Receptor tyrosine kinase (RTK) pathways are aberrantly activated in cancer, and gain-of-function mutations and alterations in RTKs serve as attractive drug targets.

Comprising 20 families, the 58 known human RTKs each contain an extracellular domain (ECD), single transmembrane helix (TM), and cytoplasmic domain with juxtamembrane (JM) and C-terminal (CT) regulatory regions flanking a tyrosine kinase domain (TKD). A database of breast cancer patients treated at West Cancer Center (Memphis, TN) from 2013-2015 was reviewed.

Tumor profiling with next-generation sequencing (NGS) can reveal novel non-synonymous single nucleotide polymorphisms (nsSNPs) along RTKs' entire amino acid sequence that need further classification.

We sought to classify nsSNPs within RTKs among breast cancers identified by NGS.

**METHODS**

Institutional review board approval was obtained. A database of breast cancer patients treated at West Cancer Center (Memphis, TN) from 2013-2015 was reviewed.

**Inclusion Criteria:**
- Known ER, PR, HER2 status
- Received tumor profiling including NGS with a 592 cancer-related gene panel from Caris Life Sciences

Caris NGS interrogated 29 RTKs. All mutations test-defined as either pathogenic (PATH) or nsSNPs deemed variants of undetermined significance (VUS) were included. All variants had >99% detection confidence based upon allele frequency and amplicon coverage.

nsSNPs were arranged by amino acid location including the ECD, TM, JM, TKD, or CT.

In order to classify VUS, nsSNPs underwent in silico analysis using PolyPhen 2 (Harvard)3,4 to predict pathogenicity, denoted pnsSNP.

**RESULTS**

100% triple-positive patients (6/8 were pnsSNPs). 69% ER+/HER2- (18/35), 60% ER-/HER2+ (2/10) and 58% triple-negative (3/4) had RTK pnsSNPs.

ROS1 and ALK nsSNPs were most frequently seen in ER+/HER2- patients (9/10 were pnsSNPs) and triple-positive patients (3/4). ER-/HER2+ patients (0/2) and triple-negative patients (0/3) were less frequently seen.

**CONCLUSIONS**

- 66% of breast cancer patients carried ≥1 RTK nsSNP, with 35% patients harboring a predicted-damaging lesion (pnsSNP) following in silico analysis with PolyPhen 2.
- RTK nsSNPs were distributed in various breast cancer phenotypes and included frequent mutations in potentially actionable genes such as ROS1 and ALK.
- 26% (9/35) of ER+/HER2- patients had pnsSNPs in ROS1 or ALK.
- nsSNPs in the ECD or TKD were most frequent and also most likely to be damaging.

Novel RTK pnsSNPs identified in breast cancer patients warrant further classification and collaboration.

**REFERENCES**


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