## Proposed EC/sub-subclass

Not yet assigned

## Accepted name

Hematopoietic cell kinase

## Synonyms

HCK; p59HCK; p61HCK

## Phylogeny

HCK belongs to the Tyrosine Kinase (TK) group of the eukaryotic protein kinase superfamily and clusters within the Src family of non-receptor tyrosine kinases (Manning et al., 2002; Sicheri & Kuriyan, 1997). The human Src family comprises nine members; HCK, LCK, FGR, BLK, LYN and YRK are largely restricted to hematopoietic or lineage-specific cells, whereas SRC, YES and FYN are broadly expressed (Poh et al., 2015; Roversi et al., 2017).

## Reaction catalysed

ATP + protein-L-tyrosyl → ADP + H⁺ + protein-O-phospho-L-tyrosyl (Alvarado et al., 2010; Guiet et al., 2008; Tintori et al., 2013).

## Cofactor requirements

• ATP is the phosphoryl donor (Alvarado et al., 2010; Poh et al., 2015).  
• A divalent cation is essential; ATP-Mg²⁺ supports catalysis, and Mn²⁺ can substitute and is preferred in vitro (Banavali & Roux, 2007; UnknownAuthors, 2008).

## Specificity

Positional preferences around the phospho-Tyr (0) are:  
P-3 = His/Arg, P-1 = Lys, P + 1 = Gln, P + 3 = Asn (Yaron-Barir et al., 2024).

## Structure

Canonical Src-family domain layout: N-terminal region – SH3 – SH2 – kinase (SH1) – C-terminal tail (Poh et al., 2015; Sicheri & Kuriyan, 1997).  
• Catalytic domain is bilobal; the active site lies between the small N-lobe (with αC-helix) and large C-lobe (Selzer et al., 2024).  
• Key motifs: Lys295–Glu310 ion pair, DFG motif, activation loop Tyr416 (Src numbering) (Sicheri & Kuriyan, 1997; Selzer et al., 2024).  
Structural resources  
– SH3 domain (NMR: PDB 4HCK, 5HCK) (Horita et al., 1998).  
– SH3-SH2 linker (3NHN) and near full-length/inhibitor-bound constructs (1QCF, 4LUE, 5ZJ6) (Alvarado et al., 2010; Selzer et al., 2024).  
– AlphaFold model for UniProt P08631.

## Regulation

Autoinhibition is maintained by phosphorylation of Tyr522 in the C-terminal tail by CSK/CHK; the resulting pTyr binds the SH2 domain while the SH3 domain engages the SH2-kinase linker, locking a closed conformation (Pene-Dumitrescu et al., 2008; Sicheri & Kuriyan, 1997; Dorman et al., 2019).  
Activation sequence:  
1. Dephosphorylation of Tyr522 by phosphatases such as CD45, PTPα, TCPTP or RPTP-T (Poh et al., 2015; Carvalho et al., 2024).  
2. Relief of intramolecular restraints permits trans-autophosphorylation of activation-loop Tyr410 (human p61HCK) for full activity (Roversi et al., 2017; Selzer et al., 2024).  
Engagement of SH3/SH2 with partner proteins also promotes activation and structural data support SH3-dominant regulation (Alvarado et al., 2010).

## Function

Expression / isoforms: Predominantly found in myeloid cells (macrophages, neutrophils) and B-lymphocytes as two isoforms, p59HCK and p61HCK (Poh et al., 2015; Carvalho et al., 2024).  
Upstream inputs: Cytokine receptors (IL-2, IL-6, GM-CSF, EpoR), immunoreceptors (TLR4, FcγRs), integrins, oncogenic BCR/ABL, TEL/ABL and mutant MYD88 (Poh et al., 2015; Roversi et al., 2017; Yang et al., 2016).  
Downstream/partners: Activates PI3K/AKT, MAPK/ERK, STAT3/STAT5 pathways; interacts with STAT3, RasGAP, paxillin, FLT3, CAMK2G and HIV-1 Nef (Poh et al., 2015; UnknownAuthors, 2008).  
Physiological roles: Regulates macrophage and neutrophil phagocytosis, degranulation and migration, and contributes to erythropoiesis and myeloid differentiation (Carvalho et al., 2024; Roversi et al., 2017).

## Inhibitors

Broad-spectrum Src-family inhibitors active on HCK: dasatinib, bosutinib, saracatinib, imatinib, SU6656, A-419259, PP1, PP2 (Pene-Dumitrescu et al., 2008; Poh et al., 2015).  
Other agents: Ibrutinib (direct), iHCK-37, RK-20449, KIN-8194 (dual HCK/BTK) (Yang et al., 2016; Roversi et al., 2017; Carvalho et al., 2024).

## Other Comments

Aberrant HCK activation or over-expression is linked to AML, CML, multiple myeloma, Waldenström’s macroglobulinemia and several solid tumours (Poh et al., 2015; Roversi et al., 2017; Yang et al., 2016). In AML, high HCK correlates with poor prognosis (Carvalho et al., 2024). Engineered mutations highlight functional sites: gatekeeper T338M confers A-419259 resistance, and Y527F (equivalent to Tyr522) is constitutively active and oncogenic (Pene-Dumitrescu et al., 2008).

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