## Proposed EC/sub-subclass:

Not yet formally assigned

## Accepted name:

Fructosamine-3-kinase

## Synonyms:

FN3K; fructoselysine-3-kinase; protein-D-fructosamine 3-kinase

## Phylogeny

FN3K is highly conserved in vertebrates (mammals, birds, amphibians and fish) but has no close homologues in yeasts or insects. It arose after duplication of an ancestral fructosamine-3-kinase-related protein (FN3K-RP). FN3K and FN3K-RP share ~65 % sequence identity yet have diverged in substrate specificity and regulation (Avemaria et al., 2015; Conner et al., 2005). Distant relationships link FN3K to small-molecule kinases such as aminoglycoside phosphotransferases within the protein-kinase-like superfamily (Beisswenger et al., 2001; Delpierre & Van Schaftingen, 2003).

## Reaction Catalyzed

ATP + fructosamine-[protein] ⇌ ADP + fructosamine-3-phosphate-[protein]  
The unstable fructosamine-3-phosphate then decomposes non-enzymatically to yield free lysine, inorganic phosphate and 3-deoxyglucosone (Beisswenger et al., 2001; Delpierre & Van Schaftingen, 2003).

## Cofactor Requirements

Requires Mg²⁺ for ATP coordination (Beisswenger et al., 2001; Tsai et al., 2006).

## Substrate Specificity

Displays high selectivity for protein-bound fructoselysine adducts, showing much lower activity toward free sugars. It can also act on related psicosamine and ribulosamine adducts but preferentially targets long-lived glycated proteins such as haemoglobin (Avemaria et al., 2015; Beeraka et al., 2021; Delpierre & Van Schaftingen, 2003).

## Structure

Monomeric 309-residue kinase (~35 kDa) that adopts a classical bilobal protein-kinase-like fold. Key catalytic residues include Lys41 (ATP binding), Glu55 and Asp244 (substrate/metal positioning). A conserved glycine-rich P-loop supports nucleotide binding, and the compact substrate pocket is adapted for small-molecule fructosamine substrates (Beisswenger et al., 2001; Fortpied et al., 2005; Garg et al., 2025).

## Regulation

Activity varies between tissues and correlates with intracellular glucose; erythrocytes, lens, and brain exhibit higher activity (Avemaria et al., 2015; Veiga-da-Cunha et al., 2006). Polymorphisms in the FN3K gene modulate enzymatic activity and haemoglobin glycation levels (Delpierre et al., 2006). No extensive post-translational control has been reported; modulation appears largely through substrate access and possibly redox state (Beisswenger et al., 2001; Tsai et al., 2006).

## Function

FN3K repairs glycated proteins by converting fructoselysine to an unstable phosphate ester that decomposes, restoring unmodified lysine and preventing accumulation of advanced glycation end products. This repair mechanism is critical in cells lacking protein turnover, e.g., erythrocytes (Beisswenger et al., 2001; Delpierre & Van Schaftingen, 2003). Deglycation of regulatory proteins such as NRF2 links FN3K to antioxidant responses (Beeraka et al., 2021). FN3K is expressed ubiquitously, with higher levels in tissues exposed to elevated glucose (Veiga-da-Cunha et al., 2006; Conner et al., 2005).

## Inhibitors

Substrate analogues such as 1-deoxy-1-morpholinofructose (DMF) competitively inhibit FN3K, increasing cellular glycation (Tsai et al., 2006). These compounds have been used to probe FN3K function and highlight challenges in designing selective inhibitors due to the enzyme’s unique substrate pocket (Szwergold & Loomes, 2007).

## Other Comments

Altered FN3K activity is linked to diabetic complications through enhanced AGE formation, making the enzyme a potential therapeutic target (Avemaria et al., 2015; Szwergold et al., 2011).

## References

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