

# Role of HIPK2 in the Physiology of Nervous System

## Abstract

HIPK2 is a transformative preserved serine/threonine kinase with multifunctional jobs in pressure reaction, undeveloped turn of events and obsessive circumstances, like malignant growth and fibrosis. The heterogeneity of its interactors and targets makes HIPK2 action firmly subject to the phone setting, and permits it to tweak various flagging pathways, eventually directing cell destiny and multiplication. Both the central and peripheral nervous systems express HIPK2, and mice with its genetic ablation suffer neurological defects. In addition, HIPK2 plays a crucial role in the pathogenesis of neurological disorders by participating in processes and pathways like the endoplasmic reticulum stress response and protein aggregate accumulation. The implications for the pathogenesis of neurological disorders and HIPK2's potential as a therapeutic target and diagnostic or prognostic marker are highlighted in this review of the data regarding its role in neuronal development, survival, and homeostasis.

**Keywords:** Endoplasmic reticulum • Tyrosine phosphorylation-regulated kinases • Homeodomain transcription factors

## Introduction

The most studied member of the HIPK family, which consists of four members in vertebrates, is homeodomain-interacting protein kinase 2 (HIPK2). While HIPK4 is the most distinct member of the family, HIPK1-3, which was discovered to be able to interact with homeodomain transcription factors, shares a high degree of homology. HIPK2 is a pressure responsive kinase acting downstream a few sign transduction pathways, because of a developing rundown of different improvements, for example, DNA harm, oxidative pressure, endoplasmic reticulum (trama center) stress, hypoxia, and glucose/supplement hardship. In like manner, adjustments of this kinase have been accounted for in obsessive circumstances like disease and fibrosis[1-3]. These modifications are very heterogeneous, and give off an impression of being cell-and setting subordinate. Some tumors, like thyroid and breast cancer, have lower levels of HIPK2 expression, while others, like cervical cancer pilocytic astrocytoma, have higher levels. These errors have been made sense of thinking about that the movement of HIPK2 unequivocally relies upon its post-translational changes, intracellular confinement, and sub-atomic associations, all elements that can be distinctively controlled in assorted cell types.

A growing body of evidence also suggests that HIPK2 is involved in the physiology and pathology of neurons. While the job of HIPK2 in malignant growth is all around portrayed somewhere else for model in the accompanying audits here we survey the atomic and practical exchange among HIPK2 and key neurological flagging pathways, calling attention to its physiological job in sensory system improvement and homeostasis, and its expected association in neurological problems, including neurodegenerative sicknesses[4-6].

The isoform of HIPK2-e8, which was made by skipping the 8th exon, lacks only 27 amino acids, which are necessary for binding to the Siah-1 E3 ubiquitin ligase. Unlike the full-length protein, HIPK2-e8 cannot be digested by the proteasome. The HIPK2 variant with a short splice (Ensemble ID ENST00000342645.7; which is known as HIPK2-S, lacks the last two exons but keeps the 13th intron. These results in a protein with 1018 amino acids, a large portion of the AID domain missing, and 30 extra amino acids at the C-terminus. The existence of spliced variants in other vertebrates is unknown. The question of whether they are a distinguishing

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feature of humans will be intriguing.

## Discussion

We will refer to the kinase as HIPK2 in this review to describe its general properties and functions, while specific characteristics of alternative spliced variants will be discussed when they are available. HIPK2 is a member of the CMGC family of protein kinases, which includes the dual-specificity tyrosine phosphorylation-regulated kinases (DYRKs) and the Cyclin-dependent kinases (CDK), Mitogen-activated protein kinases, glycogen synthase kinases, and CDK-like kinases. CMGC kinases have a typical enactment component in light of the phosphorylation of a saved tyrosine buildup in the enactment circle, that is Y361 for HIPK2, inside a Pen theme. This change happens through cis-autophosphorylation during ribosomal biosynthesis, a component guaranteeing that the recently integrated particle is constitutively enacted. Using NM\_022740.5 as a reference, we can say that the catalytic activity of HIPK2 depends on the presence of a crucially conserved lysine residue (K228) in its kinase domain [7–10].

This kinase has very little structural information available. As of late, the precious stone design of HIPK2 kinase space was acquired. Even though this domain shares a lot with the other CMGC kinases, it has some unique characteristics that make it possible to make inhibitors that are more selective for a specific target.

Expression of HIPK2 varies in response to various cellular stimuli. MicroRNAs, circular RNAs, alternative splicing, and circular RNAs all play a role in HIPK2 mRNA transcription, translation, and degradation; whereas protein stability, activity, and localization are altered by post-translational modifications. An extremely mind boggling set of post-translational changes, including phosphorylation, ubiquitylation, SUMOylation, acetylation and caspase cleavage have been accounted for to influence HIPK2 action and regulate its tissue-explicit and cell-setting subordinate capabilities. The effects of these post-translational modifications are combinatorial. As a result, the existence of a modification code that enables HIPK2 to integrate a variety of signaling cues and respond to stimuli of varying types and intensities has been proposed. Different signaling pathways are differentially coordinated by HIPK2 as a result.

For instance, the activity of various E3-ubiquitin

ligases, such as Siah1, Siah2, MDM2, and WSB-1, causes HIPK2 protein levels to typically be extremely low in conditions of basal activity; However, its levels rise in response to genotoxic stress as a result of protein stabilization and a number of post-translational modifications that work together to alter its functions. It is still unclear how various regulatory mechanisms permit the fine-tuning of HIPK2 activity and levels in various spatio-temporal conditions. The possibility of attempting specific targeting and fully comprehending HIPK2-specific functions could emerge from further research in this area.

The HIPK2 gene is abundantly present in a variety of human tissues. Contrasted with different tissues, the focal sensory system (CNS) shows extremely elevated degrees of HIPK2 articulation, indicating that this kinase is controlled in a different way in the neuronal compartments and plays a crucial role in brain functions. Particularly, the tissues of the brain and spinal cord express the full-length HIPK2 transcript at high levels. Analyzing the expression of the HIPK2-e8 isoform yielded comparable outcomes in the same tissues. The HIPK2-S transcript has a widespread expression pattern that is characterized by varying levels of expression and very low expression in brain tissues.

## Conclusion

Interestingly, full-length and e8 isoform expression is lowest in the cerebellum, a part of the brain where expression has been observed to occur at a different time than in other parts of the mouse nervous system. In point of fact, while expression of Hipk2 reaches its highest point at p1 and then decreases in the hippocampus, cortex, and striatum, it increases over time in the cerebellum and reaches its highest point at the most recent time point analyzed (p245). In adult mice, the genetic deletion of Hipk2 is consistently linked to atrophic cerebellar lobules, a significant decrease in cerebellar Purkinje neurons, and astrogliosis. It would be fascinating to assess whether HIPK2 mRNA articulation levels increment during maturing in the cerebellum of human grown-ups also.

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