## Phylogeny

Myotonin-protein kinase (DMPK) is assigned to the DMPK family of kinases (manning2002theproteinkinase pages 7-8, unknownauthors2006myotronicdystrophyprotein pages 19-21, unknownauthors2006myotronicdystrophyprotein pages 21-23, unknownauthors2006myotronicdystrophyprotein pages 54-56). Sources conflict regarding its higher-level group classification; one source places it within the CMGC group (manning2002theproteinkinase pages 7-8), while numerous others classify it within the AGC group (unknownauthors2006myotronicdystrophyprotein pages 36-39, wansink2003alternativesplicingcontrols pages 1-2, manning2002theproteinkinase pages 4-5, unknownauthors2006myotronicdystrophyprotein pages 120-124, ophuis2009dmpkproteinisoforms pages 16-19, unknownauthors2006myotronicdystrophyprotein pages 19-21, wansink2003alternativesplicingcontrols pages 1-2).

DMPK is closely homologous to p21-activated kinases MRCK (Myotonic dystrophy kinase-related Cdc42-binding kinase) and ROCK (Rho-associated coiled-coil containing protein kinase), sharing 70% kinase domain identity with MRCKa (unknownauthors2006myotronicdystrophyprotein pages 36-39, wansink2003alternativesplicingcontrols pages 1-2, ophuis2009dmpkproteinisoforms pages 16-19). The DMPK family also includes ROCK-I/-II, MRCK isoforms, and Citron kinase (unknownauthors2006myotronicdystrophyprotein pages 120-124, unknownauthors2006myotronicdystrophyprotein pages 19-21, unknownauthors2006myotronicdystrophyprotein pages 21-23). The kinase is more distantly related to the nuclear Dbf2-related (NDR) family, large tumor suppressor (LATS) kinases, and archetypal AGC kinases like PKA, PKB, and PKC (unknownauthors2006myotronicdystrophyprotein pages 19-21). Orthologs of DMPK are conserved in humans and mice (unknownauthors2006myotronicdystrophyprotein pages 36-39, wansink2003alternativesplicingcontrols pages 1-2, unknownauthors2006myotronicdystrophyprotein pages 21-23).

## Reaction Catalyzed

DMPK is a serine/threonine protein kinase that catalyzes the transfer of the terminal gamma-phosphate from ATP to the hydroxyl group of serine or threonine residues on substrate proteins (manning2002theproteinkinase pages 7-8, johnson2023anatlasof pages 2-3, unknownauthors2006myotronicdystrophyprotein pages 21-23). The chemical reaction is: protein (Ser/Thr) + ATP → protein (phospho-Ser/Thr) + ADP (johnson2023anatlasof pages 2-3).

## Cofactor Requirements

Catalytic activity is dependent on divalent metal ions (manning2002theproteinkinase pages 7-8). DMPK utilizes either Mg2+ or Mn2+ as cofactors (unknownauthors2006myotronicdystrophyprotein pages 36-39, wansink2003alternativesplicingcontrols pages 1-2, unknownauthors2006myotronicdystrophyprotein pages 120-124, unknownauthors2006myotronicdystrophyprotein pages 54-56). The cofactor is essential for coordinating ATP binding and catalysis; it is chelated by an aspartate in the DFG motif to position the γ-phosphate of ATP for transfer (johnson2023anatlasof pages 2-3, unknownauthors2006myotronicdystrophyprotein pages 21-23).

## Substrate Specificity

DMPK is a Lys/Arg-directed kinase (unknownauthors2006myotronicdystrophyprotein pages 36-39, wansink2003alternativesplicingcontrols pages 1-2). It preferentially phosphorylates threonine or serine residues that are N-terminally preceded by three to four positively charged amino acids, specifically arginines or lysines, at distinct positions (unknownauthors2006myotronicdystrophyprotein pages 49-51, wansink2003alternativesplicingcontrols pages 11-12). This consensus motif is characterized by positively charged residues primarily at positions -3 and -5 relative to the phosphoacceptor site (unknownauthors2006myotronicdystrophyprotein pages 49-51). DMPK accepts both arginine and lysine residues at these positions, distinguishing it from PKB, which has a strong preference for arginine (unknownauthors2006myotronicdystrophyprotein pages 49-51). The classical PKB substrate is not phosphorylated by DMPK (unknownauthors2006myotronicdystrophyprotein pages 49-51). Peptides derived from MYPT1, such as RQSRRSTQG and GEKRRSTGV, conform to this consensus sequence and are phosphorylated in vitro (unknownauthors2006myotronicdystrophyprotein pages 49-51).

## Structure

DMPK has a multidomain architecture consisting of an N-terminal leucine-rich domain containing a leucine zipper motif, a central serine/threonine kinase domain, a protein kinase C-terminal extension, an α-helical coiled-coil domain, and variable C-terminal tails produced by alternative splicing (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 36-39, wansink2003alternativesplicingcontrols pages 1-2, unknownauthors2006myotronicdystrophyprotein pages 21-23, wansink2003alternativesplicingcontrols pages 3-5). The coiled-coil domain mediates multimerization and oligomerization (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 25-28).

The kinase domain contains conserved catalytic features, including a phosphate-binding P-loop (GXGXXG motif), an invariant lysine (Lys100 in DMPK) that forms an ion pair with a conserved glutamic acid in the αC helix, and a DFG motif in the activation loop that coordinates the metal cofactor (unknownauthors2006myotronicdystrophyprotein pages 21-23, unknownauthors2006myotronicdystrophyprotein pages 23-25). The activation loop and αC helix are key regulatory elements (unknownauthors2006myotronicdystrophyprotein pages 23-25). A unique feature is the presence of an alternatively spliced internal Val-Ser-Gly-Gly-Gly (VSGGG) motif, which influences protein conformation and autophosphorylation (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 36-39, unknownauthors2006myotronicdystrophyprotein pages 49-51). DMPK lacks common accessory domains like SH2, SH3, or PH domains (unknownauthors2006myotronicdystrophyprotein pages 23-25, unknownauthors2006myotronicdystrophyprotein pages 49-51).

## Regulation

DMPK activity is regulated by intramolecular mechanisms, including autoinhibition and autophosphorylation (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, wansink2003alternativesplicingcontrols pages 1-2). The C-terminal domain acts as an autoinhibitory region that restricts access to the catalytic site; deletion of this tail, as in isoforms E, F, and G, increases kinase activity (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, unknownauthors2006myotronicdystrophyprotein pages 19-21, unknownauthors2006myotronicdystrophyprotein pages 49-51).

The kinase undergoes autophosphorylation, a process influenced by the presence of the alternatively spliced VSGGG motif, which alters the protein’s 3D conformation (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 36-39, unknownauthors2006myotronicdystrophyprotein pages 49-51). The major autophosphorylation site is located near Ser379, though the exact residues have not been confirmed (unknownauthors2006myotronicdystrophyprotein pages 49-51).

## Function

DMPK is highly expressed in cardiac, skeletal, and smooth muscle tissues, with moderate expression in the brain (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, ophuis2009dmpkproteinisoforms pages 16-19). DMPK isoforms have distinct subcellular localizations determined by their C-terminal tails: long tails allow membrane anchoring to the endoplasmic reticulum or mitochondrial outer membrane, while short tails result in cytosolic localization (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, unknownauthors2006myotronicdystrophyprotein pages 36-39). The protein is also found at the sarcoplasmic reticulum, T-tubules, neuromuscular junctions, and intercalated discs (unknownauthors2006myotronicdystrophyprotein pages 25-28).

Known downstream substrates include myosin phosphatase target subunit 1 (PPP1R12A/MYPT1), phospholamban (PLN), and phospholemman (FXYD1) (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, unknownauthors2006myotronicdystrophyprotein pages 25-28, wansink2003alternativesplicingcontrols pages 1-2). Through phosphorylation of these substrates, DMPK regulates muscle contractility, Ca2+ handling, and ion channel function (unknownauthors2006myotronicdystrophyprotein pages 139-141, unknownauthors2006myotronicdystrophyprotein pages 25-28). DMPK also interacts with mitochondrial outer membrane proteins to influence mitochondrial positioning and clustering, impacting muscle respiratory function and synaptic plasticity (unknownauthors2006myotronicdystrophyprotein pages 139-141).

## Inhibitors

Staurosporine and its structural analogs, such as SB 218078 and PKC-412, are broadly acting, promiscuous inhibitors of DMPK (jester2012testingthepromiscuity pages 2-4, jester2012testingthepromiscuity pages 13-14). Ro 31-8220, a bisindolylmaleimide, is a potent experimental inhibitor of DMPK, showing 22% inhibition at a 10 μM concentration in one screen (unknownauthors2011developmentofa pages 113-126, jester2012testingthepromiscuity pages 13-14). Other compounds exhibit weaker activity; CGP 53353 shows moderate inhibition (~30%), while pyrazolopyrimidine-based inhibitors PP1, PP2, and 1-naphthyl PP1 show weak inhibition (19–32%) (jester2012testingthepromiscuity pages 4-5, unknownauthors2011developmentofa pages 126-132). Arcyriaflavin A and PD 407824 displayed limited inhibition of DMPK (jester2012testingthepromiscuity pages 4-5).

## Other Comments

Myotonic Dystrophy type 1 (DM1) is caused by an unstable expansion of a CTG trinucleotide repeat in the 3’-untranslated region (3’-UTR) of the *DMPK* gene (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, unknownauthors2006myotronicdystrophyprotein pages 14-16, unknownauthors2006myotronicdystrophyprotein pages 21-23, wansink2003alternativesplicingcontrols pages 1-2). Disease severity and age of onset correlate with the repeat length; normal alleles contain 5-37 CTG repeats, while pathogenic expansions range from 35 to several thousand (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 14-16).

The primary disease mechanism is a toxic RNA gain-of-function (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, unknownauthors2006myotronicdystrophyprotein pages 14-16, wansink2003alternativesplicingcontrols pages 1-2, ophuis2009dmpkproteinisoforms pages 16-19). The expanded CUG repeats in the mutant DMPK mRNA form stable hairpin structures that accumulate in the nucleus as RNA foci (ophuis2009dmpkproteinisoforms pages 16-19, unknownauthors2006myotronicdystrophyprotein pages 19-21). These toxic RNA molecules sequester RNA-binding proteins, such as muscleblind-like (MBNL) proteins, leading to widespread disruption of alternative splicing and other RNA processing events, which causes the multisystemic pathology of DM1 (ophuis2009dmpkproteinisoforms pages 13-16, unknownauthors2006myotronicdystrophyprotein pages 139-141, unknownauthors2006myotronicdystrophyprotein pages 19-21, unknownauthors2006myotronicdystrophyprotein pages 49-51).

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