**Accepted name:** Non‐receptor tyrosine‐protein kinase TYK2, gene: TYK2, Uniprot: P29597  
**Synonyms:** TYK2 kinase, Non‐receptor tyrosine kinase 2

## 1. Phylogeny

TYK2 is a member of the Janus kinase (JAK) family, which comprises four closely related non‐receptor tyrosine kinases: JAK1, JAK2, JAK3, and TYK2. Within the diverse human kinome, TYK2 belongs to a distinct subfamily that plays an essential role in the downstream signaling of cytokine receptors. Evolutionarily, the JAK family is highly conserved across vertebrate species, and TYK2 orthologs have been identified in all mammals as well as other vertebrates. This conservation is particularly pronounced in TYK2’s catalytic (JH1) and regulatory (JH2, also called the pseudokinase) domains, which indicates that the enzyme’s dual function—both catalytic and regulatory—has been maintained since early vertebrate evolution. Studies have shown that despite the overall structural similarities shared among the JAKs, TYK2 is uniquely characterized by its ability to integrate signals from a diverse set of cytokine receptors through the formation of heterodimeric receptor complexes (bhanumathy2021proteintyrosinekinases pages 1-2, woss2019tyk2anupstream pages 3-5).

Phylogenetic reconstructions place TYK2 in a discrete cluster with its JAK counterparts; however, several sequence motifs and domain arrangements are unique to TYK2. For example, specialized regulatory elements in the JH2 domain contribute to its autoinhibition and subsequent activation when engaged by cytokine-bound receptors. Recent de‐novo functional classifications based on multi‐domain architecture and specificity–determining residues have refined our understanding of TYK2’s evolutionary context, grouping it in subfamilies that emphasize its dual role as both a modulator of receptor stability and as a catalytic enzyme (adeyelu2023kinfamsdenovoclassification pages 1-2). Moreover, the evolutionary conservation extends to the overall organization of the receptor complexes in which it participates; the TYK2-associated receptor chains (e.g., IFNAR1, IL12RB1, IL10RB, IL13RA1) and the partner kinases (JAK1 or JAK2) are themselves evolutionarily conserved, ensuring that the signal transduction machinery critical for innate and adaptive immunity is preserved. Thus, TYK2 represents an evolutionary conserved module that has been finely tuned to regulate immune responses and maintain organismal homeostasis over millions of years (bhanumathy2021proteintyrosinekinases pages 1-2, woss2019tyk2anupstream pages 3-5).

## 2. Reaction Catalyzed

TYK2 acts as an ATP‐dependent kinase, catalyzing the transfer of a phosphate group from ATP to tyrosine residues present on target proteins. The overall chemical reaction can be schematically described as:  
  ATP + protein–Tyr → ADP + protein–phosphotyrosine + H⁺  
This phosphorylation event is critically important in the context of cytokine signaling. Upon cytokine binding to corresponding heterodimeric receptor complexes, TYK2 becomes activated and phosphorylates specific tyrosine residues on the intracellular domains of the receptor chains. These phosphorylated tyrosines then serve as high‐affinity docking sites for the SH2 domains of STAT transcription factors (such as STAT1, STAT3, STAT4, and STAT6) (borcherding2021tyk2incancer pages 14-16, gerstenberger2020demonstrationofin pages 2-3).

The reaction mechanism involves several key steps. First, cytokine binding induces a conformational rearrangement within the receptor dimer, bringing the associated TYK2 molecules into close proximity. This facilitates trans‐autophosphorylation on several key tyrosine residues in the kinase domain, relieving autoinhibition imposed by the JH2 pseudokinase domain. Once activated, TYK2 phosphorylates tyrosines on the receptor intracellular domains, thus creating binding sites for STAT family members. These STAT proteins, upon recruitment, are themselves phosphorylated on a tyrosine residue, prompting homodimerization or heterodimerization that precedes their nuclear translocation and initiation of gene transcription (bhanumathy2021proteintyrosinekinases pages 1-2, gerstenberger2020demonstrationofin pages 8-9).

Interestingly, TYK2 can also mediate non-canonical phosphorylation events. In addition to the classical cascade that results in STAT activation, TYK2 phosphorylates STAT3 at an alternative tyrosine residue. This phosphorylation event does not promote its typical signaling function but rather acts as a negative regulatory mechanism, tempering STAT3’s transcriptional activity and thereby fine-tuning the overall immune response (borcherding2021tyk2incancer pages 14-16). This dual capacity—both activating and attenuating downstream signaling pathways—illustrates the sophisticated regulatory mechanisms orchestrated by TYK2 that enable precise modulation of cell signaling in response to diverse extracellular cues.

## 3. Cofactor Requirements

The catalytic activity of TYK2, as with most kinases, is strictly dependent on the coordinated binding of ATP and divalent metal ions. In the active site of the kinase domain, ATP binds in a cleft formed between the N-terminal and C-terminal lobes of the enzyme’s bilobal structure. Magnesium ions (Mg²⁺) are the principal cofactors required for TYK2’s enzymatic function, as they act by coordinating with the phosphate groups of ATP to facilitate the correct orientation for the gamma-phosphate transfer (abdulkhader…2023proteinkinasestructure pages 18-21, wang2025atripleactioninhibitory pages 21-24).

The role of Mg²⁺ is twofold: first, it stabilizes the charge on the phosphate groups and, second, it assists in the positioning of ATP within the active site, which is essential for catalysis. Although experimental studies with other kinases occasionally indicate that Mn²⁺ can substitute under certain in vitro conditions, physiological evidence supports Mg²⁺ as the primary ion utilized by TYK2 (wang2025atripleactioninhibitory pages 21-24). No evidence from the context implies the requirement of any additional cofactors such as organic molecules or prosthetic groups; thus, the ATP/Mg²⁺ system constitutes the minimal cofactor requirement necessary for its catalytic function.

## 4. Substrate Specificity

Substrate specificity is a defining feature that enables TYK2 to coordinate complex cytokine signaling cascades with high fidelity. Physiologically, TYK2 primarily targets the intracellular domains of cytokine receptors that are part of heterodimeric complexes. Receptors such as IFNAR1, IL12RB1, IL10RB, and IL13RA1 are the preferred substrates for TYK2 phosphorylation. Upon ligand binding, these receptor chains undergo tyrosine phosphorylation by TYK2, resulting in the generation of phosphotyrosine motifs that serve as binding platforms for STAT proteins (bhanumathy2021proteintyrosinekinases pages 1-2, woss2019tyk2anupstream pages 3-5).

Once these docking sites are established, STAT proteins—but especially STAT1, STAT3, STAT4, and STAT6—are recruited to the receptor complex. These STAT proteins contain Src homology 2 (SH2) domains that specifically recognize the phosphorylated tyrosine residues embedded in short linear motifs present in the receptor tails. The phosphorylation of the recruited STATs by TYK2 converts them from their unphosphorylated (uSTAT) to phosphorylated (pSTAT) states, leading to dimerization and subsequent nuclear translocation where they modulate gene transcription (abdulkhader…2023proteinkinasestructure pages 18-21, mingione2023allostericregulationand pages 7-9).

In an additional layer of regulatory complexity, TYK2 selectively phosphorylates STAT3 at an alternative tyrosine site that diverges from the canonical activation site. This alternative phosphorylation event serves to negatively regulate STAT3, thereby potentially moderating excessive pro-inflammatory signals (borcherding2021tyk2incancer pages 14-16). Although a precise consensus motif for TYK2 substrates has not been fully elucidated, the substrate recognition appears to depend more on the three-dimensional context provided by receptor engagement and the spatial positioning of tyrosine residues rather than on a strictly linear amino acid sequence. This dynamic substrate recognition system ensures that TYK2 can respond appropriately to various cytokine signals while avoiding cross-activation of unrelated signaling pathways.

## 5. Structure

The structural architecture of TYK2 is a hallmark feature that underpins its function and regulation within the JAK-STAT pathway. TYK2 is organized into several distinct domains that each contribute to its overall activity and specificity. Starting at the N-terminus, TYK2 contains a FERM domain (comprising subdomains JH7 to JH4), which is critical for mediating the physical interaction with the intracellular portions of cytokine receptors. Adjacent to the FERM domain lies an atypical SH2-like domain (JH3), which further stabilizes receptor binding and contributes to the formation of high-affinity complexes with specific receptor chains (eshaq2024nonreceptortyrosinekinases pages 1-2, woss2019tyk2anupstream pages 3-5).

Central to TYK2’s regulatory function is its pseudokinase domain (JH2). Although the JH2 domain lacks the full complement of catalytic residues necessary for conventional phosphotransfer, it plays an indispensable role in moderating the activity of the adjacent catalytically active kinase domain (JH1). In the autoinhibited conformation, the JH2 domain interacts closely with the JH1 kinase domain to restrict ATP access and substrate binding, effectively maintaining TYK2 in an inactive state until proper receptor engagement triggers conformational changes (tomoni2019pseudokinasesfromallosteric pages 10-13, wang2025atripleactioninhibitory pages 24-32).

The C-terminal JH1 domain of TYK2 displays the canonical bilobal kinase fold, with a smaller, mostly β-strand–rich N-terminal lobe and a larger, predominantly α-helical C-terminal lobe. The ATP-binding cleft is situated in the interface between these lobes and is characterized by conserved motifs that are essential for catalysis. Key among these are the glycine-rich loop (P-loop), which assists in the proper positioning of ATP, the HRD (His-Arg-Asp) motif within the catalytic loop that is critical for proton transfer and residue positioning, and the DFG (Asp-Phe-Gly) motif, which coordinates the binding of Mg²⁺ ions necessary for catalysis (abdulkhader…2023proteinkinasestructure pages 18-21, mingione2023allostericregulationand pages 7-9).

Within the JH1 domain, a conserved lysine residue is responsible for stabilizing the phosphates of ATP, while a glutamate from the αC helix reinforces the active conformation of the enzyme. Structural studies have revealed that the interplay between the JH2 and JH1 domains is not static; rather, TYK2 alternates between autoinhibited states and fully active conformations. Recent crystal structures and advanced homology models demonstrate that receptor engagement induces domain rotations and conformational “breathing” motions that free the active site of the kinase domain for substrate phosphorylation (wang2025atripleactioninhibitory pages 17-21, majeski2020theroleof pages 35-39).

In summary, TYK2’s structure is defined by a modular design that includes receptor-binding domains (FERM and SH2), a regulatory pseudokinase domain (JH2) that governs autoinhibition, and a catalytic kinase domain (JH1) that executes phosphorylation reactions. This intricate architecture not only ensures precise regulation of its kinase activity but also provides multiple opportunities for selective inhibitor design, as evidenced by the development of compounds that target the JH2 domain allosterically.

## 6. Regulation

The activity of TYK2 is regulated by multiple overlapping mechanisms that integrate extracellular cytokine signals with intracellular control processes. Central to this regulation is the autoinhibitory role of the JH2 pseudokinase domain, which interacts with the JH1 kinase domain to keep the enzyme in an inactive conformation under basal conditions. In the absence of cytokine stimulation, this interaction minimizes unwanted autophosphorylation and prevents spurious signaling events (eshaq2024nonreceptortyrosinekinases pages 1-2, tomoni2019pseudokinasesfromallosteric pages 10-13).

Upon cytokine binding to the heterodimeric receptor complexes, significant conformational rearrangements occur. The receptor dimerization brings TYK2 into close proximity with partner JAKs such as JAK1 or JAK2, thereby facilitating trans-autophosphorylation. This phosphorylation typically occurs on multiple tyrosine residues within the JH1 activation loop and in other regulatory regions, leading to the release of the autoinhibition imposed by the JH2 domain (wang2025atripleactioninhibitory pages 1-5, kim2024tyk2regulatestau pages 16-22). These phosphorylation events not only enhance the catalytic efficiency of TYK2 but also create additional docking sites for STAT proteins, effectively propagating the cytokine signal.

In addition to receptor-induced activation, TYK2 is subject to further regulation by post-translational modifications. Protein tyrosine phosphatases (PTPs) can dephosphorylate key tyrosine residues, thereby attenuating signaling once the cytokine stimulus is removed. Also, regulators such as suppressor of cytokine signaling (SOCS) proteins bind phosphorylated tyrosine residues and target TYK2 for ubiquitination and subsequent proteasomal degradation (borcherding2021tyk2incancer pages 14-16, raivolaUnknownyearmolecularregulationof pages 105-107).

A notable regulatory mechanism is the action of allosteric inhibitors that selectively target the TYK2 JH2 domain. One prominent example is deucravacitinib, which binds to the pseudokinase region with subnanomolar affinity (approximately IC50 ~0.2 nM) and locks TYK2 in its autoinhibited conformation. Deucravacitinib prevents the conformational changes required for ATP binding and for the kinase domain to adopt an active state, thereby effectively reducing both autophosphorylation and downstream STAT activation. This allosteric mode of inhibition offers enhanced selectivity compared to inhibitors that target the more conserved ATP-binding pocket, thereby minimizing off-target effects commonly observed with pan-JAK inhibitors (dalle2024targetingproteinkinases pages 3-5, rusinol2023tyk2targetingin pages 15-16).

Moreover, the coordinated effects of receptor binding, phosphorylation, and negative regulatory proteins ensure that TYK2 activity is precisely modulated. This multifaceted regulation is critical: it enables robust signaling in the presence of cytokines while preventing excessive or prolonged activation that could lead to pathological inflammation.

## 7. Function

TYK2 is a central node in the transmission of cytokine- and interferon-induced signals, making it indispensable for normal immune function and cellular homeostasis. Functionally, TYK2 is involved in both the initiation and modulation of signaling cascades that control cell proliferation, differentiation, survival, and migration. It associates with heterodimeric cytokine receptor complexes that contain a partner receptor chain (such as IFNAR1, IL12RB1, IL10RB, or IL13RA1) and an accompanying JAK family member (typically JAK1 or JAK2). Upon cytokine engagement, TYK2 phosphorylates these receptor subunits, thereby generating docking sites for STAT transcription factors. The recruited STAT proteins, once phosphorylated by TYK2, dimerize and translocate to the nucleus where they regulate the expression of genes involved in critical immune responses (bhanumathy2021proteintyrosinekinases pages 1-2, castelosoccio2023proteinkinasesdrug pages 1-2).

The functional versatility of TYK2 is further highlighted by its ability to engage in both positive and negative regulation of downstream signaling. For example, while phosphorylation typically results in the activation of STAT proteins, TYK2 also phosphorylates STAT3 at an alternative tyrosine residue that serves to temper its activity. This regulatory switch is thought to be essential for maintaining a balance between pro-inflammatory and anti-inflammatory signals, thereby safeguarding against runaway immune responses that could lead to autoimmunity (borcherding2021tyk2incancer pages 14-16, muromoto2022currentunderstandingof pages 1-2).

TYK2’s biological functions extend to antiviral defense; through its role in type I interferon signaling, TYK2 helps mediate the rapid induction of interferon-stimulated genes (ISGs) that are crucial for establishing an antiviral state. In addition to its role in innate immunity, TYK2 also influences the adaptive immune system by modulating T cell differentiation. For instance, signaling via the IL-12 receptor, which involves TYK2, is integral to the differentiation of CD4⁺ T cells into Th1 subsets, while IL-23 signaling—also dependent on TYK2—promotes the formation and maintenance of Th17 cells, both of which are central to the immune response against intracellular pathogens as well as in autoimmune inflammation (abdulkhader…2023proteinkinasestructure pages 18-21, woss2019tyk2anupstream pages 3-5).

Dysregulation of TYK2, whether through aberrant expression or mutations that affect its kinase activity, has been linked to a range of clinical disorders. Both hyperactive and deficient TYK2 signaling have been implicated in autoimmune diseases and inflammatory disorders, as well as in certain cancers where altered cytokine signaling contributes to tumor progression and immune evasion. As such, TYK2 is not only a central mediator in physiological signaling pathways but also represents a critical therapeutic target, with its activity serving as both a biomarker of disease and as a controllable element in targeted drug interventions.

## 8. Other Comments

The clinical and therapeutic significance of TYK2 has catalyzed the development of numerous inhibitors, which are being actively evaluated for their efficacy and safety in treating a variety of immune-mediated inflammatory diseases (IMIDs). Recent advances in drug discovery have yielded highly selective allosteric inhibitors like deucravacitinib, which target the regulatory JH2 pseudokinase domain rather than the conserved ATP-binding site. This strategy not only enhances selectivity by exploiting subtle structural differences between TYK2 and other JAK family members but also mitigates the off-target toxicities frequently observed with less selective pan-JAK inhibitors (dalle2024targetingproteinkinases pages 3-5, rusinol2023tyk2targetingin pages 15-16).

Mutations in the TYK2 gene have also attracted considerable research interest due to their association with several pathological conditions. Both gain-of-function and loss-of-function mutations have been documented, with the former potentially leading to hyperactive signaling that may contribute to pathological inflammation or oncogenesis, and the latter predisposing individuals to immunodeficiency syndromes. Specific mutations that affect the structural integrity of the pseudokinase domain can disrupt the delicate balance of autoinhibition, thereby altering kinase activity and influencing STAT-driven transcriptional programs (tomoni2019pseudokinasesfromallosteric pages 10-13, wang2025atripleactioninhibitory pages 1-5).

Beyond its role in classic cytokine signaling, TYK2 is increasingly being explored as a biomarker for disease prognosis in oncology. Aberrant expression or constitutive activation of TYK2 has been identified in several cancers, where it can impact tumor progression and the efficacy of immune surveillance mechanisms. In these contexts, targeting TYK2 may prove beneficial not only in reducing tumor cell proliferation and survival but also in modulating the tumor microenvironment to enhance anti-tumor immunity (woss2019tyk2anupstream pages 3-5, mingione2023allostericregulationand pages 7-9).

Ongoing research efforts are also focused on elucidating the full spectrum of TYK2’s interactions with other signaling molecules and identifying additional layers of regulation. Structural dynamics studies, including high-resolution crystallography and advanced molecular modeling, continue to provide new insights into the conformational states of TYK2. These insights are critical for the rational design of next-generation inhibitors that can achieve optimal efficacy while minimizing adverse effects. The interplay between TYK2’s catalytic activity, its regulatory domains, and its multiple protein-protein interactions remains a vibrant area of investigation that is likely to yield further therapeutic innovations in the near future.

## 9. References

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