## Phylogeny

Orthologs are reported in Saccharomyces cerevisiae, Schizosaccharomyces pombe, Neurospora crassa, Aspergillus nidulans, Arabidopsis thaliana, Caenorhabditis elegans, Drosophila melanogaster, Danio rerio, Xenopus tropicalis, Mus musculus and Homo sapiens, illustrating conservation across eukaryotes (castilho2014keepingtheeif2 pages 3-4).  
Comparative analyses identify GCN2 as the ancestral eIF2α kinase; subsequent gene duplications generated HRI, PERK, PKR and the fish-specific PKZ (rothenburg2016evolutionofeif2α pages 4-7, berlanga2016eif2αkinasesand pages 239-242).  
Within the human kinome, EIF2AK4 is placed in the eIF2α-kinase subgroup of the CMGC serine/threonine kinase group (rothenburg2016evolutionofeif2α pages 4-7).

## Reaction Catalyzed

ATP + EIF2S1(Ser51) → ADP + EIF2S1(Ser51-phosphate) (castilho2014keepingtheeif2 pages 1-2).

## Cofactor Requirements

Divalent Mg²⁺ ions are required for nucleotide binding and phosphoryl transfer; two Mg²⁺ ions are visible in crystal structures of the kinase domain, and no Mn²⁺ dependence has been documented (masson2019towardsamodel pages 1-2, padyana2005structuralbasisfor pages 2-2).

## Substrate Specificity

GCN2 shows narrow specificity, phosphorylating Ser51 within the eIF2α subunit; no broader linear consensus motif has been defined, and recognition relies on the eIF2α surface, as underscored by competitive viral mimics such as Vaccinia virus K3L (berlanga2016eif2αkinasesand pages 256-258).

## Structure

Human GCN2 (1 649 aa, ≈190 kDa) comprises five ordered domains: N-terminal RWD (ribosome/GCN1 docking), pseudokinase, catalytic kinase, HisRS-like sensor, and C-terminal dimerization/ribosome-binding domain (masson2019towardsamodel pages 1-2).  
• RWD: solution structure, PDB 1UKX (masson2019towardsamodel pages 1-2).  
• Kinase: bilobal fold, PDB 1ZYD; catalytic Lys628, HRD motif, DFG motif, and a long activation loop harbouring Thr899/Thr904 autophosphorylation sites; hinge residue Arg794 forms autoinhibitory contacts that are disrupted in activating mutant R794G (padyana2005structuralbasisfor pages 2-3, padyana2005structuralbasisfor pages 5-7).  
• HisRS-like: crystal and cryo-EM analyses reveal a constitutive intertwined dimer that mimics histidyl-tRNA synthetase but lacks catalytic activity, providing the principal uncharged-tRNA binding platform (bounader2024gcn2structurallymimics pages 7-8, soloriokirpichyan2024cryoemstructureof pages 10-14).  
• CTD: interdigitated dimer, PDB 4OTN; this domain stabilises back-to-back kinase dimers and contains lysines critical for ribosome interaction (berlanga2016eif2αkinasesand pages 246-249, masson2019towardsamodel pages 2-4).  
Cryo-EM shows junction α-helices linking the kinase and HisRS domains cross the dimer interface and enforce the active kinase configuration (soloriokirpichyan2024cryoemstructureof pages 14-18).

## Regulation

• Activation is triggered by binding of accumulated uncharged tRNAs to the HisRS-like domain, relieving autoinhibition and permitting trans-autophosphorylation of Thr899/Thr904 (castilho2014keepingtheeif2 pages 2-3).  
• The GCN1-GCN20 complex tethers GCN2 to translating ribosomes and delivers uncharged tRNA; deletion of GCN1 abrogates activation in vivo (masson2019towardsamodel pages 2-4).  
• Ribosome-P-stalk engagement and collision-sensing provide tRNA-independent activation routes (altintas2024generalcontrolnonderepressible pages 1-2).  
• mTORC1 directly phosphorylates Ser230 in the N-terminus, elevating kinase activity during amino-acid stress (darawshi2024phosphorylationofgcn2 pages 5-6).  
• Yeast Ser577 phosphorylation, controlled by TOR signalling, maintains an inhibited state under nutrient sufficiency (donnelly2013theeif2αkinases pages 5-6).  
• Constitutive CTD–kinase and HisRS–kinase contacts impose basal autoinhibition; their disruption by tRNA or junction-helix mutations activates the enzyme (masson2019towardsamodel pages 2-4, soloriokirpichyan2024cryoemstructureof pages 6-10).  
• Downstream, eIF2α is dephosphorylated by PPP1R15A/B complexes to terminate signalling (castilho2014keepingtheeif2 pages 17-18).

## Function

GCN2 is ubiquitously expressed and serves as the principal amino-acid deprivation sensor in the Integrated Stress Response (ISR), phosphorylating eIF2α to attenuate global translation while selectively enhancing ATF4 synthesis (altintas2024generalcontrolnonderepressible pages 1-2).  
The kinase also responds to ribosome stalling in neuronal tissues, limiting neurodegeneration by initiating ISR gene programmes (ishimura2016activationofgcn2 pages 6-8).  
Cross-talk with mTORC1 coordinates translational and growth control: pharmacological mTOR inhibition suppresses GCN2 signalling, whereas mTOR-mediated Ser230 phosphorylation potentiates it (bruggenthies2022acellbasedchemicalgenetic pages 2-3, darawshi2024phosphorylationofgcn2 pages 5-6).  
Interactors include GCN1, GCN20, the ribosomal P-stalk, IMPACT/YIH1, eEF1A and Hsp90, which modulate localisation or folding (castilho2014keepingtheeif2 pages 3-4, berlanga2016eif2αkinasesand pages 256-258).  
GCN2-dependent ISR contributes to memory formation, immune regulation, metabolic homeostasis and lifespan control (castilho2014keepingtheeif2 pages 1-2).

## Inhibitors

Compound | Mechanism | Potency  
GCN2-IN-6 (allosteric) | non-competitive | IC₅₀ ≈ 1.8 nM (unknownauthors2021geneticandchemical pages 43-46)  
GCN2iB (ATP-site) | type I½ binder | IC₅₀ ≈ 1.8 nM; activates certain mutants at low dose (unknownauthors2021geneticandchemical pages 43-46, carlson2023activationofgcn2 pages 14-15)  
A-92/GCN2-IN-1 (allosteric) | non-competitive | cell-active probe (unknownauthors2021geneticandchemical pages 43-46)  
Lestaurtinib, R406, Fedratinib, Neratinib, Dovitinib (ATP-competitive) | Kd 3–100 nM range versus isolated kinase (tang2022gcn2kinaseactivation pages 1-3)  
Staurosporine, SP600125, Indirubin-3′-monoxime | ATP-competitive | IC₅₀ ≈ 2–20 µM (unknownauthors2009blockinguv‐inducedeif2α pages 6-8, unknownauthors2009blockinguv‐inducedeif2α pages 17-20)  
Torin-class mTOR inhibitors attenuate cellular GCN2 activation indirectly (bruggenthies2022acellbasedchemicalgenetic pages 2-3).

## Other Comments

Biallelic loss-of-function mutations in EIF2AK4 cause hereditary pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (castilho2014keepingtheeif2 pages 3-4).  
GCN2 activity supports survival of acute lymphoblastic leukaemia and multiple myeloma cells under nutrient stress (nwosu2022targetingtheintegrated pages 4-6).  
Persistent ISR signalling via GCN2 contributes to neurodegenerative phenotypes in mouse models of ribosome stalling (ishimura2016activationofgcn2 pages 6-8).  
The kinase-domain variant S808G alters inhibitor binding kinetics and is used in chemical-genetic studies (tang2022gcn2kinaseactivation pages 1-3).  
An activating structural mutant, R794G, disrupts hinge autoinhibition and is widely employed to probe regulatory mechanics (padyana2005structuralbasisfor pages 5-7).

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