

The clinical impact of somatic variants in genes involved in resistance to trastuzumab therapy in HER2-positive breast cancer

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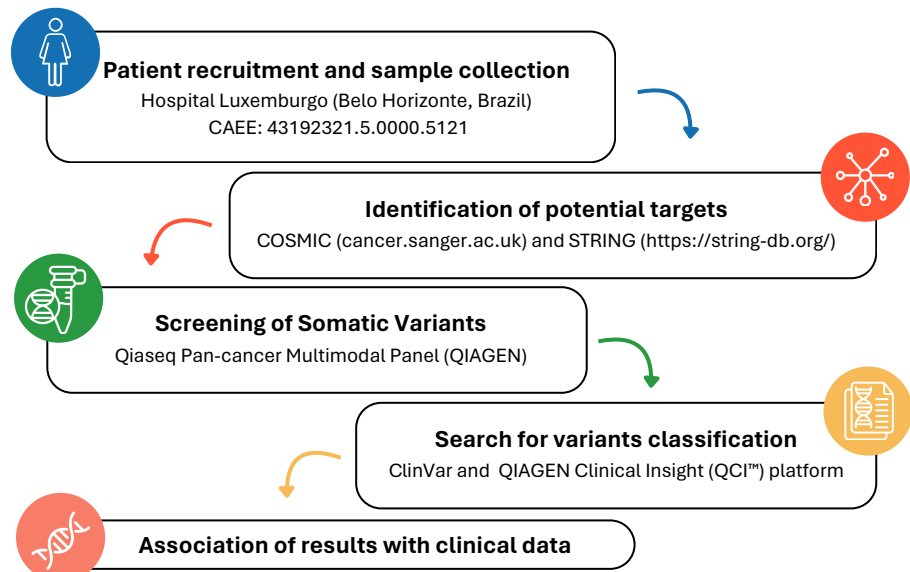
INTRODUCTION

The human epidermal growth factor receptor 2 (HER2) is overexpressed or amplified in approximately 15–20% of breast cancer (BC) cases and is associated with a poor prognosis. The treatment of these types of BC is based on trastuzumab, a monoclonal antibody that specifically targets HER2¹. This biological agent inhibits tumor cell proliferation and induces apoptosis through multiple mechanisms of action. Despite being used for years, some patients have intrinsic or acquired resistance to this treatment. Mutations in *PIK3CA* and *PTEN* genes, along with alterations in other components of the HER2 receptor signaling network, have been recognized as key molecular mechanisms contributing to trastuzumab resistance^{2,3}.

OBJECTIVE

This study aimed to investigate the *in silico* clinical impact of somatic variants in genes involved in resistance to trastuzumab therapy in HER2-positive BC.

METHODS



RESULTS AND DISCUSSION

Four patients with invasive ductal carcinoma were evaluated, with a mean age of 50.5 years (range 45–55). All had tumors classified as Luminal B/HER2-positive and received trastuzumab therapy. The sequencing data identified 162 variants across 15 genes (*PIK3CA*, *TP53*, *MTOR*, *ERBB2*, *AKT1*, *PTEN*, *EGFR*, *IGF1R*, *CCND1*, *CDK4*, *CDK6*, *SRC*, *BCL2*, *CDKN1B* and *ERBB3*), including 134 missense, 13 intronic, 13 stop-gain, one frameshift, and one 3'UTR variant (Figure 1).

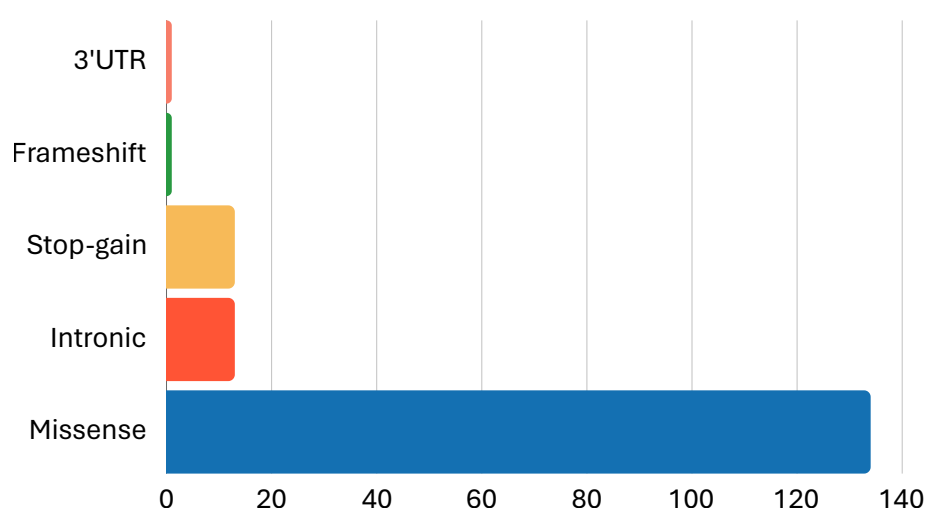


Figure 1 – Molecular consequences of the identified variants.

The search for classification in ClinVar revealed 17 variants of uncertain significance (VUS), four variants with conflicting impact, two benign variants, and two pathogenic variants (both in the *TP53*). However, 137 variants are not yet reported in the database (Figure 2a). In parallel, the QCI™ platform classified two benign variants, six pathogenic variants, and 141 VUS. In addition, 13 variants not previously reported in ClinVar were classified as likely pathogenic (Figure 2b).

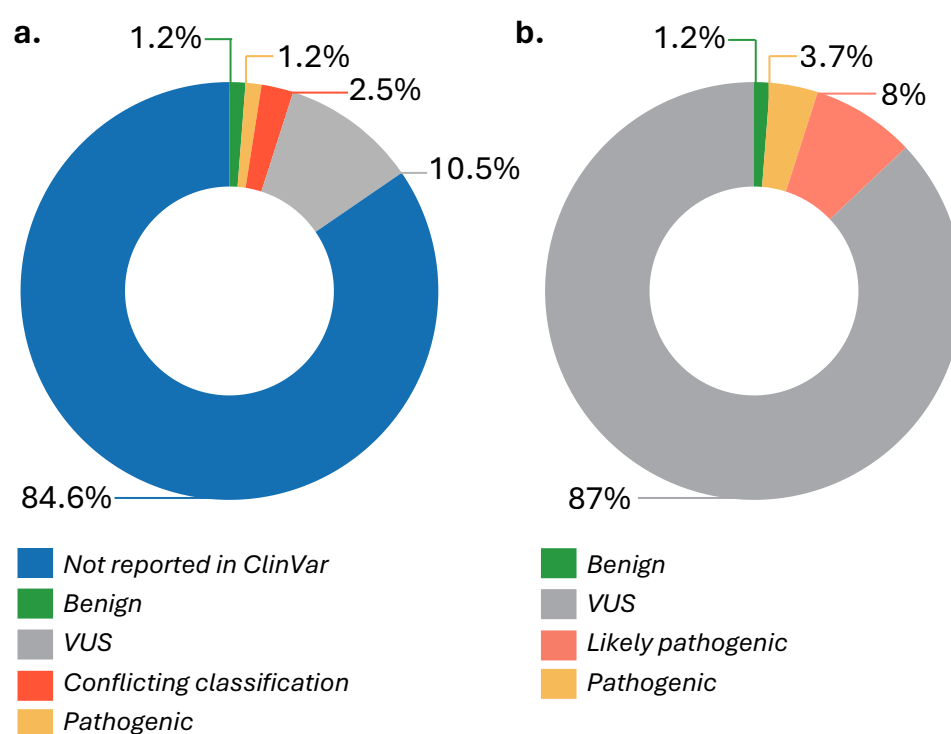


Figure 2. Pathogenicity classification of variants according to Clinvar (a) and QCI™ platform (b).

Of the 19 pathogenic/likely pathogenic variants, 18 were detected in patient PCM-11, who experienced disease recurrence. Among these, seven were located in the *TP53* gene, including five pathogenic variants (p.R282Q, p.R158C, p.P151S, p.P98S, and p.S241F). A single variant (*TP53* p.S247F) was identified in PCM-53, who reported a family history of breast cancer in her sister. Given that *TP53* mutations occur in approximately 30% of BC cases and are associated with poor prognosis and therapy resistance^{4,5}, these findings underscore the clinical importance of *TP53* alterations.

CONCLUSION

In summary, further research is needed to validate the clinical significance of the identified variants, as this may contribute to the development of a genetic signature of trastuzumab resistance in HER2-positive breast cancer. Furthermore, this highlights the importance of integrating and expanding variant classification information to advance the understanding of clinical significance.

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REFERENCES

