Kataegis in clinical and molecular subgroups of primary breast cancer

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Conclusion[5]

Kataegis is a common hypermutation phenomenon in established breast cancer subgroups, particularly in HER2p subgroups, coinciding with an aggressive tumor phenotype in ERpHER2n disease. In TNBC, the molecular implications and associations of kataegis are less clear, including its prognostic value.

Background[1,2]

- Kataegis is a hypermutation phenomenon characterized by localized clusters of single base pair substitution (SBS) reported in multiple cancer types. Despite a high frequency in breast cancer, large scale analyses of kataegis patterns and associations with clinicopathological and molecular variables in established breast cancer subgroups are lacking.

- This study aimed to comprehensively describe, characterize, and analyse the association of kataegis with clinicopathological and molecular factors, transcriptional patterns, and patient outcome with a focus on established **clinical** and **molecular** subgroups defined by ER, PR, HER2, PAM50, and homologous recombination deficiency (**HRD**) status.

Method[4,5]

- WGS profiled primary breast cancers (n=791) with associated clinical and molecular data layers like RNA-sequencing data were analyzed.

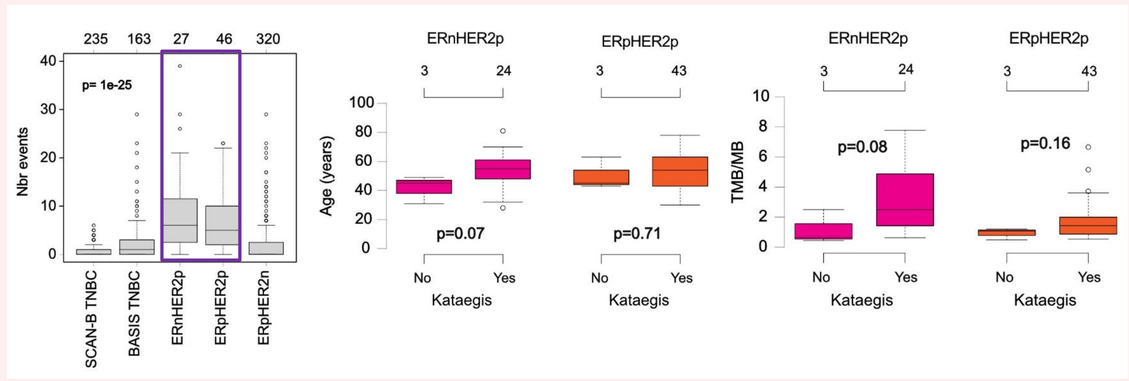
- Kataegis frequency, recurrence, and associations with genomic contexts and functional elements, transcriptional patterns, driver alterations, homologous recombination deficiency (HRD), and prognosis were investigated in tumor subgroups defined by ER, PR, and HER2/ERBB2 status.

Clinicopathological information, molecular subtype, and HRD status per cohort

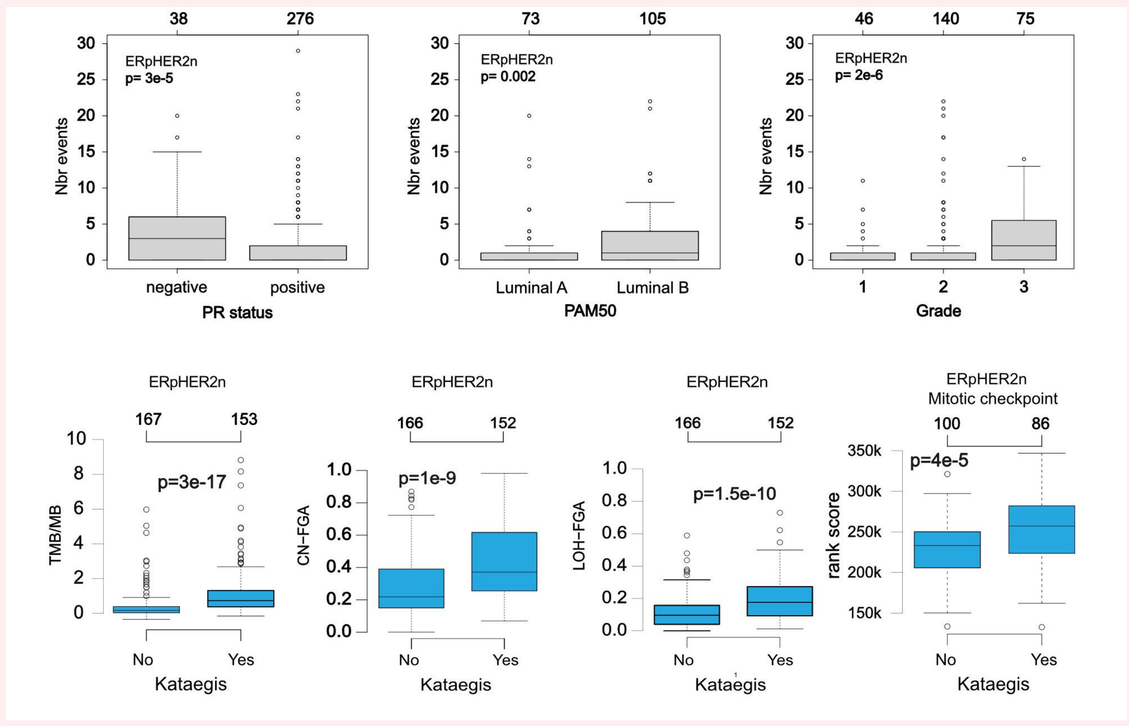
Feature	SCANB TNBC	BASIS TNBC	BASIS ERpHER2n	BASIS HER2-positive
Number of samples with WGS	100% (235)	100% (163)	100% (320)	100% (73)
Number of RNA-sequenced tumors	100% (235)	44.8% (73)	58.1% (186)	5.5% (4)
Clinical subgroups				
TNBC	100% (235)	100% (163)	0% (0)	0% (0)
ER-positive & HER2-negative (ERpHER2n)	0% (0)	0% (0)	100% (320)	0% (0)
ER-positive & HER2-positive (ERpHER2p)	0% (0)	0% (0)	0% (0)	63% (46)
ER-negative & HER2-positive (ERnHER2p)	0% (0)	0% (0)	0% (0)	37% (27)
PAM50 subtypes				
Basal-like	79.9% (187)	83.6% (61)	0.5% (1)	25% (1)
HER2-enriched (HER2E)	14.5% (34)	8.2% (6)	2.2% (4)	0% (0)
Luminal A	2.1% (5)	1.4% (1)	39.2% (73)	25% (1)
Luminal B	0.4% (1)	4.1% (3)	56.5% (105)	50% (2)
Normal-like	3.0% (7)	2.7% (2)	1.6% (3)	0% (0)
HRD-negative	40.9% (96)	51.5% (84)	91.6% (293)	95.9% (70)
HRD-positive	59.1% (139)	48.5% (79)	8.4% (27)	4.1% (3)

Results

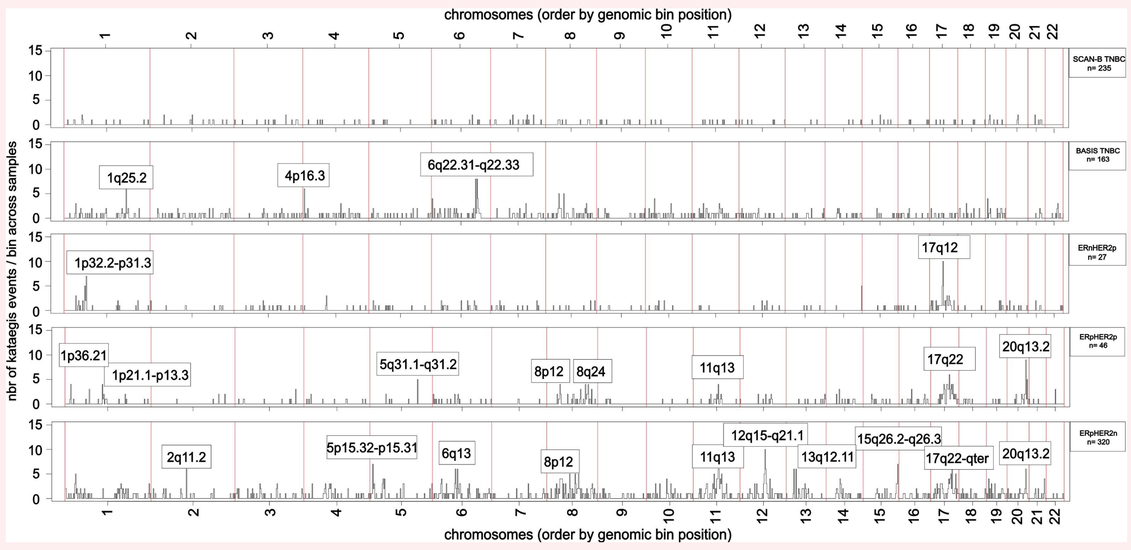
- Kataegis frequency was **highest in the HER2-positive(p)** subgroups, including both ER-**negative**(n)/**positive**(p) tumors (ERn/p HER2p), regardless of age and tumor mutational burden (TMB).



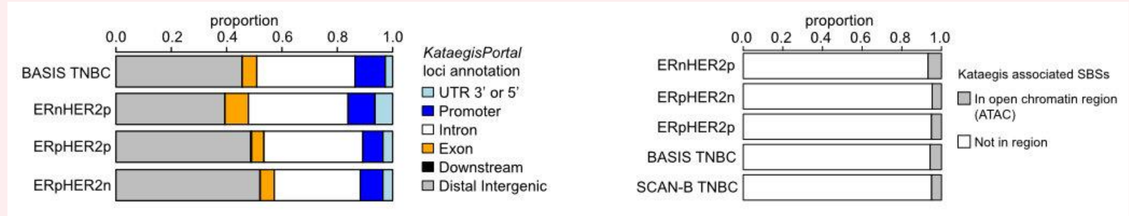
- In ERpHER2n tumors, kataegis was associated with aggressive characteristics including **PR-negativity**, **molecular Luminal B subtype**, **higher grade**, **higher mutational burden**, **and expression of proliferation-associated genes**.



- Recurrent kataegis loci frequently targeted regions commonly amplified in ERp tumors, while few recurrent loci were observed in TNBC.



- SBSs in kataegis loci appeared enriched in regions of open chromatin.



References

1. Koh G, Degasperi A, Zou X, Momen S, Nik-Zainal S: **Mutational signatures: emerging concepts, caveats and clinical applications.** *Nat Rev Cancer* 2021, **21:**619-637.
2. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, BehjaM S, Biankin AV, et al: **Signatures of mutational processes in human cancer.** *Nature* 2013, **500:**415-421.
3. Staaf J, Glodzik D, Bosch A, Vallon-Christersson J, Reutersward C, Hakkinen J, et al: **Whole-genome sequencing of triple-negative breast cancers in a population-based clinical study.** *Nat Med* 2019, **25:**1526-1533.
4. Nik-Zainal S, Davies H, Staaf J, Ramakrishna M, Glodzik D, Zou X, et al: **Landscape of somatic mutations in 560 breast cancer whole-genome sequences.** *Nature* 2016,**534:**47-54.
5. Veerla et al. Preprint: https://www.researchsquare.com/article/rs-3831383/v1. **IN PRESS NPJ BREAST CANCER**.

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Study sponsored by the Swedish Research Council and the Swedish Cancer Society