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CatSper and Two-Pore channels (TPC) in GtoPdb v.2022.1

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Abstract

CatSper channels (CatSper1-4, **nomenclature as agreed by NC-IUPHAR [14]**) are putative 6TM, voltage-gated, alkalinization-activated calcium permeant channels that are presumed to assemble as a tetramer of α-like subunits and mediate the current $I_{CatSper}$ [23]. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca_V) [40]. CatSper1 [40], CatSper2 [37] and CatSpers 3 and 4 [27, 21, 36], in common with a putative 2TM auxiliary CatSperβ protein [26] and two putative 1TM associated CatSperγ and CatSperδ proteins [46, 12], are restricted to the testis and localised to the principle piece of sperm tail. The novel cross-species CatSper channel inhibitor, RU1968, has been proposed as a useful tool to aid characterisation of native CatSper channels [41].

Two-pore channels (TPCs) are structurally related to CatSpers, Ca_Vs and Na_Vs. TPCs have a 2x6TM structure with twice the number of TMs of CatSpers and half that of Ca_Vs. There are three animal TPCs (TPC1-TPC3). Humans have TPC1 and TPC2, but not TPC3. TPC1 and TPC2 are localized in endosomes and lysosomes [5]. TPC3 is also found on the plasma membrane and forms a voltage-activated, non-inactivating Na^+ channel [6]. All the three TPCs are Na^+-selective under whole-cell or whole-organelle patch clamp recording [48, 8, 7]. The channels may also conduct Ca^{2+} [31].

Contents

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References

1. Avenarius MR, Hildebrand MS, Zhang Y, Meyer NC, Smith LL, Kahrizi K, Najmabadi H and Smith RJ. (2009) Human male infertility caused by mutations in the CATSPER1 channel protein. *Am J Hum Genet* **84**: 505-10 [PMID:19344877]
2. Avidan N, Tamary H, Dgany O, Cattan D, Pariente A, Thulliez M, Borot N, Moati L, Barthelme A and Shalmon L *et al.*. (2003) CATSPER2, a human autosomal nonsyndromic male infertility gene. *Eur J Hum Genet* **11**: 497-502 [PMID:12825070]
3. Brenker C, Goodwin N, Weyand I, Kashikar ND, Naruse M, Krähling M, Müller A, Kaupp UB and Strünker T. (2012) The CatSper channel: a polymodal chemosensor in human sperm. *EMBO J* **31**: 1654-65 [PMID:22354039]
4. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
5. Calcraft PJ, Ruas M, Pan Z, Cheng X, Arredouani A, Hao X, Tang J, Rietdorf K, Teboul L and Chuang KT *et al.*. (2009) NAADP mobilizes calcium from acidic organelles through two-pore channels. *Nature* **459**: 596-600 [PMID:19387438]
6. Cang C, Aranda K and Ren D. (2014) A non-inactivating high-voltage-activated two-pore Na^+ channel that supports ultra-long action potentials and membrane bistability. *Nat Commun* **5**: 5015 [PMID:25256615]
7. Cang C, Bekele B and Ren D. (2014) The voltage-gated sodium channel TPC1 confers endolysosomal excitability. *Nat Chem Biol* **10**: 463-9 [PMID:24776928]
8. Cang C, Zhou Y, Navarro B, Seo YJ, Aranda K, Shi L, Battaglia-Hsu S, Nissim I, Clapham DE and Ren D. (2013) mTOR regulates lysosomal ATP-sensitive two-pore Na(+) channels to adapt to metabolic state. *Cell* **152**: 778-90 [PMID:23394946]
9. Carlson AE, Burnett LA, del Camino D, Quill TA, Hille B, Chong JA, Moran MM and Babcock DF. (2009) Pharmacological targeting of native CatSper channels reveals a required role in maintenance of sperm hyperactivation. *PLoS ONE* **4**: e6844 [PMID:19718436]
10. Carlson AE, Quill TA, Westenbroek RE, Schuh SM, Hille B and Babcock DF. (2005) Identical phenotypes of CatSper1 and CatSper2 null sperm. *J Biol Chem* **280**: 32238-44 [PMID:16036917]
11. Carlson AE, Westenbroek RE, Quill T, Ren D, Clapham DE, Hille B, Garbers DL and Babcock DF. (2003) CatSper1 required for evoked Ca2+ entry and control of flagellar function in sperm. *Proc Natl Acad Sci USA* **100**: 14864-8 [PMID:14657352]
12. Chung JJ, Navarro B, Krapivinsky G, Krapivinsky L and Clapham DE. (2011) A novel gene required for male fertility and functional CATSPER channel formation in spermatozoa. *Nat Commun* **2**: 153 [PMID:21224844]
13. Chung JJ, Shim SH, Everley RA, Gygi SP, Zhuang X and Clapham DE. (2014) Structurally distinct Ca(2+) signaling domains of sperm flagella orchestrate tyrosine phosphorylation and motility. *Cell* **157**: 808-22 [PMID:24813608]
14. Clapham DE and Garbers DL. (2005) International Union of Pharmacology. L. Nomenclature and structure-function relationships of CatSper and two-pore channels. *Pharmacol Rev* **57**: 451-4 [PMID:16382101]
15. Gerndt S, Chen CC, Chao YK, Yuan Y, Burgstaller S, Scotto Rosato A, Krogsaeter E, Urban N, Jacob K and Nguyen ONP *et al.*. (2020) Agonist-mediated switching of ion selectivity in TPC2 differentially promotes lysosomal function. *Elife* **9** [PMID:32167471]
16. Grimm C, Holdt LM, Chen CC, Hassan S, Müller C, Jörs S, Cuny H, Kissing S, Schröder B and Butz E *et al.*. (2014) High susceptibility to fatty liver disease in two-pore channel 2-deficient mice. *Nat Commun* **5**: 4699 [PMID:25144390]
17. Hildebrand MS, Avenarius MR, Fellous M, Zhang Y, Meyer NC, Auer J, Serres C, Kahrizi K, Najmabadi H and Beckmann JS *et al.*. (2010) Genetic male infertility and mutation of CATSPER ion channels. *Eur J Hum Genet* **18**: 1178-84 [PMID:20648059]
18. Ho K, Wolff CA and Suarez SS. (2009) CatSper-null mutant spermatozoa are unable to ascend beyond the oviductal reservoir. *Reprod Fertil Dev* **21**: 345-50 [PMID:19210926]
19. Ishibashi K, Suzuki M and Imai M. (2000) Molecular cloning of a novel form (two-repeat) protein related to voltage-gated sodium and calcium channels. *Biochem Biophys Res Commun* **270**: 370-6 [PMID:10753632]
20. Jin J, Jin N, Zheng H, Ro S, Tafolla D, Sanders KM and Yan W. (2007) Catsper3 and Catsper4 are essential for

sperm hyperactivated motility and male fertility in the mouse. *Biol Reprod* **77**: 37-44 [PMID:17344468]
21. Jin JL, O'Doherty AM, Wang S, Zheng H, Sanders KM and Yan W. (2005) Catsper3 and catsper4 encode two cation channel-like proteins exclusively expressed in the testis. *Biol Reprod* **73**: 1235-42 [PMID:16107607]
22. Kirichok Y and Lishko PV. (2011) Rediscovering sperm ion channels with the patch-clamp technique. *Mol Hum Reprod* **17**: 478-99 [PMID:21642646]
23. Kirichok Y, Navarro B and Clapham DE. (2006) Whole-cell patch-clamp measurements of spermatozoa reveal an alkaline-activated Ca2+ channel. *Nature* **439**: 737-40 [PMID:16467839]
24. Lishko PV, Botchkina IL and Kirichok Y. (2011) Progesterone activates the principal Ca2+ channel of human sperm. *Nature* **471**: 387-91 [PMID:21412339]
25. Lishko PV and Kirichok Y. (2010) The role of Hv1 and CatSper channels in sperm activation. *J Physiol (Lond.)* **588**: 4667-72 [PMID:20679352]
26. Liu J, Xia J, Cho KH, Clapham DE and Ren D. (2007) CatSperbeta, a novel transmembrane protein in the CatSper channel complex. *J Biol Chem* **282**: 18945-52 [PMID:17478420]
27. Lobley A, Pierron V, Reynolds L, Allen L and Michalovich D. (2003) Identification of human and mouse CatSper3 and CatSper4 genes: characterisation of a common interaction domain and evidence for expression in testis. *Reprod Biol Endocrinol* **1**: 53 [PMID:12932298]
28. Lucas JB, Salyer RD and Watson DW. (2003) Gangrenous primary cutaneous mucormycosis of the scalp in an iatrogenically immunosuppressed trauma patient. *Otolaryngol Head Neck Surg* **128**: 912-4 [PMID:12825050]
29. Martínez-López P, Santi CM, Treviño CL, Ocampo-Gutiérrez AY, Acevedo JJ, Alisio A, Salkoff LB and Darszon A. (2009) Mouse sperm K+ currents stimulated by pH and cAMP possibly coded by Slo3 channels. *Biochem Biophys Res Commun* **381**: 204-9 [PMID:19338774]
30. Miki K and Clapham DE. (2013) Rheotaxis guides mammalian sperm. *Curr Biol* **23**: 443-52 [PMID:23453951]
31. Morgan AJ and Galione A. (2014) Two-pore channels (TPCs): current controversies. *Bioessays* **36**: 173-83 [PMID:24277557]
32. Müller M, Gerndt S, Chao YK, Zisis T, Nguyen ONP, Gerwien A, Urban N, Müller C, Gegenfurtner FA and Geisslinger F *et al.*. (2021) Gene editing and synthetically accessible inhibitors reveal role for TPC2 in HCC cell proliferation and tumor growth. *Cell Chem Biol* **28**: 1119-1131.e27 [PMID:33626324]
33. Navarro B, Kirichok Y and Clapham DE. (2007) KSper, a pH-sensitive K+ current that controls sperm membrane potential. *Proc Natl Acad Sci USA* **104**: 7688-92 [PMID:17460039]
34. Netcharoensirisuk P, Abrahamian C, Tang R, Chen CC, Rosato AS, Beyers W, Chao YK, Filippini A, Di Pietro S and Bartel K *et al.*. (2021) Flavonoids increase melanin production and reduce proliferation, migration and invasion of melanoma cells by blocking endolysosomal/melanosomal TPC2. *Sci Rep* **11**: 8515 [PMID:33875769]
35. Nikpoor P, Mowla SJ, Movahedin M, Ziaee SA and Tiraihi T. (2004) CatSper gene expression in postnatal development of mouse testis and in subfertile men with deficient sperm motility. *Hum Reprod* **19**: 124-8 [PMID:14688170]
36. Qi H, Moran MM, Navarro B, Chong JA, Krapivinsky G, Krapivinsky L, Kirichok Y, Ramsey IS, Quill TA and Clapham DE. (2007) All four CatSper ion channel proteins are required for male fertility and sperm cell hyperactivated motility. *Proc Natl Acad Sci USA* **104**: 1219-23 [PMID:17227845]
37. Quill TA, Ren D, Clapham DE and Garbers DL. (2001) A voltage-gated ion channel expressed specifically in spermatozoa. *Proc Natl Acad Sci USA* **98**: 12527-31 [PMID:11675491]
38. Quill TA, Sugden SA, Rossi KL, Doolittle LK, Hammer RE and Garbers DL. (2003) Hyperactivated sperm motility driven by CatSper2 is required for fertilization. *Proc Natl Acad Sci USA* **100**: 14869-74 [PMID:14657366]
39. Reardon AJ, Le Goff M, Briggs MD, McLeod D, Sheehan JK, Thornton DJ and Bishop PN. (2000) Identification in vitreous and molecular cloning of opticin, a novel member of the family of leucine-rich repeat proteins of the extracellular matrix. *J Biol Chem* **275**: 2123-9 [PMID:10636917]
40. Ren D, Navarro B, Perez G, Jackson AC, Hsu S, Shi Q, Tilly JL and Clapham DE. (2001) A sperm ion channel required for sperm motility and male fertility. *Nature* **413**: 603-9 [PMID:11595941]
41. Rennhack A, Schiffer C, Brenker C, Fridman D, Nitao ET, Cheng YM, Tamburrino L, Balbach M, Stölting G and Berger TK *et al.*. (2018) A novel cross-species inhibitor to study the function of CatSper Ca^{2+} channels in sperm. *Br J Pharmacol* **175**: 3144-3161 [PMID:29723408]
42. Roychoudhury C, Jacobs BS, Baker PL, Schultz D, Mehta RH and Levine SR. (2004) Acute ischemic stroke in hospitalized medicare patients: evaluation and treatment. *Stroke* **35**: e22-3 [PMID:14657452]
43. Sakurai Y, Kolokoltsov AA, Chen CC, Tidwell MW, Bauta WE, Klugbauer N, Grimm C, Wahl-Schott C, Biel M and Davey RA. (2015) Ebola virus. Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment. *Science* **347**: 995-8 [PMID:25722412]
44. Smith JF, Syritsyna O, Fellous M, Serres C, Mannowetz N, Kirichok Y and Lishko PV. (2013) Disruption of the principal, progesterone-activated sperm Ca2+ channel in a CatSper2-deficient infertile patient. *Proc Natl Acad*

Sci USA **110**: 6823-8 [PMID:23530196]
45. Strünker T, Goodwin N, Brenker C, Kashikar ND, Weyand I, Seifert R and Kaupp UB. (2011) The CatSper channel mediates progesterone-induced Ca2+ influx in human sperm. *Nature* **471**: 382-6 [PMID:21412338]
46. Wang H, Liu J, Cho KH and Ren D. (2009) A novel, single, transmembrane protein CATSPERG is associated with CATSPER1 channel protein. *Biol Reprod* **81**: 539-44 [PMID:19516020]
47. Wang X, Zhang X, Dong XP, Samie M, Li X, Cheng X, Goschka A, Shen D, Zhou Y and Harlow J *et al.*. (2012) TPC proteins are phosphoinositide- activated sodium-selective ion channels in endosomes and lysosomes. *Cell* **151**: 372-83 [PMID:23063126]
48. Xia J and Ren D. (2009) Egg coat proteins activate calcium entry into mouse sperm via CATSPER channels. *Biol Reprod* **80**: 1092-8 [PMID:19211808]
49. Zeng XH, Yang C, Kim ST, Lingle CJ and Xia XM. (2011) Deletion of the Slo3 gene abolishes alkalization-activated K+ current in mouse spermatozoa. *Proc Natl Acad Sci USA* **108**: 5879-84 [PMID:21427226]
50. Zhang Y, Malekpour M, Al-Madani N, Kahrizi K, Zanganeh M, Lohr NJ, Mohseni M, Mojahedi F, Daneshi A and Najmabadi H *et al.*. (2007) Sensorineural deafness and male infertility: a contiguous gene deletion syndrome. *J Med Genet* **44**: 233-40 [PMID:17098888]