## Phylogeny

ATM is a member of the Phosphatidylinositol 3-Kinase-related Kinase (PIKK or PI3KK) family, a group of large serine/threonine kinases (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, guleria2016atmkinasemuch pages 2-2). Kinome classification by Manning et al. places ATM within this distinct family, which also includes ATR, DNA-PKcs, and mTOR (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, shiloh2013theatmprotein pages 2-3). The PIKK family members are evolutionarily related, sharing a conserved domain architecture that includes a C-terminal kinase domain, a FAT domain, and a FATC domain, which reflects a shared lineage and forms a distinct clade within the protein kinase superfamily (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, paull2015mechanismsofatm pages 3-4). ATM orthologs are found broadly across eukaryotes, including yeast (*S. cerevisiae* Tel1p, *S. pombe* rad3), *Drosophila melanogaster* (mei-41), and mammals (mouse Atm), indicating a conserved role in DNA damage signaling and cellular homeostasis (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, hoekstra1997responsestodna pages 5-6, lee2021cellularfunctionsof pages 3-4, putti2021atmkinasedead pages 1-2).

## Reaction Catalyzed

ATM catalyzes the transfer of the γ-phosphate group from an ATP molecule to a protein substrate (paull2015mechanismsofatm pages 3-4, guleria2016atmkinasemuch pages 2-3). The reaction is: ATP + a protein substrate → ADP + a phosphoprotein substrate (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, paull2015mechanismsofatm pages 3-4).

## Cofactor Requirements

The catalytic reaction requires ATP as the phosphate donor (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, guleria2016atmkinasemuch pages 2-3). Optimal *in vitro* kinase activity is dependent on divalent metal ions, specifically Mn²⁺ (kim1999substratespecificitiesand pages 1-2, kim1999substratespecificitiesand pages 3-3). Some studies report a requirement for either Mn²⁺ or Mg²⁺ (putti2021atmkinasedead pages 7-8). Unlike DNA-PKcs, ATM activity does not require DNA ends or Ku proteins (kim1999substratespecificitiesand pages 1-2, kim1999substratespecificitiesand pages 5-6).

## Substrate Specificity

ATM is a serine/threonine kinase that recognizes and phosphorylates the consensus sequence [S/T]-Q, where a glutamine residue is located at the +1 position relative to the serine or threonine phospho-acceptor site (johnson2023anatlasof pages 2-3, kim1999substratespecificitiesand pages 1-2, shiloh2013theatmprotein pages 2-3). Substrate recognition is enhanced by hydrophobic amino acids (e.g., Leucine, Isoleucine) located in the positions immediately preceding the SQ/TQ motif (kim1999substratespecificitiesand pages 4-5). Conversely, positively charged amino acids, such as lysine or arginine, near the phosphorylation site reduce substrate recognition (kim1999substratespecificitiesand pages 5-6). A comprehensive analysis of the human kinome confirmed that ATM substrate motifs cluster with other kinases that select for glutamine at the +1 position, and a motif-based computational model accurately predicted known ATM-substrate interactions, including the phosphorylation of p53 at Ser15 (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 3-4).

## Structure

ATM is a large, ~350–370 kDa protein that exists as an inactive, non-covalently linked homodimer in its resting state (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, guleria2016atmkinasemuch pages 2-2). The protein’s domain architecture includes a large N-terminal region composed of α-helical HEAT repeats that serve as scaffolds for protein-protein interactions, a central FAT (FRAP-ATM-TRRAP) domain, a C-terminal bi-lobed kinase domain, and a terminal FATC (FAT C-terminal) domain (paull2015mechanismsofatm pages 3-4, ueno2022atmfunctionsof pages 1-2). In the inactive dimer, the kinase domain’s catalytic site is autoinhibited and sequestered within a deep cleft, with the FAT domain restricting substrate access (choy2018neurodegenerationinataxia‐telangiectasia pages 1-5, choy2018neurodegenerationinataxia‐telangiectasia pages 5-8). Structural studies have identified ‘closed’ inactive and ‘open’ partially active dimer conformations (ueno2022atmfunctionsof pages 2-4, lee2021cellularfunctionsof pages 3-4). The kinase domain shares structural homology with PI3-kinases and contains conserved catalytic and activation loops responsible for ATP binding and coordinating phosphotransfer (paull2015mechanismsofatm pages 13-15, paull2015mechanismsofatm pages 3-4).

## Regulation

ATM is primarily activated by DNA double-strand breaks (DSBs) through a mechanism dependent on the MRN sensor complex (Mre11-Rad50-NBS1) (choy2018neurodegenerationinataxia‐telangiectasia pages 5-8). The MRN complex recruits ATM to DSB sites, triggering the dissociation of the inactive homodimer into active monomers (choy2018neurodegenerationinataxia‐telangiectasia pages 5-8, paull2015mechanismsofatm pages 1-3). This conformational change facilitates full activation through a series of post-translational modifications (PTMs). The hallmark PTM is autophosphorylation at Ser1981, which is a widely used marker of ATM activation (guleria2016atmkinasemuch pages 2-2, lee2021cellularfunctionsof pages 3-4). Other autophosphorylation sites, including Ser367 and Ser1893, also contribute to its activation (choy2018neurodegenerationinataxia‐telangiectasia pages 5-8). Additionally, acetylation at Lys3016 relieves auto-inhibition and promotes kinase activity (lee2021cellularfunctionsof pages 3-4, ueno2022atmfunctionsof pages 2-4). ATM can also be activated independently of the MRN complex and DSBs in response to oxidative stress, a process that involves cysteine oxidation (lee2021cellularfunctionsof pages 3-4, paull2015mechanismsofatm pages 1-3).

## Function

ATM is an apical kinase in the DNA damage response (DDR) signaling network, where it functions as a sensor for DSBs and other genotoxic stresses (shiloh2013theatmprotein pages 1-2, jin2019atmindna pages 1-2). While localized predominantly in the nucleus, ATM also has functions in the cytoplasm, mitochondria, and peroxisomes (choy2018neurodegenerationinataxia‐telangiectasia pages 5-8). Upon activation by the upstream MRN complex, ATM phosphorylates a multitude of downstream substrates to orchestrate cellular processes including cell cycle checkpoints, DNA repair, and apoptosis (choy2018neurodegenerationinataxia‐telangiectasia pages 5-8, shiloh2013theatmprotein pages 1-2). Key downstream substrates include the tumor suppressor p53, checkpoint kinase 2 (CHK2), and the histone variant H2AX, which is phosphorylated at Ser139 to form γH2AX at sites of DNA damage (lee2021cellularfunctionsof pages 3-4, guleria2016atmkinasemuch pages 2-2, mckinnon2004atmandataxia pages 1-2). Beyond the DDR, ATM is involved in maintaining cellular homeostasis, regulating oxidative stress responses, and mitochondrial function (guleria2016atmkinasemuch pages 2-2, choy2018neurodegenerationinataxia‐telangiectasia pages 1-5).

## Inhibitors

Several experimental and clinical inhibitors targeting ATM kinase activity have been developed (jin2019atmindna pages 1-2). Experimental inhibitors include KU-55933, KU-60019, KU-59403, and CP-466722 (jin2019atmindna pages 1-2). More selective inhibitors developed for clinical investigation include AZD0156 and AZD1390, the latter of which is capable of crossing the blood-brain barrier (jin2019atmindna pages 1-2). ATM is also sensitive to inhibition by wortmannin, a phosphatidylinositol 3-kinase inhibitor (hoekstra1997responsestodna pages 5-6).

## Other Comments

Mutations in the *ATM* gene cause Ataxia-Telangiectasia (A-T), a pleiotropic autosomal recessive disorder (guleria2016atmkinasemuch pages 2-2, shiloh2013theatmprotein pages 1-2). A-T is characterized by progressive neurodegeneration (specifically cerebellar ataxia), immunodeficiency, telangiectasias, extreme sensitivity to ionizing radiation, and a strong predisposition to cancer, particularly lymphoid malignancies (paull2015mechanismsofatm pages 1-3, ueno2022atmfunctionsof pages 1-2, choy2018neurodegenerationinataxia‐telangiectasia pages 5-8). A significant portion of A-T-causing mutations (~70%) result in protein truncation and a complete loss of function, while kinase-dead missense mutations are also associated with genomic instability and cancer predisposition (guleria2016atmkinasemuch pages 2-2, putti2021atmkinasedead pages 10-11).

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