## Phylogeny

Hydroxylysine kinase (HYKK, gene symbol AGPHD1) belongs to the aminoglycoside phosphotransferase (APH) super-family and is distantly related to the aminotransferase III family (Veiga-da-Cunha et al., 2012). Vertebrate HYKK shares ~26 % sequence identity with bacterial homologues and clusters with the mammalian aminotransferases AGXT2L1 and AGXT2L2 (Veiga-da-Cunha et al., 2012). Orthologues are present from bacteria (e.g., Erwinia carotovora) to mammals (mouse, chicken) (Hiles et al., 1972; Veiga-da-Cunha et al., 2012). HYKK is not listed in the Manning et al. eukaryotic kinome classification (Piggott & Attwood, 2017).

## Reaction Catalyzed

ATP + 5-hydroxy-L-lysine ⇄ ADP + 5-O-phosphohydroxy-L-lysine  
(Contradictory studies report higher catalytic efficiency with GTP as the phosphate donor; Veiga-da-Cunha et al., 2012; Piggott & Attwood, 2017).

## Cofactor Requirements

Catalysis requires a divalent cation; Mg²⁺ is essential and Mn²⁺ can substitute (Piggott & Attwood, 2017; Veiga-da-Cunha et al., 2012).

## Substrate Specificity

• Acts exclusively on the free amino acid 5-hydroxy-L-lysine, not on proteins (Hiles et al., 1972; Piggott & Attwood, 2017).  
• Strict for the L-enantiomer; no activity toward 5-hydroxy-D-lysine (Piggott & Attwood, 2017).  
• Does not phosphorylate serine, threonine, hydroxyproline, homoserine or choline (Piggott & Attwood, 2017; Veiga-da-Cunha et al., 2012).  
• Both threo (2S,5R) and allo (2S,5S) epimers are accepted; the allo form shows 1.5–3-fold higher k\_cat (Piggott & Attwood, 2017).

## Structure

HYKK adopts an APH-like fold comprising a central β-sheet flanked by α-helices that create the nucleotide-binding cleft (Veiga-da-Cunha et al., 2012). The architecture lacks hallmark eukaryotic protein-kinase elements such as the activation loop and the canonical Lys-Glu salt bridge (Black et al., 2022). AlphaFold and homology models predict binding pockets tailored for GTP/ATP and 5-hydroxy-L-lysine (Piggott & Attwood, 2017; Veiga-da-Cunha et al., 2012).

## Regulation

No post-translational regulation has been reported (Veiga-da-Cunha et al., 2012). Functional specificity is imparted by the enzyme’s narrow substrate range and by its preference for GTP over ATP in kinetic assays (Piggott & Attwood, 2017).

## Function

HYKK catalyses the first committed step in hydroxylysine catabolism, converting dietary or collagen-derived 5-hydroxy-L-lysine to 5-phosphohydroxy-L-lysine, the substrate for the phospholyase AGXT2L2 (Veiga-da-Cunha et al., 2012; Piggott & Attwood, 2017). Expression is highest in liver and kidney, the principal sites of hydroxylysine degradation (Veiga-da-Cunha et al., 2012).

## Other Comments

Deficiency of the downstream enzyme AGXT2L2 causes phosphohydroxylysinuria, leading to accumulation of 5-phosphohydroxy-L-lysine (Piggott & Attwood, 2017). HYKK mutations have been proposed to underlie hydroxylysinuria/hydroxylysinemia with neurological manifestations, although definitive clinical evidence is lacking (Veiga-da-Cunha et al., 2012). Elevated O-phosphohydroxylysine is observed in liver and kidney of vitamin B₆-deficient rats (Hiles et al., 1972).

## References

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