Protein: Transient receptor potential cation channel subfamily M member 7 (TRPM7, Chak1/LTRPC7) – UniProt Q96QT4

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Phylogeny  
• Orthologous genes are reported in Mus musculus (Trpm7) and Danio rerio (trpm7, meltdown mutant), confirming conservation across vertebrates (duan2018structureofthe pages 1-1, unknownauthors2023rolesoftransient pages 60-61).  
• The closest human paralogue is TRPM6; TRPM6/TRPM7 heteromers illustrate recent gene duplication within the TRPM6/7 branch (cai2017massspectrometricanalysis pages 12-13).  
• The catalytic region belongs to the atypical α-kinase clade, sharing distant homology with elongation factor-2 kinase and classified within the “Other/α-kinase” family of the human kinome (cai2017massspectrometricanalysis pages 1-3, cai2017massspectrometricanalysis pages 13-13).

Reaction Catalyzed  
• ATP + [protein]-L-Ser/Thr → ADP + [protein]-O-phospho-L-Ser/Thr (cai2017massspectrometricanalysis pages 1-3).

Cofactor Requirements  
• Catalytic activity requires divalent metal–nucleotide complexes; Mn²⁺·ATP supports maximal turnover, while Mg²⁺·ATP functions both as cofactor and channel inhibitor (cai2017massspectrometricanalysis pages 12-13, visser2014functionandregulation pages 11-11).

Substrate Specificity  
• Phosphorylation targets serine/threonine residues embedded within α-helical secondary structure rather than a strict linear consensus (cai2017massspectrometricanalysis pages 1-3).  
• Documented substrates: non-muscle myosin heavy chain IIA, annexin I, phospholipase C γ2 and core histones (cai2017massspectrometricanalysis pages 1-3).

Structure  
• Domain organisation: N-terminal melastatin homology/ankyrin repeat region, six-transmembrane channel core (S1–S6) with pore loop, intracellular TRP helix, tetrameric coiled-coil, serine/threonine-rich autophosphorylation segment and C-terminal α-kinase domain (unknownauthors2019domainspecificroleof pages 23-26, cai2017massspectrometricanalysis pages 1-3).  
• Cryo-EM structures (3.3–4.1 Å) show a closed pore stabilised by a Cys1056–Cys1066 disulfide bond (duan2018structureofthe pages 1-1, duan2018structureofthe pages 6-8).  
• The lower gate is formed by N1097/N1098, residues essential for Mg²⁺-dependent channel inhibition (schmidt2022structuralmechanismof pages 3-4).  
• A Zn²⁺ ion coordinates within the kinase core, reinforcing tertiary stability (duan2018structureofthe pages 1-1).  
• Kinase domains dimerise via an exchange segment that swaps β-strands between protomers, a prerequisite for catalysis (cai2017massspectrometricanalysis pages 1-3).  
• Inhibitor-bound human structure (PDB 8W2L) reveals CCT128930 occupying a vanilloid-like pocket; F924 is critical for ligand engagement (nadezhdin2024structuralbasisof pages 24-27, nadezhdin2024structuralbasisof pages 27-28).

Regulation  
• >20 autophosphorylation sites detected; key residues include S1777 in the catalytic loop and S1565 in the exchange segment (cai2017massspectrometricanalysis pages 1-3, cai2017massspectrometricanalysis pages 3-3).  
• Phosphomimetic substitution at S1777 diminishes kinase activity, whereas phosphorylation at S1565 restricts substrate access without disrupting dimerisation (cai2017massspectrometricanalysis pages 1-3).  
• TRPM6 trans-phosphorylates TRPM7 within heteromeric assemblies, adding regulatory phosphosites (cai2017massspectrometricanalysis pages 12-13).  
• Intracellular Mg²⁺ and Mg·ATP bind near N1097/N1098, producing synergistic channel inhibition (schmidt2022structuralmechanismof pages 3-4).  
• Hydrolysis or depletion of membrane PIP₂ through PLC pathways leads to rapid current inactivation (chubanov2018trpm7reflectedin pages 3-3, zhelay2018depletionofplasma pages 12-14).  
• Proteolytic cleavage liberates the kinase domain, which can relocalise to the nucleus (nadezhdin2023structuralmechanismsof pages 12-13).

Function  
• Ubiquitously expressed with highest levels in heart, kidney and brain; constitutive expression begins in early embryogenesis (unknownauthors2010theproteininteractions pages 20-26, hu2021roleoftrpm7 pages 1-2).  
• Global knockout causes embryonic lethality and organogenesis defects, indicating essential physiological roles (duan2018structureofthe pages 1-1).  
• Functions as a constitutively active conduit for Mg²⁺, Ca²⁺ and Zn²⁺, maintaining intracellular divalent cation homeostasis (sun2015trpm7andits pages 30-33).  
• Operates as a vesicular Zn²⁺ release channel and modulator of intracellular Ca²⁺ signalling (unknownauthors2023rolesoftransient pages 60-61).  
• Kinase activity phosphorylates cytoskeletal and trafficking effectors including myosin IIA, annexin I, PLC γ2 and snapin (cai2017massspectrometricanalysis pages 1-3, unknownauthors2010theproteininteractions pages 20-26).  
• Interaction network comprises TRPM6, snapin, synapsin I, synaptotagmin I and PLC γ2 (cai2017massspectrometricanalysis pages 12-13, unknownauthors2010theproteininteractions pages 20-26).  
• Engages in magnesium-sensitive Socs3a signalling that governs epithelial proliferation (visser2014functionandregulation pages 11-11).

Inhibitors  
• CCT128930 – selective antagonist; sub-micromolar inhibition of TRPM7 Ca²⁺ influx; binds vanilloid-like pocket (nadezhdin2024structuralbasisof pages 15-16, nadezhdin2024structuralbasisof pages 24-27).  
• NS8593 – pore blocker that suppresses TRPM7-mediated Ca²⁺ entry (nadezhdin2024structuralbasisof pages 15-16).  
• VER155008 – reduces channel activity in high-throughput screens (nadezhdin2024structuralbasisof pages 24-27).  
• Waixenicin A – marine diterpenoid inhibitor acting in a Mg²⁺-dependent manner (visser2014functionandregulation pages 11-11).

Other Comments  
• Dysregulation is associated with cardiac fibrosis, cancer progression and immune dysfunction (hu2021roleoftrpm7 pages 1-2, nadezhdin2024structuralbasisof pages 15-16).  
• Mutations D922E, F924W, F924A alter inhibitor sensitivity; E1047Q reduces conductance; N1097Q/N1098Q abolish Mg²⁺-dependent inhibition (duan2018structureofthe pages 6-8, schmidt2022structuralmechanismof pages 3-4, nadezhdin2024structuralbasisof pages 27-28).

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References

1. (cai2017massspectrometricanalysis pages 1-3): Na Cai, Zhiyong Bai, Vikas Nanda, and Loren W. Runnels. Mass spectrometric analysis of trpm6 and trpm7 phosphorylation reveals regulatory mechanisms of the channel-kinases. Scientific Reports, Feb 2017. URL: https://doi.org/10.1038/srep42739, doi:10.1038/srep42739. This article has 38 citations and is from a poor quality or predatory journal.
2. (cai2017massspectrometricanalysis pages 12-13): Na Cai, Zhiyong Bai, Vikas Nanda, and Loren W. Runnels. Mass spectrometric analysis of trpm6 and trpm7 phosphorylation reveals regulatory mechanisms of the channel-kinases. Scientific Reports, Feb 2017. URL: https://doi.org/10.1038/srep42739, doi:10.1038/srep42739. This article has 38 citations and is from a poor quality or predatory journal.
3. (cai2017massspectrometricanalysis pages 13-13): Na Cai, Zhiyong Bai, Vikas Nanda, and Loren W. Runnels. Mass spectrometric analysis of trpm6 and trpm7 phosphorylation reveals regulatory mechanisms of the channel-kinases. Scientific Reports, Feb 2017. URL: https://doi.org/10.1038/srep42739, doi:10.1038/srep42739. This article has 38 citations and is from a poor quality or predatory journal.
4. (nadezhdin2024structuralbasisof pages 15-16): Kirill D. Nadezhdin, Leonor Correia, Alexey Shalygin, Muhammed Aktolun, Arthur Neuberger, Thomas Gudermann, Maria G. Kurnikova, Vladimir Chubanov, and Alexander I. Sobolevsky. Structural basis of selective trpm7 inhibition by the anticancer agent cct128930. Cell Reports, 43:114108, Apr 2024. URL: https://doi.org/10.1016/j.celrep.2024.114108, doi:10.1016/j.celrep.2024.114108. This article has 6 citations and is from a highest quality peer-reviewed journal.
5. (nadezhdin2024structuralbasisof pages 24-27): Kirill D. Nadezhdin, Leonor Correia, Alexey Shalygin, Muhammed Aktolun, Arthur Neuberger, Thomas Gudermann, Maria G. Kurnikova, Vladimir Chubanov, and Alexander I. Sobolevsky. Structural basis of selective trpm7 inhibition by the anticancer agent cct128930. Cell Reports, 43:114108, Apr 2024. URL: https://doi.org/10.1016/j.celrep.2024.114108, doi:10.1016/j.celrep.2024.114108. This article has 6 citations and is from a highest quality peer-reviewed journal.
6. (schmidt2022structuralmechanismof pages 3-4): Eva Schmidt, Chamali Narangoda, Wolfgang Nörenberg, Miyuki Egawa, Anna Rössig, Marion Leonhardt, Michael Schaefer, Susanna Zierler, Maria G. Kurnikova, Thomas Gudermann, and Vladimir Chubanov. Structural mechanism of trpm7 channel regulation by intracellular magnesium. Cellular and Molecular Life Sciences, Apr 2022. URL: https://doi.org/10.1007/s00018-022-04192-7, doi:10.1007/s00018-022-04192-7. This article has 27 citations and is from a domain leading peer-reviewed journal.
7. (unknownauthors2019domainspecificroleof pages 23-26): Domain-specific role of the channel-kinase TRPM7 in cell signaling
8. (unknownauthors2023rolesoftransient pages 60-61): Roles of Transient Receptor Potential (TRP) cation channels in primary pulmonary fibroblasts
9. (cai2017massspectrometricanalysis pages 3-3): Na Cai, Zhiyong Bai, Vikas Nanda, and Loren W. Runnels. Mass spectrometric analysis of trpm6 and trpm7 phosphorylation reveals regulatory mechanisms of the channel-kinases. Scientific Reports, Feb 2017. URL: https://doi.org/10.1038/srep42739, doi:10.1038/srep42739. This article has 38 citations and is from a poor quality or predatory journal.
10. (chubanov2018trpm7reflectedin pages 3-3): Vladimir Chubanov, Lorenz Mittermeier, and Thomas Gudermann. Trpm7 reflected in cryo-emirror. Cell Calcium, 76:129-131, Dec 2018. URL: https://doi.org/10.1016/j.ceca.2018.11.004, doi:10.1016/j.ceca.2018.11.004. This article has 7 citations and is from a peer-reviewed journal.
11. (duan2018structureofthe pages 1-1): Jingjing Duan, Zongli Li, Jian Li, Raymond E. Hulse, Ana Santa-Cruz, William C. Valinsky, Sunday A. Abiria, Grigory Krapivinsky, Jin Zhang, and David E. Clapham. Structure of the mammalian trpm7, a magnesium channel required during embryonic development. Proceedings of the National Academy of Sciences, 115:E8201-E8210, Aug 2018. URL: https://doi.org/10.1073/pnas.1810719115, doi:10.1073/pnas.1810719115. This article has 133 citations.
12. (hu2021roleoftrpm7 pages 1-2): Feng Hu, Meiyong Li, Feng Qi Han, Qing Zhang, Yuhao Zeng, Weifang Zhang, and Xiaoshu Cheng. Role of trpm7 in cardiac fibrosis: a potential therapeutic target (review). Experimental and Therapeutic Medicine, Dec 2021. URL: https://doi.org/10.3892/etm.2020.9604, doi:10.3892/etm.2020.9604. This article has 15 citations and is from a peer-reviewed journal.
13. (nadezhdin2023structuralmechanismsof pages 12-13): Kirill D. Nadezhdin, Leonor Correia, Chamali Narangoda, Dhilon S. Patel, Arthur Neuberger, Thomas Gudermann, Maria G. Kurnikova, Vladimir Chubanov, and Alexander I. Sobolevsky. Structural mechanisms of trpm7 activation and inhibition. Nature Communications, May 2023. URL: https://doi.org/10.1038/s41467-023-38362-3, doi:10.1038/s41467-023-38362-3. This article has 46 citations and is from a highest quality peer-reviewed journal.
14. (unknownauthors2010theproteininteractions pages 20-26): The Protein Interactions and Functions of Transient Receptor Potential Melastatin 7 (TRPM7) Ion Channel
15. (visser2014functionandregulation pages 11-11): Daan Visser, Jeroen Middelbeek, Frank N. van Leeuwen, and Kees Jalink. Function and regulation of the channel-kinase trpm7 in health and disease. European Journal of Cell Biology, 93:455-465, Oct 2014. URL: https://doi.org/10.1016/j.ejcb.2014.07.001, doi:10.1016/j.ejcb.2014.07.001. This article has 93 citations and is from a peer-reviewed journal.
16. (duan2018structureofthe pages 6-8): Jingjing Duan, Zongli Li, Jian Li, Raymond E. Hulse, Ana Santa-Cruz, William C. Valinsky, Sunday A. Abiria, Grigory Krapivinsky, Jin Zhang, and David E. Clapham. Structure of the mammalian trpm7, a magnesium channel required during embryonic development. Proceedings of the National Academy of Sciences, 115:E8201-E8210, Aug 2018. URL: https://doi.org/10.1073/pnas.1810719115, doi:10.1073/pnas.1810719115. This article has 133 citations.
17. (nadezhdin2024structuralbasisof pages 27-28): Kirill D. Nadezhdin, Leonor Correia, Alexey Shalygin, Muhammed Aktolun, Arthur Neuberger, Thomas Gudermann, Maria G. Kurnikova, Vladimir Chubanov, and Alexander I. Sobolevsky. Structural basis of selective trpm7 inhibition by the anticancer agent cct128930. Cell Reports, 43:114108, Apr 2024. URL: https://doi.org/10.1016/j.celrep.2024.114108, doi:10.1016/j.celrep.2024.114108. This article has 6 citations and is from a highest quality peer-reviewed journal.
18. (sun2015trpm7andits pages 30-33): Yuyang Sun, Pramod Sukumaran, Anne Schaar, and Brij B Singh. Trpm7 and its role in neurodegenerative diseases. Channels, 9:253-261, Sep 2015. URL: https://doi.org/10.1080/19336950.2015.1075675, doi:10.1080/19336950.2015.1075675. This article has 88 citations and is from a peer-reviewed journal.
19. (zhelay2018depletionofplasma pages 12-14): Tetyana Zhelay, Krystyna B. Wieczerzak, Pavani Beesetty, Gerald M. Alter, Masayuki Matsushita, and J. Ashot Kozak. Depletion of plasma membrane–associated phosphoinositides mimics inhibition of trpm7 channels by cytosolic mg2+, spermine, and ph. Journal of Biological Chemistry, 293:18151-18167, Nov 2018. URL: https://doi.org/10.1074/jbc.ra118.004066, doi:10.1074/jbc.ra118.004066. This article has 28 citations and is from a domain leading peer-reviewed journal.