CASE REPORT

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A CASE REPORT: A RARE *CASR* MUTATION ASSOCIATED WITH HER2-POSITIVE BREAST CANCER

Although highly penetrant genes such as *BRCA1, BRCA2, TP53, PALB2, CHEK2,* and *ATM* are well known in hereditary breast cancer, genes with low penetrance may also contribute to the disease risk. The *CASR* (Calcium-Sensing Receptor) gene, located on chromosome 3q13.3–q21, encodes a G-protein-coupled receptor that regulates calcium homeostasis and parathyroid hormone secretion. Here we describe the clinical course and genetic findings in a breast cancer patient diagnosed with HER2-positive (HER2/neu +++) and ER/PR-negative infiltrating ductal carcinoma with a rare *CASR* mutation and explore its potential role in the hereditary breast cancer predisposition. Next-generation sequencing revealed a heterozygous *CASR* variant, c.2265G>T (p.Glu755Asp), classified as a variant of uncertain significance (VUS). No pathogenic mutations were found in *BRCA1/2, CHEK2,* or *PALB2*. The patient underwent neoadjuvant chemotherapy, right-sided mastectomy, and trastuzumab therapy, achieving complete pathological regression (pCR) with no recurrence after ten months of follow-up. Although the *CASR* p.Glu755Asp variant's pathogenic role is unproven, emerging evidence links *CASR* overexpression with HER2-positive breast cancers, promoting tumor progression via calcium-dependent signaling pathways (PI3K/AKT, MAPK). This case highlights the potential role of *CASR* as a low-penetrance susceptibility gene in breast cancer and supports further functional and genomic studies to clarify its clinical impact.

Keywords: breast cancer, family history, *CASR* gene mutation, HER2+++, trastuzumab, Ukraine.

Breast cancer (BC) remains one of the most commonly diagnosed cancers in women worldwide. The familial and hereditary components account for approximately 5—10% of all BC cases. Mutations in various genes can lead to the development of BC by disrupting the regulation of cell growth, division, and apoptosis. The most well-known of these include *BRCA1, BRCA2, TP53, PALB2, CHEK2,* and *ATM*, which are associated with hereditary forms of the disease [1, 2]. Additionally, other genes with low or moderate penetrance may also contribute to the BC risk, especially when combined with the environmental factors [3].

The *CASR* (Calcium-Sensing Receptor) gene is currently considered a low-penetrance gene and is not classified among the major high-risk BC susceptibility genes [4, 5]. The *CASR* gene is located on chromosome 3q13.3–q21. It encodes a G-pro-

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tein-coupled receptor that plays a pivotal role in maintaining calcium homeostasis by regulating parathyroid hormone (PTH) secretion and renal calcium reabsorption [6]. The pathogenic mutations in *CASR* are associated with such conditions as familial hypocalciuric hypercalcemia (FHH), familial isolated hyperparathyroidism, chronic pancreatitis, and idiopathic generalized epilepsy [7].

This report aims to describe the clinical course and genetic findings in a BC patient with a rare *CASR* gene mutation and to explore the potential role of *CASR* in hereditary BC predisposition.

Case presentation

Patient C., a 50-year-old woman from a small town in Ukraine, presented with symptoms in May 2022 and was diagnosed with BC in June 2022. On May 31, 2022, a core needle biopsy of the breast was performed. The histology report (No. 26305), dated June 1, 2022, confirmed the infiltrating Grade 2 (G2) ductal carcinoma. The immunohistochemistry results, dated June 09, 2022, showed that the estrogen receptor (ER) and progesterone receptor (PR) were negative, c-erbB2 (Her2/neu) was strongly positive (+++), and the Ki-67 proliferation index was 20%. The chest X-ray, dated May 30, 2022, and the hepatobiliary ultrasound, dated June 01, 2022, revealed no malignant lesions. The heart ultrasound performed on June 13, 2022, showed the heart chambers to be within normal limits. The global segmental contractility was preserved. No pathological abnormalities were detected. The function of the atrioventricular valves was intact.

The patient's medical history revealed no previous history of chickenpox, tuberculosis, or sexually transmitted diseases. The woman had no known allergies to medications or vaccines. Written informed consent was obtained from the patient for the publication of the depersonalized case report and any accompanying data. The patient was fully informed about the purpose of the study, the use of her anonymized medical information, and her right to withdraw consent at any time without affecting her medical care. All procedures were conducted in accordance with the Declaration of Helsinki and the relevant institutional ethical standards.

Menstruation started at the age of 13 and lasted up to five days. It was regular until the age of 49, with a cycle of approximately 28 days. Reproductive history: 1st and 2nd pregnancies — medical abortion, 3rd pregnancy (at the age of 42) — a healthy girl, who was five years old at the time of the mother's diagnosis. Her family history revealed two maternal aunts affected by BC: one who died at the age of 50 and the other who survived up to the age of 80 following surgical treatment performed two decades earlier (Fig. 1). In the patient's family, both parents died of stroke at the ages of 80 and 82, and her maternal aunt died at the age of 70. Her paternal uncle died at the age of 64 from thrombosis.

The woman worked for over 25 years as a timekeeper in an office at a mine, where she was exposed to harmful environmental factors, including poor ventilation and lighting, background industrial noise, vibrations, and dust in the office area. Although the work was office-based, it was not entirely free from environmental hazards. The main harmful factors for the patient included visual strain, immobility, stress, and potentially adverse microclimate conditions.

The physical examination revealed a satisfactory general condition, normal body habitus, and adequate nutritional status (weight 70 kg, height 168 cm, BMI 24.8). Skin and visible mucous membranes were unremarkable. The vesicular breath sounds were auscultated bilaterally in the lungs. The heart sounds were clear and rhythmic. Blood pressure was 120/90 mmHg, pulse 69 bpm, and body temperature 36.6 °C. The patient's ECOG performance status was 1. The abdomen was soft and non-tender on palpation; the liver and spleen were not palpable. The bowel movements were physiological and normal. The indicators of complete blood count, blood biochemical analysis, and urinalysis were within normal limits.

Molecular genetic testing by NGS, performed at the Invitae Clinical Laboratory (USA) in July 2022, revealed the heterozygous carrier status for a variant in the *CASR* gene within a multiple-gene panel of 93 analyzed genes (including *ATM, BRCA1/2, CDH1, CHEK2, NBN, NF1, PALB2, RAD51C, STK11, TP53*, etc.). The panel content was defined by the laboratory according to current clinical knowledge and established gene-disease associations. While expanded panels may detect additional variants, their clinical relevance and interpretability may be limited. The selected panel was therefore deemed suitable for the study objectives. The specific mutation identified

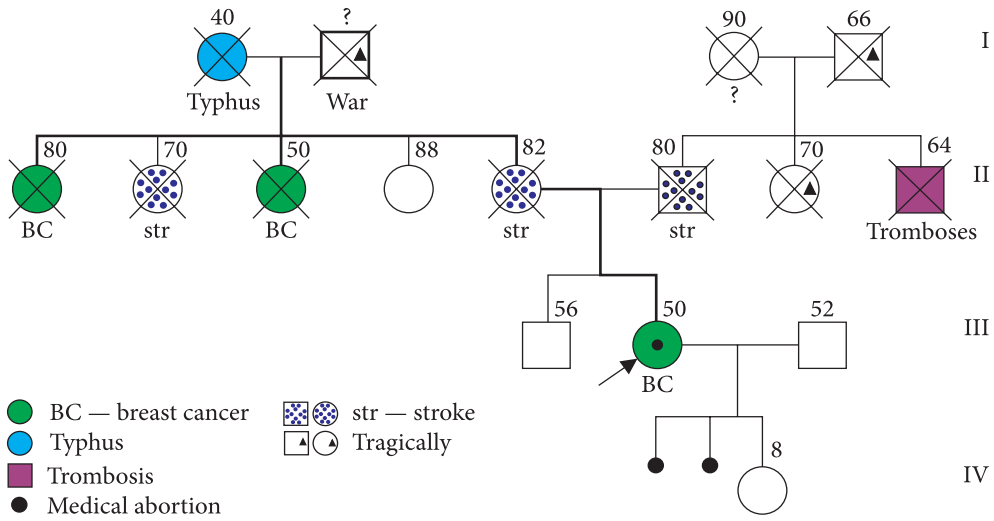

Fig. 1. Family tree of a female BC patient carrying a *CASR* gene mutation

was c.2265G>T in the *CASR* gene, resulting in a missense substitution: p.Glu755Asp. No pathogenic variants were detected in the *BRCA1, BRCA2, CHEK2,* and *PALB2* genes. The *CASR* variant (Table) identified has not been conclusively associated with BC and is currently classified as a Variant of Uncertain Significance (VUS).

Between June 16 and August 18, 2022, four cycles of neoadjuvant chemotherapy (NACHT) were performed, consisting of endoxan 600 mg/m² IV and epirubicin 75 mg/m² IV every three weeks. From September 8 to September 29, 2022, the patient received two cycles of paclitaxel at a dose of 175 mg/m² IV every three weeks. One month later, from October 20 to November 10, 2022, two cycles of docetaxel at a dose of 80 mg/m² IV every three weeks were administered. The side effects of chemotherapy included nausea (Grade 1) and hair loss (Grade 3).

After NACHT, the patient underwent a computed tomography (CT) scan of the chest at the end of October 2022 (Fig. 2). On preoperative CT in axial (*a*), coronal (*b*), and sagittal (*c*) reconstructions on the border of the upper quadrants of the right breast, approximately at 11—12 o'clock on the conventional dial, a small focus of 11 × 8 × 10 mm of irregular shape, low-intensity accumulation of contrast with fuzzy contours and a homogeneous structure was visualized. The low degree of contrast enhancement of the formation was a result of the therapy (arrow). In the right axillary region, several lymph nodes measuring 6 × 5 × 6 mm were visible (in dynamics, compared with mammography, they decreased) (thick arrow).

A simple unilateral right-sided mastectomy and radical axillary lymph node dissection were performed on December 9, 2022. Histological examination on December 20, 2022, revealed nipple tissue without pathological features and breast tissue with fibrosis. Ten lymph nodes demonstrated sinus histiocytosis, consistent with complete pathological regression (pCR). Diagnosis: right BC, clinical stage cT3cN1M0 (stage IIIA), pathological stage after NACHT — ypT0ypN0M0.

A bone scan on November 03, 2023, revealed no metastasis in the bones.

From November 2022 to December 2023, the patient received 17 intravenous injections of trastuzumab 6 mg/kg every three weeks (the first dose was 8 mg/kg). Trastuzumab, a targeted therapy, was prescribed for the treatment of HER2+++ BC to specifically block tumor growth, enhance treatment effectiveness, reduce the risk of recurrence after surgery, and improve overall survival.

CT scan performed on April 5, 2024: Findings indicated a condition after combined treatment (NACHT and right-sided mastectomy with radical removal of lymph nodes in the axillary cavity) for right breast cancer, stage pT3N0M0. No signs of local recurrence were detected at the time of examination. Additionally noted were a cyst in the upper posterior mediastinum (possibly enterogenic), functional gallbladder disorders, dolichosigma, and degenerative changes in the spine consistent with spondylosis. A focus of enostosis was observed in the body of L3 and in the left lateral masses.

After ten months, the patient's condition was satisfactory, with laboratory results showing normal

values. A CT scan was performed on February 21, 2025: Findings indicated a condition after combined treatment (NACHT and right-sided mastectomy, radical removal of lymph nodes in the axillary cavity) for right breast cancer, pT3N0M0. Fig. 3 shows the results of a postoperative CT scan of the chest in axial (*a*), coronal (*b*), and sagittal (*c*) projections, where no pathological formations were detected along the postoperative scar. CT findings: Status after NACT, right-sided mastectomy, and radical removal of lymph nodes in the right axillary fossa. The postoperative scar changes in the right axillary area. No enlarged cervical, supraclavicular, infraclavicular, or axillary lymph nodes were visible. No signs of local recurrence were detected at the time of examination. Additional findings included functional disorders of the gallbladder, a small liver cyst, a dolichosigmoid, and degenerative changes in the spine consistent with spondylosis. The focus of enostosis was observed in the body of L3 and in the left lateral masses. Compared to the previous CT scan, no negative dynamics were observed. At the time of the examination in October 2025, the patient was in remission, her weight was 67 kg, BMI was 23.7.

Discussion

This case report, although demonstrating a potential association between a rare *CASR* mutation and BC, has several important limitations. First, the identified *CASR* variant (c.2265G>T, p.lu755Asp) is classified as a VUS, and to date, there is no direct evidence of its pathogenicity or functional impact on the receptor. Second, we were unable to perform family sequencing to determine whether the mutation was inherited and whether other family members, especially the patient's daughter (due to the cost of the analysis) or similarly diagnosed relatives (who were deceased at the time of the proband's diagnosis), limited our ability to define the role of *CASR* in the familial oncogenetic context.

The identification of a heterozygous *CASR* c.2265G>T (p.Glu755Asp) variant in this patient, currently classified as a VUS, raises intriguing questions regarding its potential oncological relevance. Although no direct association between this specific mutation and BC has been previously reported, emerging evidence underscores the pathophysiological role of *CASR* in tumor progression and metastasis, particularly in breast malignancies.

While pathogenic *CASR* mutations are primarily associated with disorders such as FHH and autosomal dominant hypocalcemia, emerging data indicate that *CASR* signaling may play a role in the development and progression of several cancers, including BC [11—13]. CASR activation may be a potent therapeutic target to reduce chemotherapy-associated diarrhea [14].

In BC models, the overexpression of CASR enhances osteolytic metastasis and tumor migration through the activation of the PTH-related protein (PTHrP)–Ca^{2+}–CaSR axis, forming a positive feedback cycle that promotes bone invasion via PTHrP secretion [15, 16]. This mechanism aligns with clinical observations showing higher CASR expression in HER2+++ carcinomas, similar to the strong (+++) HER2/neu status in our patient, and associates with higher Ki-67 and nodal involvement. At

Key molecular annotation of *CASR* c.2265G>T (p.Glu755Asp)

Parameter	Description	Source
Gene	*CASR* (Calcium-Sensing Receptor)	https://www.genenames.org
Variant (cDNA)	c.2265G>T	NGS assay (Invitae)
Protein Change	p.Glu755Asp	https://www.uniprot.org
Variant Type	Missense	Sequence analysis
Population Frequency	Rare variant	Karczewski et al. [8] https://gnomad.broadinstitute.org
ClinVar Classification	Variant of Uncertain Significance (VUS)	Landrum et al. [9] https://www.ncbi.nlm.nih.gov/clinvar
ClinGen Interpretation	No validated association with breast cancer	https://clinicalgenome.org
ACMG/AMP Classification	Variant of Uncertain Significance	Richards et al. [10]
Clinical Significance	Uncertain; no direct clinical implication	Consensus interpretation

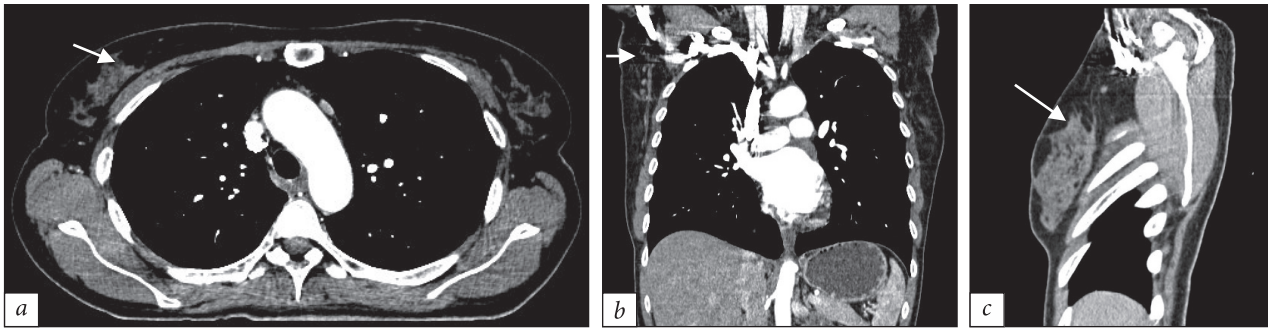

Fig. 2. Computed tomography scan of the chest in axial (*a*), coronal (*b*), and sagittal (*c*) reconstructions at the level of the upper quadrants of the right breast in a woman with breast cancer after neoadjuvant chemotherapy. A small lesion measuring 11 × 8 × 10 mm with an irregular shape, low-intensity contrast enhancement, indistinct margins, and a homogeneous internal structure is visualized

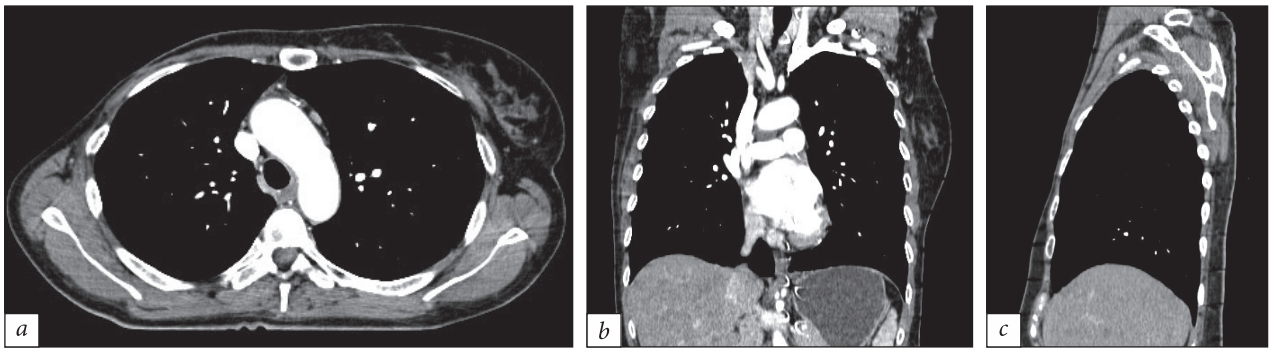

Fig. 3. Postoperative computed tomography scan of the chest in axial (*a*), coronal (*b*), and sagittal (*c*) views along the course of the postoperative scar. No pathological formations were detected. Condition after NACT, right-sided mastectomy, and radical excision of the lymph nodes in the right armpit

the cellular signaling level, CASR stimulates the Gβγ–PI3K–AKT–mTORC2–Rac pathway, enhancing cancer cell migration and survival [17]. This oncogenic signaling may synergize with HER2 pathways in HER2+++ tumors, further amplifying invasive and metastatic behavior. Furthermore, CASR activation can stimulate the PI3K/AKT and MAPK signaling pathways, which are critical for breast cancer cell survival and invasion [13].

In breast tumors, CASR appears to promote proliferation and inhibit apoptosis via intracrine PTHrP mechanisms, thereby enhancing survival in calcium-rich microenvironments, such as bone [13]. Given the patient's HER2+++ status, the presence of a *CASR* variant might hypothetically contribute to tumor aggressiveness or influence the therapeutic response, particularly in calcium-rich environments or in the context of bone microenvironments.

Importantly, this patient had a positive family history of BC on the maternal side, with two aunts affected, although no *BRCA1/2* mutations were detected. This observation is compatible with a multifactorial model of disease, in which genetic predisposition may involve variants outside the classical high-penetrance genes. Within this framework, the *CASR* c.2265G>T (p.Glu755Asp) variant may be interpreted cautiously as a component of background genetic variability with potential low-penetrance effects rather than an independent pathogenic alteration. Rare variants of uncertain significance could hypothetically influence disease susceptibility or clinical heterogeneity through interactions with other genetic and environmental factors. The aggregation of complex disorders observed in the family is consistent with this polygenic and multifactorial paradigm.

A mutation in the *CASR* gene does not protect, but rather contributes to the development of stroke damage [18]. Therefore, in the proband's pedigree, the mother and her sister died of stroke. It is possible that they were also carriers of the mutation in this gene.

Importantly, while studies to date have focused on CASR expression and signaling, the functional consequences of rare *CASR* missense mutations —

like p.Glu755Asp — remain unclear. The p.Glu755Asp substitution, located in the intracellular C-terminal region, could plausibly alter \the receptor conformation or downstream coupling, similar to other clinically significant *CASR* mutants [19]. Finally, while *BRCA1/2* were negative, the identification of this novel *CASR* variant expands the genetic inquiry beyond classical susceptibility genes. It exemplifies the value of comprehensive sequencing approaches in uncovering rare variants with unclear but potentially actionable implications.

This case highlights the potential role of rare *CASR* mutations in BC, particularly among HER2+++ patients with a familial history but no mutations in genes with high penetrance, *BRCA1/2, CHEK2,* and *PALB2.* Although the p.Glu755Asp variant remains a VUS, the biological plausibility of *CASR* involvement in BC pathogenesis, through calcium signaling and metastatic progression, requires further investigation. Functional studies and the inclusion of *CASR* in broader BC gene panels may provide new insights into risk assessment and the development of targeted treatment strategies.

To establish a definitive causal relationship between *CASR* mutations and the development of HER2+++ BC, future multicenter studies with large patient cohorts, detailed bioinformatic analyses of *CASR* variants, and investigations of *CASR* expression in HER2+++ tumors are necessary. These efforts will enhance our understanding of the calcium receptor's potential role in breast carcinogenesis and its value as a biomarker or therapeutic target.

Conflict of interest

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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ВИПАДОК РІДКІСНОЇ МУТАЦІЇ *CASR*, ПОВ'ЯЗАНОЇ З HER2-ПОЗИТИВНИМ РАКОМ ГРУДНОЇ ЗАЛОЗИ

Гени з високою пенетрантністю, такі як *BRCA1, BRCA2, TP53, PALB2, CHEK2* та *ATM*, добре відомі при спадковому раку грудної залози, на відміну від генів з низькою пенетрантністю, котрі теж можуть відігравати важливу роль у підвищенні ризику захворювання. Ген *CASR* (Calcium-Sensing Receptor), розташований на хромосомі 3q13.3–q21, кодує рецептор, пов'язаний із G-білком, який регулює гомеостаз кальцію та секрецію паратиреоїдного гормону. В цьому повідомлені описано клінічний перебіг і генетичні особливості в пацієнтки з раком грудної залози, у якої виявлено рідкісну мутацію гена *CASR* та проаналізовано потенційну роль цього гена у спадковій схильності до розвитку раку грудної залози. Секвенування нового покоління (NGS) виявило гетерозиготний варіант *CASR* c.2265G>T (p.Glu755Asp), класифікований як варіант невизначеної значущості (VUS). Патогенних мутацій у *BRCA1/2, CHEK2* або *PALB2* не виявлено. Пацієнтка отримала неоад'ювантну хіміотерапію, їй проведено правобічну мастектомію та терапію трастузумабом. Вона досягнула повної патологічної регресії (pCR) без рецидиву впродовж 10 місяців спостереження. Незважаючи на відсутність доведеного патогенного значення варіанта *CASR* p.Glu755Asp, наявні дані свідчать, що надмірна експресія *CASR* може сприяти прогресуванню HER2-позитивного раку грудної залози через кальцій-залежні сигнальні шляхи (PI3K/AKT, MAPK). Представлений випадок підкреслює потенційну роль *CASR* як гена схильності з низькою пенетрантністю та обґрунтовує необхідність подальших функціональних і геномних досліджень для визначення його клінічного значення.

Ключові слова: рак грудної залози, сімейний анамнез, мутація гена *CASR*, HER2+++, трастузумаб, Україна.