

## Gene Section

### Mini Review

# WWOX (WW domain containing oxidoreductase)

Teresa Druck, Hoda Hagrass, Kay Huebner

Department of Molecular Virology, Immunology, and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio, USA

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## Identity

**Hugo:** WWOX

**Other names:** FOR; murine name WOX1

**Location:** 16q23.1

## DNA/RNA

### Description

WWOX is comprised of 9 coding exons in a region of approximately one million base pairs that includes the common fragile site FRA16D.

### Transcription

RT-PCR amplification of *Wwox* in normal and tumor cDNA samples has shown products apparently originating from alternative transcripts or transcript variants, respectively. Expressed truncated proteins have not been detected.

### Pseudogene

None reported.

## Protein

### Description

WWOX is a 414 amino acid protein that contains two WW domains and a short-chain dehydrogenase/reductase (SDR) domain.

### Expression

WWOX is highly expressed in secretory epithelial cells

of reproductive, endocrine and exocrine organs and is expressed in all or most other tissues at a lower level. The protein is not expressed or is expressed at low level in many tumor types, including breast, pancreatic, gastric, hepatocellular, ovarian, lung and prostate cancers. Loss of WWOX expression can be due to inactivation by promoter methylation, allelic deletion or a combination of these mechanisms.

### Localisation

Cytoplasm, mitochondria.

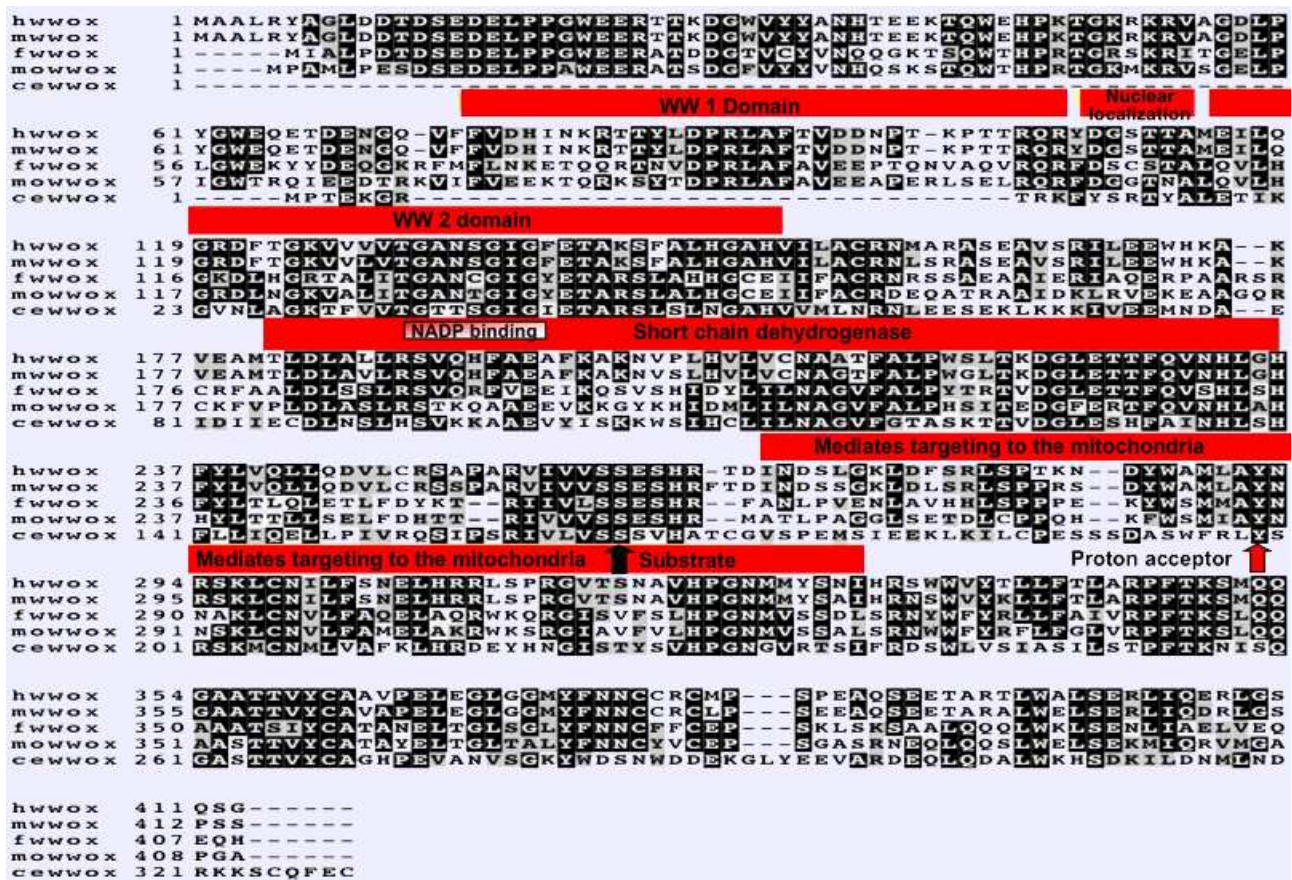
### Function

Contains an N-terminal group 1 WW domain that binds proteins with a PPXY motif. Reportedly interacts with p53, p73, JUN, ERBB4, Ap2alpha, Ap2gamma, Ezrin/VIL2, Ack1/TNK2. Probably involved in apoptosis, steroid (estrogen) metabolism and signaling pathways. Mice carrying a targeted deletion of the *Wwox* gene develop osteosarcomas in juvenile *Wwox*(-/-) and lung papillary carcinomas in adult *Wwox*(+/-) mice spontaneously. *Wwox*(+/-) mice develop significantly more ethyl nitrosourea-induced lung tumors and lymphomas than wild-type littermates.

## Mutations

### Somatic

Cancer cell lines from various tumor types, including ovarian, gastric and pancreatic, exhibit deletions within the WWOX gene, frequently in the introns surrounding exon 8.



Alignment of human (hWwox), mouse (Mwwox), fly (fWwox), mosquito (moWwox) and worm (ceWwox) Wwox proteins. The locations of the WW1 and WW2 domains are shown, as well as the predicted sites for nuclear localization, NADP binding, mitochondrial targeting, substrate binding and a proton acceptor.

## Implicated in

**Breast cancer, esophageal and non-small cell lung cancer**

### Disease

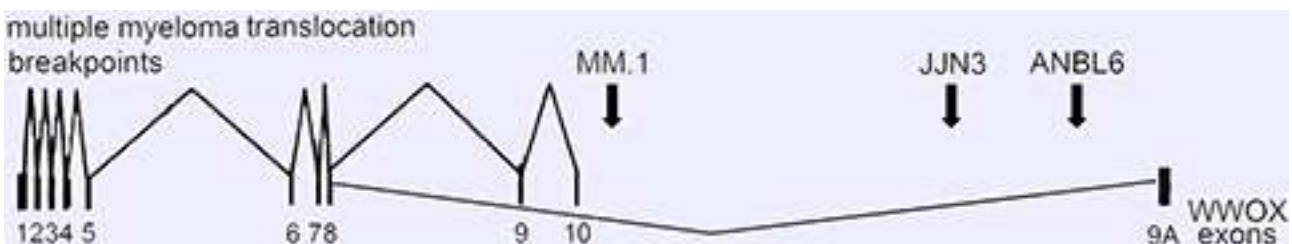
Breast, esophageal and non-small cell lung cancer show high LOH rates and low mutation rates. 27% of ER+ breast carcinomas versus 46% for ER- cases were completely negative for WWOX expression; when weakly WWOX expressing cases were included with

negative cases the significance increased. Methylation of regulatory sequences in WWOX exon 1 distinguish breast cancer DNA from normal DNA and DNA from adjacent tissue. Treatment with 5'-Aza-2'-deoxycytidine to demethylate the WWOX promoter successfully restored WWOX expression in WWOX-deficient breast cancer cells.

### Prognosis

In a sampling of 132 breast cancer tissues, high level WWOX expression was associated with better disease free survival.

## Breakpoints



Location of the t(14;16)(q32.3;q23) translocation breakpoints falling within the WWOX gene in 3 multiple myeloma cell lines.

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