1. Phylogeny  
   Serine/threonine‐protein kinase ICK (also known as CILK1, intestinal cell kinase, MAK‐related kinase, or laryngeal cancer kinase 2) is a highly conserved member of the CMGC group of the human kinome, a family that includes cyclin‐dependent kinases (CDKs), mitogen‐activated protein kinases (MAPKs), glycogen synthase kinases, and related proteins. ICK shares significant sequence and structural homology in its catalytic domain with both CDKs and MAPKs, yet it diverges from related kinases such as MAK and MOK via differences in its C‐terminal non‐catalytic domain. Orthologs of ICK are found across a broad range of eukaryotic species, indicating that the core mechanisms controlling its activity emerged early in evolution. This evolutionary conservation—as described in comparative analyses of kinase families—places ICK within an ancient clade of CMGC kinases that have maintained critical functions such as the regulation of ciliary dynamics and cell cycle progression from yeast to mammals (chen2013distinctexpressionpatterns pages 1-2, fu2006identificationofyinyang pages 1-2).
2. Reaction Catalyzed  
   ICK catalyzes the phosphorylation of serine and threonine residues on substrate proteins using ATP as the phosphate donor. The enzymatic reaction can be summarized as follows: ATP + [protein]-L-serine/threonine → ADP + [protein]-L-serine/threonine phosphate + H⁺. In addition to phosphorylating external substrates—including components of the intraflagellar transport machinery such as KIF3A—ICK can undergo autophosphorylation events that further modulate its activity (fu2006identificationofyinyang pages 1-2, oh2019ciliopathyassociatedproteinkinase pages 1-3).
3. Cofactor Requirements  
   The catalytic activity of ICK depends on the presence of divalent cations, with Mg²⁺ being essential for its function. Mg²⁺ facilitates the proper positioning and binding of ATP within the kinase active site, enabling efficient phosphate transfer during substrate phosphorylation (fu2009intestinalcellkinase pages 4-5).
4. Substrate Specificity  
   ICK exhibits substrate specificity that is characteristic of proline-directed serine/threonine kinases. Studies indicate that ICK preferentially phosphorylates substrates that contain a consensus motif of R-P-X-S/T-P, wherein the arginine residue at the −3 position is critical for substrate recognition. This substrate preference, which aligns with the motifs recognized by other MAPK/CDK-related kinases, is exemplified by ICK’s ability to phosphorylate KIF3A—a key component of the kinesin-2 complex involved in intraflagellar transport—and thereby modulate ciliary function (fu2006identificationofyinyang pages 1-2, oh2019ciliopathyassociatedproteinkinase pages 8-10).
5. Structure  
   The structural organization of ICK is defined by a conserved N-terminal catalytic domain and a long, intrinsically disordered C-terminal domain. The N-terminal portion of ICK adopts a typical kinase fold similar to those of MAPKs and CDKs, comprising an N-lobe with a glycine-rich loop, a C-helix, and an activation loop that contains a conserved TDY (or TXY) motif. This activation loop is of central importance; full catalytic activity is achieved when the threonine residue (Thr157) is phosphorylated by the upstream kinase CDK20/CCRK and the adjacent tyrosine residue is autophosphorylated. Although high-resolution crystal structures of ICK have not been extensively reported, available data and homology models suggest that the catalytic domain harbors the canonical features such as a catalytic loop and hydrophobic spines needed for phosphotransferase activity. In contrast, the C-terminal domain of ICK is predicted to be intrinsically disordered, a feature that provides conformational flexibility necessary for interactions with substrates and for targeting ICK to the primary cilium, thereby integrating regulatory signals with subcellular localization (chen2013distinctexpressionpatterns pages 1-2, oh2019ciliopathyassociatedproteinkinase pages 1-3, oh2019ciliopathyassociatedproteinkinase pages 8-10).
6. Regulation  
   The activity of ICK is intricately regulated via post-translational modifications and protein-protein interactions. Activation of ICK requires dual phosphorylation within its activation loop: first, the threonine residue (Thr157) is phosphorylated by the cell cycle–related kinase (CCRK, also known as CDK20), and subsequently, the adjacent tyrosine residue (typically Tyr159) undergoes autophosphorylation, together yielding full catalytic competence. This dual phosphorylation mechanism is counterbalanced by the action of protein phosphatases such as PP5, which dephosphorylate Thr157 and thereby modulate kinase activity. In addition to these core regulatory modifications, extracellular signals can influence ICK function; for instance, fibroblast growth factor (FGF) signaling has been reported to induce phosphorylation at a conserved tyrosine residue (such as Tyr15), leading to partial inactivation of ICK. The intrinsically disordered C-terminal domain further contributes to the regulation by mediating protein interactions that dictate proper subcellular localization—particularly in directing ICK to the primary cilium—thus coupling its enzymatic activity to its role in ciliogenesis (fu2006identificationofyinyang pages 1-2, oh2019ciliopathyassociatedproteinkinase pages 1-3).
7. Function  
   ICK fulfills critical roles in cellular physiology, most notably in the regulation of ciliogenesis. By phosphorylating substrates such as KIF3A, ICK modulates intraflagellar transport (IFT), which is essential for the assembly and maintenance of the primary cilium. Through its regulation of IFT, ICK controls ciliary length and influences the compartmentalization of signaling molecules; this includes the proper localization of Sonic Hedgehog (SHH) pathway components and other intraflagellar proteins, thereby affecting downstream developmental signaling cascades. ICK is also expressed in various tissues—with abundant expression in the proliferative crypt regions of the intestine—where it plays a role in cell cycle progression and differentiation. Altered expression levels of ICK have been observed in human colon cancer tissues and mouse intestinal adenomas, indicating a potential contribution to oncogenic processes. Beyond its canonical role in ciliary assembly, ICK’s involvement in modulating cAMP and mTORC1 signaling pathways suggests that it may influence multiple aspects of cellular metabolism and organ development, including cardiac development. These functions underscore ICK’s importance as a regulatory node that integrates kinase activity, ciliary structure, and signal transduction during development and tissue homeostasis (oh2019ciliopathyassociatedproteinkinase pages 8-10, fu2009intestinalcellkinase pages 8-9, chen2013distinctexpressionpatterns pages 1-2).
8. Other Comments  
   Beyond its fundamental cellular roles, ICK has been implicated in several disease states. Genetic studies and data from the Open Targets Platform associate mutations in ICK with developmental disorders such as endocrine-cerebro-osteodysplasia syndrome, cranioectodermal dysplasia, and juvenile myoclonic epilepsy. The designation of ICK as laryngeal cancer kinase 2 also points to its potential involvement in cancer, and aberrant expression of ICK may contribute to tumorigenesis, as evidenced by its elevated levels in human colon cancer tissues. Although the current literature does not yet present well‐characterized small molecule inhibitors that target ICK specifically, the kinase’s regulatory importance in ciliogenesis and cell signaling has prompted interest in developing compounds that might modulate its activity therapeutically. Available sources emphasize that while inhibitors of many CMGC kinases are under active investigation, no inhibitor has been reported to be both highly specific and clinically validated for ICK, highlighting a need for continued research in this area (OpenTargets Search: -ICK,KIAA0936, chen2013distinctexpressionpatterns pages 1-2, chowdhury2023cmgckinasesin pages 25-26, oh2019ciliopathyassociatedproteinkinase pages 1-3).
9. References
10. chen2013distinctexpressionpatterns pages 1-2
11. fu2006identificationofyinyang pages 1-2
12. oh2019ciliopathyassociatedproteinkinase pages 1-3
13. oh2019ciliopathyassociatedproteinkinase pages 8-10
14. fu2009intestinalcellkinase pages 4-5
15. fu2009intestinalcellkinase pages 8-9
16. chowdhury2023cmgckinasesin pages 25-26
17. OpenTargets Search: -ICK,KIAA0936

References

1. (chen2013distinctexpressionpatterns pages 1-2): Tufeng Chen, Di Wu, C. Moskaluk, and Zheng Fu. Distinct expression patterns of ick/mak/mok protein kinases in the intestine implicate functional diversity. PLoS ONE, Nov 2013. URL: https://doi.org/10.1371/journal.pone.0079359, doi:10.1371/journal.pone.0079359. This article has 23 citations and is from a peer-reviewed journal.
2. (fu2006identificationofyinyang pages 1-2): Zheng Fu, Katherine A. Larson, Raghu K. Chitta, Sirlester A. Parker, Benjamin E. Turk, Matthew W. Lawrence, Philipp Kaldis, Konstantin Galaktionov, Steven M. Cohn, Jeffrey Shabanowitz, Donald F. Hunt, and Thomas W. Sturgill. Identification of yin-yang regulators and a phosphorylation consensus for male germ cell-associated kinase (mak)-related kinase. Molecular and Cellular Biology, 26:8639-8654, Nov 2006. URL: https://doi.org/10.1128/mcb.00816-06, doi:10.1128/mcb.00816-06. This article has 93 citations and is from a domain leading peer-reviewed journal.
3. (oh2019ciliopathyassociatedproteinkinase pages 1-3): Yoon Seon Oh, Eric J. Wang, Casey D. Gailey, David L. Brautigan, Benjamin L. Allen, and Zheng Fu. Ciliopathy-associated protein kinase ick requires its non-catalytic carboxyl-terminal domain for regulation of ciliogenesis. Cells, 8:677, Jul 2019. URL: https://doi.org/10.3390/cells8070677, doi:10.3390/cells8070677. This article has 25 citations and is from a peer-reviewed journal.
4. (oh2019ciliopathyassociatedproteinkinase pages 8-10): Yoon Seon Oh, Eric J. Wang, Casey D. Gailey, David L. Brautigan, Benjamin L. Allen, and Zheng Fu. Ciliopathy-associated protein kinase ick requires its non-catalytic carboxyl-terminal domain for regulation of ciliogenesis. Cells, 8:677, Jul 2019. URL: https://doi.org/10.3390/cells8070677, doi:10.3390/cells8070677. This article has 25 citations and is from a peer-reviewed journal.
5. (OpenTargets Search: -ICK,KIAA0936): Open Targets Query (-ICK,KIAA0936, 3 results). Buniello, A. et al. (2025). Open Targets Platform: facilitating therapeutic hypotheses building in drug discovery. Nucleic Acids Research.
6. (fu2009intestinalcellkinase pages 4-5): Zheng Fu, Jungeun Kim, Alda Vidrich, Thomas W. Sturgill, and Steven M. Cohn. Intestinal cell kinase, a map kinase-related kinase, regulates proliferation and g1cell cycle progression of intestinal epithelial cells. American Journal of Physiology-Gastrointestinal and Liver Physiology, 297:G632-G640, Oct 2009. URL: https://doi.org/10.1152/ajpgi.00066.2009, doi:10.1152/ajpgi.00066.2009. This article has 48 citations.
7. (fu2009intestinalcellkinase pages 8-9): Zheng Fu, Jungeun Kim, Alda Vidrich, Thomas W. Sturgill, and Steven M. Cohn. Intestinal cell kinase, a map kinase-related kinase, regulates proliferation and g1cell cycle progression of intestinal epithelial cells. American Journal of Physiology-Gastrointestinal and Liver Physiology, 297:G632-G640, Oct 2009. URL: https://doi.org/10.1152/ajpgi.00066.2009, doi:10.1152/ajpgi.00066.2009. This article has 48 citations.
8. (chowdhury2023cmgckinasesin pages 25-26): Iftekhar Chowdhury, Giovanna Dashi, and S. Keskitalo. Cmgc kinases in health and cancer. Cancers, Jul 2023. URL: https://doi.org/10.3390/cancers15153838, doi:10.3390/cancers15153838. This article has 19 citations and is from a peer-reviewed journal.