## Phylogeny

The ABL2 kinase belongs to the tyrosine kinase (TK) group and the ABL family of nonreceptor tyrosine kinases (nRTKs) (manning2002theproteinkinase pages 3-3, colicelli2010abltyrosinekinases pages 10-12, colicelli2010abltyrosinekinases pages 5-7). The ABL family is part of a primary clade of 22 human nRTKs, most of which have an SH3-SH2-TK domain architecture (colicelli2010abltyrosinekinases pages 1-2). Phylogenetically, ABL kinases are grouped with SRC family kinases, indicating a close evolutionary relationship (colicelli2010abltyrosinekinases pages 10-12).

ABL2 is a paralog of ABL1, having arisen from a gene duplication event of a single ancestral Abl gene early in vertebrate evolution (manning2002theproteinkinase pages 3-3, colicelli2010abltyrosinekinases pages 1-2, unknownauthors2022thecharacterizationof pages 17-24). This is supported by high sequence identity (>90%) within the SH3-SH2-tyrosine kinase (TK) domain cassette and conserved intron-exon boundaries between the two genes (colicelli2010abltyrosinekinases pages 1-2, unknownauthors2022thecharacterizationof pages 17-24). Human ABL1 and ABL2 are more closely related to each other and their fly ortholog than to any other nonreceptor tyrosine kinases (colicelli2010abltyrosinekinases pages 1-2).

Orthologs of ABL kinases are found in all metazoans, indicating an early evolutionary origin (colicelli2010abltyrosinekinases pages 1-2). A single ABL gene is present in nonvertebrate metazoans like the fruit fly (*Drosophila melanogaster*), sea urchin, and *Caenorhabditis elegans* (colicelli2010abltyrosinekinases pages 1-2, unknownauthors2022thecharacterizationof pages 17-24). Kinases with an ABL-like SH3-SH2-TK cassette are also present in unicellular protists such as *Monosiga brevicollis* (colicelli2010abltyrosinekinases pages 1-2). In vertebrates, ABL2 orthologs are conserved across species including primates, rodents, marsupials, birds, amphibians, and fish (colicelli2010abltyrosinekinases pages 27-36).

## Reaction Catalyzed

ABL2 catalyzes the transfer of the gamma-phosphate group from an ATP molecule to a tyrosine residue on a protein substrate (colicelli2010abltyrosinekinases pages 5-7, yaronbarir2024theintrinsicsubstrate pages 3-4).

## Cofactor Requirements

The catalytic activity of ABL2 requires ATP as a cofactor and is dependent on the coordination of a divalent cation, such as Mg2+, which is essential for catalysis (colicelli2010abltyrosinekinases pages 5-7, irgit2025structureanddynamics pages 4-5).

## Substrate Specificity

The intrinsic substrate motif for ABL kinases shows a preference for proline (P) at the +3 position and alanine (A) at the +1 position relative to the phosphorylated tyrosine (pY) (yaronbarir2024theintrinsicsubstrate pages 3-4). Aliphatic residues are favored at the -1 position (yaronbarir2024theintrinsicsubstrate pages 3-4). ABL2 and ABL1 share a similar substrate specificity motif characterized by the pattern (L/I/V)-pY-x-x-P, with a preference for hydrophobic amino acids (leucine, isoleucine, or valine) at the -1 position and proline at +3 (colicelli2010abltyrosinekinases pages 5-7). Additionally, acidic residues such as aspartate or glutamate are enriched at the -4, -3, and +1 positions (colicelli2010abltyrosinekinases pages 5-7).

## Structure

ABL2 is a multi-domain protein composed of an N-terminal CAP domain, an SH3 domain, an SH2 domain, a kinase (SH1) domain, and a long, divergent C-terminal region (unknownauthors2022thecharacterizationof pages 17-24, hantschel2012structureregulationsignaling pages 1-2). The kinase domain has a bilobal architecture with a smaller N-terminal lobe and a larger C-terminal lobe (irgit2025structureanddynamics pages 3-4). The C-terminal region contains unique features that distinguish ABL2 from ABL1, including a calponin homology (CH)–type F-actin–binding domain, a second internal F-actin binding domain with an I/LWEQ motif, and a microtubule-binding domain (MTBD) (unknownauthors2022thecharacterizationof pages 17-24, colicelli2010abltyrosinekinases pages 7-8, greuber2013roleofabl pages 1-2).

Key regulatory elements within the kinase domain control its catalytic activity: - **Activation Loop (A-loop)**: This flexible loop contains the highly conserved DFG motif. In the active state (DFG-in), the A-loop is open, allowing substrate access, with the aspartate residue facing the ATP-binding site. In the inactive state (DFG-out), the loop adopts a closed conformation that blocks the active site (irgit2025structureanddynamics pages 4-5). Crystal structures of ABL2 have also revealed an intermediate DFG conformation (salah2011crystalstructuresof pages 1-2). - **αC helix**: This helix in the N-lobe switches between an “in” conformation, which is required for catalysis, and an “out” conformation that stabilizes the inactive state (irgit2025structureanddynamics pages 4-5, dorey2001phosphorylationandstructurebased pages 1-2). - **Hydrophobic Spine**: This is a network of spatially conserved hydrophobic residues, including the phenylalanine from the DFG motif, that links the N- and C-lobes. The spine stabilizes the kinase’s active conformation, and its disruption contributes to autoinhibition in the inactive state (salah2011crystalstructuresof pages 1-2, irgit2025structureanddynamics pages 4-5).

Alternative splicing of ABL2 generates isoforms, such as the 1b isoform, which contains an N-terminal glycine that is myristoylated and binds to a hydrophobic pocket in the kinase C-lobe (greuber2013roleofabl pages 1-2, wang2015theemergingrole pages 2-4, unknownauthors2022thecharacterizationof pages 24-29).

## Regulation

ABL2 kinase activity is tightly controlled by an autoinhibitory mechanism (unknownauthors2022thecharacterizationof pages 17-24). In the inactive state, the SH3 and SH2 domains form a “clamp,” with the SH3 domain binding the SH2-kinase linker and the SH2 domain docking onto the kinase C-lobe (hantschel2012structureregulationsignaling pages 1-2, wang2015theemergingrole pages 2-4). In the 1b isoform, binding of the N-terminal myristoyl group to a pocket in the kinase domain further stabilizes this inhibited conformation (greuber2013roleofabl pages 19-22, unknownauthors2022thecharacterizationof pages 24-29). Key residues involved in autoinhibition include K7, W118, E157, Y158, P242, and P249 (colicelli2010abltyrosinekinases pages 4-5). Activation involves disruption of these interactions and a conformational switch of the SH2 domain (unknownauthors2022thecharacterizationof pages 24-29).

Post-translational modifications are critical for ABL2 regulation: - **Phosphorylation**: Tyrosine phosphorylation modulates activity. Phosphorylation by SRC family kinases, PDGFR, or autophosphorylation at Y272 (SH2-kinase linker) and Y439 (activation loop) increases kinase activity by stabilizing the active conformation (colicelli2010abltyrosinekinases pages 4-5, wang2015theemergingrole pages 2-4, greuber2013roleofabl pages 19-22). Phosphorylation at Y261 promotes protein stabilization (colicelli2010abltyrosinekinases pages 4-5). - **Dephosphorylation**: Protein tyrosine phosphatases (PTPs), including PTPN1, PTPN6, PTPN11 (SHP-2), PTPN12, and PTPN18, act as negative regulators (colicelli2010abltyrosinekinases pages 7-8). - **Ubiquitination**: The E3 ligase CBL mediates ubiquitination of ABL2, which can lead to its degradation (colicelli2010abltyrosinekinases pages 4-5).

Allosteric regulation occurs via binding to filamentous actin and the lipid phosphatidylinositol 4,5-bisphosphate (PIP2), both of which inhibit kinase activity (colicelli2010abltyrosinekinases pages 7-8, wang2015theemergingrole pages 2-4).

## Function

ABL2 is a widely expressed cytoplasmic kinase that localizes to F-actin-rich structures such as focal adhesions, adherens junctions, invadopodia, and phagocytic cups (greuber2013roleofabl pages 1-2, wang2015theemergingrole pages 2-4, colicelli2010abltyrosinekinases pages 2-4). It functions to link extracellular stimuli to intracellular pathways controlling cell growth, survival, adhesion, and motility (greuber2013roleofabl pages 1-2). Upstream signals that activate ABL2 include those from receptor tyrosine kinases (RTKs), integrins, cadherins, chemokines, and oxidative stress (greuber2013roleofabl pages 26-27). Its primary role is in regulating cytoskeletal dynamics, which it achieves by binding and bundling F-actin and by phosphorylating cytoskeletal proteins like TUBA, TUBB, tau, and paxillin (colicelli2010abltyrosinekinases pages 1-2, colicelli2010abltyrosinekinases pages 7-8, colicelli2010abltyrosinekinases pages 8-10).

ABL2 interacts with numerous signaling proteins, including SH3 domain-containing adaptors like CRK, CRKL, NCK1, ABI1, and ABI2 via its PxxP motifs (colicelli2010abltyrosinekinases pages 7-8, colicelli2010abltyrosinekinases pages 8-10). It also interacts with cortactin and WAS-family proteins, promoting actin reorganization through the ARP2/3 complex (colicelli2010abltyrosinekinases pages 8-10). ABL2 can form heterodimers with ABL1, which enhances catalytic activity (colicelli2010abltyrosinekinases pages 7-8).

## Inhibitors

Small molecule inhibitors that target the ATP-binding site of ABL family kinases include imatinib and dasatinib (salah2011crystalstructuresof pages 1-2, yaronbarir2024theintrinsicsubstrate pages 5-5).

## Other Comments

Activation of ABL2 is found in various solid tumors, such as breast, colon, lung, and kidney carcinomas, and melanoma (greuber2013roleofabl pages 1-2). In hematological malignancies, ABL2 is activated by chromosomal translocation in acute myeloid leukemia (AML) (colicelli2010abltyrosinekinases pages 12-13).

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