## Proposed EC/sub-subclass:

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## Accepted name:

General Control Nonderepressible-2 protein kinase (GCN2)

## Synonyms:

EIF2AK4; eIF2α kinase 4; General control nonderepressible-2; GCN2p (yeast)

## Phylogeny

GCN2 is one of the most ancient and ubiquitous eIF2α kinases, with orthologues in yeast, plants, fungi, and animals (Rothenburg et al., 2016; Tatara et al., 2024). Its evolutionary lineage pre-dates the divergence of the other eIF2α-kinase family members (PKR, HRI, PERK) and is characterized by a conserved N-terminal RWD domain and a HisRS-like module that couple environmental cues to translational control (Rothenburg et al., 2016; Donnelly et al., 2013).

## Reaction catalysed

ATP + eIF2α → ADP + eIF2α-P + H⁺  
Phosphorylation occurs at the conserved Ser-51 residue of eIF2α (Xu, 2011).

## Cofactor requirements

Mg²⁺ is essential for ATP binding and catalysis (Rothenburg et al., 2016).

## Substrate specificity

The kinase selectively phosphorylates the α-subunit of eIF2 at Ser-51; recognition depends on local sequence context and structural contacts afforded by GCN2 regulatory domains (Zhao et al., 2023; Dey, 2012).

## Structure

Multidomain protein comprising:  
• N-terminal RWD domain for interaction with GCN1/GCN20 (Tatara et al., 2024).  
• Pseudokinase domain that modulates catalytic output.  
• Canonical serine/threonine kinase domain with bi-lobed fold, activation loop autophosphorylation site, and conserved DFG motif (Miles, 2021; Rothenburg et al., 2016).  
• HisRS-like domain that binds uncharged tRNA and relieves autoinhibition (Lokdarshi & von Arnim, 2022).  
• C-terminal dimerisation/ribosome-association region (Lokdarshi & von Arnim, 2022).  
Crystallographic and AlphaFold models reveal a back-to-back dimer in which regulatory modules are positioned to sense uncharged tRNA and stalled ribosomes (Rothenburg et al., 2016).

## Regulation

• Activation by accumulation of uncharged tRNAs that bind the HisRS-like and C-terminal regions, promoting dimerisation and autophosphorylation (Altintas & MacArthur, 2024; Zhao et al., 2023).  
• GCN1 serves as a ribosomal scaffold, transferring uncharged tRNA from the A-site to GCN2; GCN20 assists this process (Tatara et al., 2024).  
• Additional inputs include glucose limitation, oxidative stress, UV irradiation and ribosome stalling, which impinge on tRNA charging state or GCN1/GCN20 interactions (Anda et al., 2017; Zhao et al., 2023).  
• Crosstalk with mTORC1: amino-acid sufficiency via mTORC1 suppresses GCN2 signalling (Zhao et al., 2023; Altintas & MacArthur, 2024).

## Function

Activated GCN2 phosphorylates eIF2α, globally dampening cap-dependent translation while enabling selective translation of stress-adaptive mRNAs (e.g., ATF4) (Altintas & MacArthur, 2024; Dey, 2012). This integrated stress response supports amino-acid biosynthesis, redox balance, autophagy and survival during nutrient deprivation. Additional reported roles include:  
• Cell-cycle modulation through cyclin D1 and CDKN1A/p21 translation (Dey, 2012).  
• Neuronal plasticity, learning and memory (Goodman, 2019).  
• Pro-apoptotic signalling during glucose starvation (Altintas & MacArthur, 2024).  
• Antiviral defence by restricting early viral mRNA translation (Goodman, 2019).

## Inhibitors

Small-molecule inhibitors that block uncharged-tRNA binding or impede autophosphorylation have been described, though many display off-target activities; optimisation for selectivity is ongoing (Joshi et al., 2013).

## Other comments

Loss-of-function EIF2AK4 mutations cause pulmonary veno-occlusive disease/pulmonary arterial hypertension, and dysregulated GCN2-ISR signalling is linked to cancer, neurodegeneration and inflammatory disorders (Altintas & MacArthur, 2024; Zhao et al., 2023).

## References

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