# INVESTIGATION OF THE EFFECT OF WWOX AND WBP2 GENE REGULATION ON TAMOXIFEN RESISTANCE IN BREAST CANCER USING THE CRISPR/CAS9 METHOD


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## THESIS ABSTRACT


Breast cancer, particularly the estrogen receptor-positive (ER+) subtype, is one of the most common types of cancer in women, and Tamoxifen therapy is widely used for this disease. However, the development of resistance to this treatment over time remains a significant issue. The Hippo signaling pathway, which regulates cell proliferation, apoptosis, and stem cell properties, is associated with cancer development and drug resistance. The *WWOX* gene is part of the Hippo pathway and plays a tumor-suppressive role in various cancers. However, the relationship between *WBP2* and Tamoxifen resistance is not yet fully understood.
In this study, the effects of *WWOX* and *WBP2* gene regulation on Tamoxifen resistance were investigated using the CRISPR/Cas9 gene editing method. Experiments conducted on MCF-7 and Tamoxifen-resistant MCF-7 cell lines showed that *YAP/TAZ* expression increased in *WWOX* knockout cells, and this was found to be associated with EMT. Conversely, the overexpression of *WWOX* increased Tamoxifen sensitivity and inhibited the EMT process by suppressing invasion. The overexpression of *WBP2* accelerated the G1/S transition, increasing cell proliferation and suppressing apoptosis. In conclusion, low expression of *WWOX* and high expression of *WBP2* contributed to Tamoxifen resistance by affecting the Hippo pathway. These findings suggest that *WWOX* and *WBP2* genes could be potential therapeutic targets for overcoming Tamoxifen resistance. Developing treatment strategies targeting the Hippo pathway could offer new approaches to overcoming Tamoxifen resistance in ER+ breast cancer patients.


## APPLICATION AREAS OF THE THESIS RESULTS

The *WWOX* gene is a tumor suppressor, and its interaction with *WBP2* is associated with Tamoxifen resistance and *YAP/TAZ* activation in cancer cells. The reduction in *WWOX* expression plays a critical role in the progression of aggressive tumors. Reactivating *WWOX* and inhibiting the effects of *WBP2* could increase sensitivity to treatment, especially in patients resistant to hormone therapy. *WWOX* and *WBP2* influence cancer progression through the Hippo pathway. These genes play a critical role in overcoming drug resistance and serve as prognostic biomarkers in cancer treatment. Particularly, *WWOX* offers potential for personalized treatment strategies by inhibiting the EMT process.

## ACADEMIC ACTIVITIE

**Projects Contributing to the Thesis**:
**Ltp-Bap**: Innovative CRISPR/Cas9-based approaches for overcoming drug resistance mechanisms related to the Hippo pathway in estrogen receptor-positive breast cancer.
**Tüseb-Acil-A**: Investigation of the effects of CRISPR/Cas9-mediated regulation of WWOX and WBP2 genes on Tamoxifen resistance in estrogen receptor-positive breast cancer.
**Tüseb-YI**: Investigation of acquired Tamoxifen resistance in estrogen receptor-positive breast cancer cells with suppressed WWOX and WBP2 genes using transcriptomic analysis.
**The role of the WWOX tumor suppressor gene in the regulation of EMT process in breast cancer Tamoxifen resistance**,
Ebrucan Bulut, Pelinsu Kupeli, Nuseybe Huriyet, Batuhan Topuz, Rumeysa Fatma Balaban, Havva Tezcan Unlu, Unal Egeli, Gulsah Cecener, *EACR The Tumour Ecosystem Cellular Interactions and Therapeutic Opportunities*, 2024, Bergamo, Italy.
**The relationship between the WWOX gene and the Hippo signaling pathway in Tamoxifen resistance**,
Ebrucan Bulut, Gulsah Cecener, Mustafa Sehsuvar Gokgoz, Guven Ozkaya, Hulya Ozturk Nazlıoglu, Unal Egeli, *18th Medical Biology and Genetics Congress*, 2024, Ankara, Turkey.
**CRISPR-Cas9-mediated WBP2 knockout modulates Tamoxifen resistance in estrogen receptor-positive breast cancer cells via the Hippo pathway**, Ebrucan Bulut, Gulsah Cecener, Nuseybe Huriyet, Rumeysa Fatma Balaban, Mustafa Sehsuvar Gokgoz, Hulya Ozturk Nazlıoglu, Guven Ozkaya, Unal Egeli, *The CRISPR Medicine Conference*, 2024, Copenhagen, Denmark.
**Patent**
**Çeçener G., Bulut E.**: *The use of WBP2 as a prognostic and predictive biomarker in Tamoxifen resistance in breast cancer*, Patent, Section A Human Needs, Application Number: 2023/019772, Standard Registration, 2023.

## KEY WORDS

✓ EMT
✓Hippo pathway
✓ WWOX
✓ WBP2
✓ ER+

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