Somatic mutational landscapes of ductal and lobular breast carcinomas in the GENIE Cohort v8.1: real world actionable assessment in 8,756 patients

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Background

Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast typically present distinct clinicopathological characteristics and responsiveness to systemic therapies. In addition, breast cancer data from The Cancer Genome Atlas (TCGA) have shown these two pathological subtypes also present distinct genomic features when analyzed using DNA copy number arrays and whole exome sequencing platforms. More recently, the AACR Project GENIE Consortium, which is a publicly accessible international cancer registry of real-world data assembled through data sharing among leading cancer centers in the world, have allowed in-depth analyses of clinical actionability using patient-level data from clinical next-generation sequencing (NGS) assays. In this study, we assessed the somatic mutational landscapes of a large cohort (n = 8,756) of invasive breast carcinomas from 19 institutions participating in the GENIE Consortium Cohort (v8.1) and examine clinical actionability of unique mutations identified in each breast cancer subtype.

Methods

We assessed the eighth data release of the GENIE Consortium Cohort v8.1 (Fig. 1) comprising targeted sequencing data from 7,647 IDC and 1,209 ILC cases. Clinical features and somatic mutations including single-nucleotide variants, small indels, fusions, and copy number alterations (CNAs) were retrieved from cBioportal and SAGE Bionetworks. All patient samples were de-identified and encoded with GENIE sample codes. Gene actionability was examined using CIVIC, Cancers, and ESCAT publicly available knowledgebases.

Results

A gene enrichment analysis including 938 genes with point mutations and indels identified CDH1 (LR = 4.66, p = 3e-10), RHOC (LR = 2.81, p = 3e-10), PTEN (LR = 2.68, p = 2e-4), ERBB2 (LR = 1.80, p = 1e-10), TXK (LR = 1.72, p = 1e-10), FOXA1 (LR = 1.49, p = 2e-10) and RUNX1 (LR = 1.25, p = 3e-9) as genes significantly enriched in IDC tumors. On the other hand, mutations in GATA3 (LR = 1.67, p = 1e-10) and TP53 (LR = 1.55, p = 1e-10) were significantly enriched in ILC tumors (Fig. 2A, Table 1). A further mutational enrichment analysis for cognate mutations in 1129 genes showed amplification in PARP1 (LR = 1.55, p = 2e-3) and deep deletions in KLF4 (LR = 2.8, p = 2e-4) and CDH3 (LR = 1.88, p = 1e-4) as the most enriched genes with CNAs in IDC (Fig. 2B). In parallel, amplifications in ERBB2 (LR = 1.65, p = 1e-10), HNF (LR = 1.64, p = 1e-10), CDK2 (LR = 1.19, p = 1e-6), BRIP1 (LR = 2.66, p = 1e-10), CDK12 (LR = 1.55, p = 2e-6), PMP22 (LR = 3.15, p = 1e-10), RAD51C (LR = 2.85, p = 3e-8), AURKA (LR = 3.2, p = 1e-8) and deep deletion in CDKN2A (LR = 2.1, p = 1e-6) were enriched in IDC tumors (Fig. 2B, Table 2).

Conclusions

Real-world genomic data from the GENIE Consortium Cohort support that breast cancer presents distinct mutational landscapes for IDC and ILC tumors. For each histological subtype, we confirmed there are different levels of enrichments for shared mutations in actionable genes. Even though publicly available knowledgebases present curated information about commonly mutated genes in cancer, we noticed that actionability data for important cancer genes are still scarce.

References:


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