## Phylogeny

Orthologous choline/ethanolamine kinase sequences with significant similarity to ETNK2 are present in Arabidopsis thaliana, Escherichia coli, Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster and Homo sapiens (lai2016evolutionaryancestryof pages 9-11).  
Sequence and three-dimensional structural analyses place ETNK2 within the choline/ethanolamine kinase (ChK) branch that is evolutionarily proximate to canonical eukaryotic protein kinases (lai2016evolutionaryancestryof pages 3-5, lai2015investigationsofthe pages 95-103).  
In the extended human kinome classification, ETNK2 is annotated as an atypical Protein Kinase-Like (PKL) enzyme of the eukaryotic-Like Kinase (eLK) subgroup and is absent from the original Manning kinome tree (moret2020aresourcefor pages 7-10).

## Reaction Catalyzed

ATP + ethanolamine ⇌ ADP + phosphoethanolamine + H⁺ (lai2016evolutionaryancestryof pages 3-5).

## Cofactor Requirements

In vitro assays of a human ethanolamine-specific kinase were performed in the presence of 10 mM Mg²⁺, indicating a requirement for a divalent cation cofactor (lykidis2001overexpressionofa pages 3-3).

## Substrate Specificity

ETNK2 is highly specific for ethanolamine and shows no detectable choline kinase activity (lai2016evolutionaryancestryof pages 3-5).  
Because the enzyme acts on a small-molecule substrate rather than peptide substrates, no protein consensus phosphorylation motif has been defined (lai2016evolutionaryancestryof pages 3-5).

## Structure

ETNK2 is a single catalytic domain protein that adopts the canonical bilobed kinase fold, with an N-terminal β-sheet lobe and a C-terminal α-helical lobe (lai2016evolutionaryancestryof pages 3-5, lai2015investigationsofthe pages 103-109).  
Structural superposition with human choline kinase (PDB 2IG7) and protein kinase A (PDB 3DND) demonstrates conservation of key catalytic motifs, including the glycine-rich loop, the LxxLH catalytic loop signature, and the magnesium-binding DFG motif (lai2016evolutionaryancestryof pages 9-11).  
No accessory regulatory domains have been reported; the activation-segment equivalent is present but lacks a described regulatory phosphorylation site (lai2016evolutionaryancestryof pages 3-5).

## Regulation

No experimentally validated post-translational modifications or allosteric regulators have been reported for ETNK2 in the referenced literature (moret2020aresourcefor pages 57-59).  
Epigenetic control via promoter methylation has been suggested as a mechanism modulating gene expression (zheng2022theetnk2gene pages 1-2).

## Function

ETNK2 catalyzes the first committed step of the ethanolamine branch of the Kennedy pathway, supplying phosphoethanolamine for de novo phosphatidylethanolamine synthesis (lai2016evolutionaryancestryof pages 14-15, zheng2022theetnk2gene pages 1-2).  
High mRNA and protein expression is observed in liver and reproductive tissues and in multiple cancer cell lines profiled in the CCLE panel (zheng2022theetnk2gene pages 1-2, moret2020aresourcefor pages 57-59).  
ETNK2 is over-expressed in papillary thyroid carcinoma, hepatocellular carcinoma, gastric cancer, lung adenocarcinoma and squamous cell carcinoma (zheng2022theetnk2gene pages 1-2).  
Knockdown in papillary thyroid carcinoma cells reduces proliferation, migration and invasion, induces G1/S arrest and apoptosis, and decreases YAP, TAZ and N-cadherin while increasing E-cadherin, implicating ETNK2 in HIPPO and EMT pathway activation (zheng2022theetnk2gene pages 5-8, zheng2022theetnk2gene pages 8-9).  
Within lipid metabolism, ETNK2 functions upstream of CDP-ethanolamine synthase (PCYT2) and downstream enzymes such as EPT1 in phosphatidylethanolamine production (zheng2022theetnk2gene pages 5-8, lai2016evolutionaryancestryof pages 14-15).

## Inhibitors

None reported in the cited literature.

## Other Comments

ETNK2 shows frequent focal amplification in breast cancer and other tumours, highlighting potential oncogenic relevance (unknownauthors2022datadrivencomputational pages 30-34).  
In hepatocellular carcinoma, higher ETNK2 expression correlates with better differentiation and improved survival, suggesting prognostic utility (zheng2022theetnk2gene pages 1-2).  
The gene is required for normal haemostasis and placental development, underscoring its physiological significance (zheng2022theetnk2gene pages 1-2).

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