## Phylogeny

• Orthologous enzymes are documented in Saccharomyces cerevisiae CKI1 (dual-specific choline/ethanolamine kinase) (lykidis2001overexpressionofa pages 7-7), Drosophila melanogaster ethanolamine-specific kinase gene (lykidis2001overexpressionofa pages 7-7), Rattus norvegicus CKI1/CKI2/CKI3 (lykidis2001overexpressionofa pages 7-7), Mus musculus Etkn1 and Etkn2 (tian2006placentalthrombosisand pages 4-5), Plasmodium falciparum ethanolamine kinase (alberge2010comparisonofthe pages 29-32), and higher-plant spinach ethanolamine kinase (unknownauthors1994purificationandbiochemical pages 60-67).  
• ETNK1 belongs to the choline/ethanolamine kinase (CEK) family of atypical small-molecule lipid kinases whose catalytic core retains the ancestral protein-kinase fold identified by comparative sequence and structural analyses (lai2016evolutionaryancestryof pages 2-3).

## Reaction Catalyzed

ethanolamine + ATP ⇌ phosphoethanolamine + ADP + H⁺ (draus1990isolationandcharacterization pages 2-3, lykidis2001overexpressionofa pages 1-2).

## Cofactor Requirements

• Catalytic activity is strictly Mg²⁺-dependent; optimal assays employ 3 mM MgCl₂ (draus1990isolationandcharacterization pages 2-3).  
• Activity increases with Mg²⁺ concentration in plant preparations, confirming divalent-cation dependence (unknownauthors1994purificationandbiochemical pages 60-67).

## Substrate Specificity

• Human ETNK1 is highly selective for ethanolamine; choline phosphorylation is negligible under physiological conditions (lykidis2001overexpressionofa pages 1-2, draus1990isolationandcharacterization pages 2-3).  
• The enzyme acts on a small-molecule substrate; no peptide consensus motif applies.

## Structure

• Full-length protein comprises 452 residues with a single N-terminal hydrophobic segment that mediates membrane association; the remainder is cytosolic (lykidis2001overexpressionofa pages 3-4, lykidis2001overexpressionofa pages 4-5).  
• Disease hotspot residues His243, Asn244 and Gly245 lie within the conserved catalytic loop of the phosphotransferase domain (fontana2020etnk1mutationsinduce pages 1-2).  
• No experimental ETNK1 structure is available; homology to solved human choline kinase α2 (bilobal kinase fold with ATP pocket between N- and C-lobes) suggests a similar overall architecture including the Brenner motif and catalytic Lys-Asp pair (malito2006elucidationofhuman pages 1-2, malito2006elucidationofhuman pages 20-23).  
• Conserved catalytic Lys and Asp residues requisite for phosphoryl transfer are present in the CEK motif (unknownauthors2004…cytidylyltransferaseand pages 22-26).

## Regulation

• No post-translational modifications or modifying enzymes have been reported for ETNK1 in the surveyed literature (lykidis2001overexpressionofa pages 7-7).  
• Metabolic feedback: the product phosphoethanolamine competitively inhibits mitochondrial succinate dehydrogenase, linking ETNK1 flux to respiratory chain activity (fontana2020etnk1mutationsinduce pages 10-11).

## Function

• Catalyses the first and rate-controlling step of the CDP-ethanolamine (Kennedy) pathway, supplying phosphoethanolamine for phosphatidylethanolamine and phosphatidylcholine biosynthesis (lykidis2001overexpressionofa pages 1-2, fontana2020etnk1mutationsinduce pages 1-2).  
• Transcript detected broadly with highest expression in testis and notable levels in liver, kidney and brain (lykidis2001overexpressionofa pages 3-4).  
• Phosphoethanolamine generated by ETNK1 restrains succinate dehydrogenase activity, thereby limiting mitochondrial membrane potential and reactive oxygen species (fontana2020etnk1mutationsinduce pages 10-11).  
• Loss-of-function mutation or knockout reduces intracellular phosphoethanolamine, provokes mitochondrial hyperactivation, elevates ROS and DNA damage, and increases cellular mutation frequency (unknownauthors2018etnk1mutationsincrease pages 1-1, fontana2020etnk1mutationsinduce pages 10-11).

## Other Comments

• Recurrent somatic missense mutations H243Y, N244S/T/K and G245A/V cluster in the catalytic domain and are enriched in atypical chronic myeloid leukaemia, chronic myelomonocytic leukaemia, systemic mastocytosis with eosinophilia and diffuse large B-cell lymphoma (fontana2020etnk1mutationsinduce pages 1-2, lasho2015novelrecurrentmutations pages 1-2).  
• Mutations lower intracellular phosphoethanolamine ~5-fold, trigger mitochondrial complex II hyperactivation, increase ROS, γ-H2AX-marked DNA breaks and confer a mutator phenotype reversible by exogenous phosphoethanolamine (fontana2020etnk1mutationsinduce pages 10-11, unknownauthors2019characterizationofthe pages 137-142).

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