < 0.01$). Genes showing the biggest fractions of mosaic mutational clusters PRSS1 (FDR < 10-6), BARD1 (FDR < 10-5), PTEN (FDR < 10-4), ATM (FDR < 10-4), VHL (FDR < 10- 4), PMS2 (FDR < 10-4), NBN (FDR < 10-3), PTCH (FDR < 10-3), MSH6 (FDR < 10-3), and BRCA2 (FDR < 10- 2). Protein pfam domain hit most by those mosaic mutations is Tryp_SPc (trypsin-like serine protease). The most affected pathways by mosaic mutations are TP53, cell cycle, RTK-RAS and PI3K pathways. By using 34 drug-gene mutation interaction database sources for clinically actionable pathogenic mutations, we identified drug candidates for most of mosaic pathogenic mutations in this study. Furthermore, by using pharmacogenomics approach through integrating drug sensitivity, genomic mutation and expression profiling data for 1200 human cancer cell lines, we validated the drug sensitivity and effectiveness of NVP-BEZ235 and temsirolimus for RB1, Camptothecin for TP53, and AZD8055 for NF1 and MSH2 mutated cancer cell lines. Taken together, this study elucidates pathogenic mosaic germline mutational landscape in breast cancer patients and also provides pharmacologists, clinicians, clinical oncologists and surgeons with fresh guidance for choosing candidate pharmaceutical drugs for carriers with pathogenic mosaic germline mutations and for diagnosing and treating them. However, the overwhelming complexity of the cancer genome suggests that we are in the earliest phases of interpreting molecular results and translating that data into knowledge that is useful to clinicians and to treat cancer patients. Many more cancer genomes need to be analyzed in order to achieve a deeper understanding of cancers and develop additional tools for molecular analysis. Additional clinical trials with molecular criteria conducted in adult and pediatric patients are needed. Optimal exploitation of all these data through integrated analyses across the different cancer types will lead to a comprehensive understanding of the genetic events that lie at the basis of tumor development and evolution. As a result, a comprehensive map of cellular alterations will benefit all cancer patients.

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