1. Phylogeny  
   SNF‐related serine/threonine‐protein kinase (SNRK; gene: SNRK KIAA0096, also known as SNFRK; UniProt ID: Q9NRH2) belongs to the evolutionarily conserved AMPK‐related kinase family. Its homologs include yeast SNF1 and mammalian AMP‐activated protein kinase (AMPK), and it is positioned within a core set of eukaryotic kinases regulated by upstream activators such as LKB1. Orthologs of SNRK are identifiable in diverse eukaryotic taxa, indicating that the regulatory systems controlling energy homeostasis and cellular signaling have deep evolutionary origins (jaleel2005identificationofthe pages 1-2, thirugnanam2020snrkametabolic pages 1-3).
2. Reaction Catalyzed  
   SNRK catalyzes the phosphorylation of protein substrates by transferring a phosphate group from ATP to serine or threonine residues. The general chemical reaction is:  
    ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This phosphorylation reaction is central to signal transduction pathways that regulate metabolism and other cellular processes (thirugnanam2020snrkametabolic pages 1-3, wang2018crystalstructureof pages 16-22).
3. Cofactor Requirements  
   The catalytic activity of SNRK is dependent on the divalent metal ion Mg²⁺. Magnesium functions to facilitate correct ATP binding and proper positioning of the phosphate group for transfer, which is characteristic of many serine/threonine kinases (wang2018crystalstructureof pages 16-22, thirugnanam2020snrkametabolic pages 1-3).
4. Substrate Specificity  
   SNRK phosphorylates serine/threonine residues within specific sequence contexts in its substrates, a property shared with other AMPK-related kinases. Although a detailed consensus substrate motif for SNRK has not been fully delineated, studies have demonstrated its ability to target proteins involved in metabolic and inflammatory signaling. For example, SNRK has been reported to phosphorylate regulatory proteins such as components of the mTORC1 complex (e.g., raptor), as well as kinases like Rho-associated protein kinase (ROCK) and Tribbles homolog 3 (Trib3) (jaleel2005identificationofthe pages 6-7, thirugnanam2020snrkametabolic pages 6-7, li2013identificationofsucrose pages 10-10). The substrate recognition is mediated primarily by the catalytic domain, which exhibits similarities to other kinases in the AMPK family. Thus, while an explicit consensus sequence (such as RxRxxp[ST]) has not been unequivocally defined for SNRK, its substrate preferences align with those established for related serine/threonine kinases within this group (thirugnanam2020snrkametabolic pages 6-7).
5. Structure  
   High-resolution structural studies have provided detailed insights into the three-dimensional organization of SNRK. The protein is composed of an N-terminal catalytic kinase domain and an adjacent ubiquitin-associated (UBA) domain, linked by a short hinge region. The kinase domain adopts the typical bilobed structure seen in serine/threonine kinases: a smaller N-terminal lobe characterized by a concentration of β-sheet elements and an αC helix, and a larger C-terminal lobe that houses the activation loop. Central to its enzymatic function is a conserved threonine residue (T173) located in the activation loop, whose phosphorylation by upstream kinases such as LKB1 is essential for catalytic activity (wang2018crystalstructureof pages 12-16, thirugnanam2020snrkametabolic pages 3-4).

The UBA domain of SNRK binds in a distinct mode relative to other members of the AMPK family. Structural analyses have revealed that the UBA domain interacts with both the N- and C-lobes of the kinase domain via a network of hydrophobic contacts and specific polar interactions. In particular, residues from the α3 helix in the UBA domain are involved in contacts with the αC helix of the kinase domain, thereby stabilizing an autoinhibited conformation that modulates the accessibility of the catalytic cleft (wang2018crystalstructureof pages 12-16, thirugnanam2020snrkametabolic pages 3-4). This unique intramolecular association is a key regulatory feature that distinguishes SNRK from other AMPK-related kinases and is important for understanding its activation mechanisms.

1. Regulation  
   SNRK is regulated at multiple levels to ensure proper control of its kinase activity. A major regulatory mechanism involves phosphorylation of the activation loop at T173 by the LKB1:STRAD:MO25 complex. This modification is required for the transition from an inactive to an active conformation, enabling SNRK to phosphorylate its substrates (jaleel2005identificationofthe pages 2-3, thirugnanam2020snrkametabolic pages 1-3).

In addition to phosphorylation-dependent activation, SNRK activity is modulated by an intramolecular interaction between its kinase domain and the UBA domain. The binding of the UBA domain to the kinase domain stabilizes an autoinhibited conformation that likely restricts substrate access until the kinase is fully activated by phosphorylation (wang2018crystalstructureof pages 12-16). While additional post-translational modifications such as ubiquitination have been suggested as part of the regulatory landscape affecting SNRK stability, the precise details of these modifications and their functional consequences remain to be fully characterized (thirugnanam2020snrkametabolic pages 6-7).

1. Function  
   SNRK functions as a serine/threonine kinase that plays pivotal roles in various cellular processes. According to experimental evidence, SNRK may influence hematopoietic cell proliferation and differentiation. It is also proposed to act as a mediator of neuronal apoptosis, indicating a potential role in neural cell turnover and survival. In tissues such as brain and testis, SNRK protein complexes have been observed at relatively high levels, underscoring its significance in these cell types (jaleel2005identificationofthe pages 6-7).

Beyond these specified roles, SNRK has been implicated in metabolic regulation. For instance, studies in adipocytes have demonstrated that SNRK functions as a suppressor of inflammation by modulating phosphorylation events that affect mTORC1 signaling and downstream metabolic pathways. This involves effects on proteins, such as raptor and acetyl-CoA carboxylase, that govern lipid metabolism and insulin responsiveness (li2013identificationofsucrose pages 10-10). In addition, SNRK’s involvement in cardiac metabolism and vascular development has been noted; experimental models using tissue-specific knockouts have shown that loss of SNRK in cardiomyocytes leads to metabolic imbalances and cardiac dysfunction (thirugnanam2020snrkametabolic pages 16-19).

Collectively, the available data indicate that SNRK acts as a multifunctional regulator, integrating signals related to energy status, inflammation, and cell survival. Its function as an intermediary in signaling cascades controlled by LKB1 and other upstream kinases further positions SNRK as a critical node in cellular signaling networks (jaleel2005identificationofthe pages 1-2, li2013identificationofsucrose pages 10-10, thirugnanam2020snrkametabolic pages 16-19).

1. Other Comments  
   SNRK is of interest as a potential contributor to disease pathogenesis. In particular, variants or deficiencies in SNRK have been associated with dysregulation of insulin signaling and an increase in adipocyte inflammation, phenomena that are linked to metabolic disorders such as obesity and type 2 diabetes. Moreover, given that SNRK is phosphorylated by the tumor suppressor kinase LKB1—a gene frequently mutated in Peutz-Jeghers syndrome—SNRK has been proposed as a candidate for mutation screening in cases of this syndrome where LKB1 mutations are not detected (jaleel2005identificationofthe pages 1-2, li2013identificationofsucrose pages 10-10).

No specific small-molecule inhibitors targeting SNRK have been reported to date, although its kinase activity might be modulated indirectly through its regulatory interactions or by influencing the upstream LKB1 signaling axis. Due to its involvement in regulating metabolic homeostasis and in mediating signals that affect cell proliferation and neuronal survival, SNRK represents an attractive potential therapeutic target in contexts ranging from metabolic disorders to neurodegenerative conditions (thirugnanam2020snrkametabolic pages 6-7, li2019dysregulationofpp2aakt pages 10-10).

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