

Two-pore domain potassium channels (K_{2p}) in GtoPdb v.2023.1

Austin M. Baggetta¹, Douglas A. Bayliss², Gábor Czirják³, Péter Enyedi³, Steve A.N. Goldstein⁴, Florian Lesage⁵, Daniel L. Minor, Jr.⁶, Leigh D. Plant¹ and Francisco Sepúlveda⁷

1. Northeastern University, USA
2. University of Virginia Health System, USA
3. Semmelweis University, Hungary
4. University of California, Irvine, USA
5. Université de Nice, France
6. University of California San Francisco, USA
7. Centro de Estudios Científicos, Chile

Abstract

The 4TM family of K channels mediate many of the background potassium currents observed in native cells. They are open across the physiological voltage-range and are regulated by a wide array of neurotransmitters and biochemical mediators. The pore-forming α -subunit contains two pore loop (P) domains and two subunits assemble to form one ion conduction pathway lined by four P domains. It is important to note that single channels do not have two pores but that each subunit has two P domains in its primary sequence; hence the name two-pore domain, or K_{2p} channels (and not two-pore channels). Some of the K_{2p} subunits can form heterodimers across subfamilies (*e.g.* K_{2p}3.1 with K_{2p}9.1). The nomenclature of 4TM K channels in the literature is still a mixture of IUPHAR and common names. The suggested division into subfamilies, described in the [More detailed introduction](#), is based on similarities in both structural and functional properties within subfamilies and this explains the "common abbreviation" nomenclature in the tables below.

Contents

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Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

Two-pore domain potassium channels (K_{2p})

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=79>

Introduction to Two-pore domain potassium channels (K_{2p})

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=79>

Channels and Subunits

TWIK1(K_{2p}1.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=513>

TREK1(K_{2p}2.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=514>

TASK1(K_{2p}3.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=515>

TRAAK1(K_{2p}4.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=516>

TASK2(K_{2p}5.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=517>

TWIK2(K_{2p}6.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=518>

K_{2p}7.1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=519>

TASK3(K_{2p}9.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=520>

TREK2(K_{2p}10.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=521>

THIK2(K_{2p}12.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=522>

THIK1(K_{2p}13.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=523>

TASK5(K_{2p}15.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=524>

TALK1(K_{2p}16.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=525>

TALK2(K_{2p}17.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=526>

TRESK(K_{2p}18.1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=527>

References

1. Alloui A, Zimmermann K, Mamet J, Duprat F, Noël J, Chemin J, Guy N, Blondeau N, Voilley N and Rubat-Coudert C *et al.*. (2006) TREK-1, a K⁺ channel involved in polymodal pain perception. *EMBO J* **25**: 2368-76 [PMID:16675954]
2. Andres-Enguix I, Shang L, Stansfeld PJ, Morahan JM, Sansom MS, Lafrenière RG, Roy B, Griffiths LR, Rouleau GA and Ebers GC *et al.*. (2012) Functional analysis of missense variants in the TRESK (KCNK18) K channel. *Sci Rep* **2**: 237 [PMID:22355750]
3. Aryal P, Abd-Wahab F, Bucci G, Sansom MS and Tucker SJ. (2014) A hydrophobic barrier deep within the inner pore of the TWIK-1 K_{2P} potassium channel. *Nat Commun* **5**: 4377 [PMID:25001086]
4. Ashmole I, Goodwin PA and Stanfield PR. (2001) TASK-5, a novel member of the tandem pore K⁺ channel family. *Pflugers Arch* **442**: 828-33 [PMID:11680614]
5. Añazco C, Peña-Münzenmayer G, Araya C, Cid LP, Sepúlveda FV and Niemeyer MI. (2013) G protein modulation of K_{2P} potassium channel TASK-2 : a role of basic residues in the C terminus domain. *Pflugers Arch* **465**: 1715-26 [PMID:23812165]
6. Bagriantsev SN, Ang KH, Gallardo-Godoy A, Clark KA, Arkin MR, Renslo AR and Minor Jr DL. (2013) A high-throughput functional screen identifies small molecule regulators of temperature- and mechano-

- sensitive K2P channels. *ACS Chem Biol* **8**: 1841-51 [PMID:23738709]
7. Bagriantsev SN, Clark KA and Minor Jr DL. (2012) Metabolic and thermal stimuli control K(2P)2.1 (TREK-1) through modular sensory and gating domains. *EMBO J* **31**: 3297-308 [PMID:22728824]
 8. Bagriantsev SN, Peyronnet R, Clark KA, Honoré E and Minor Jr DL. (2011) Multiple modalities converge on a common gate to control K2P channel function. *EMBO J* **30**: 3594-606 [PMID:21765396]
 9. Bandulik S, Tauber P, Lalli E, Barhanin J and Warth R. (2015) Two-pore domain potassium channels in the adrenal cortex. *Pflugers Arch* **467**: 1027-42 [PMID:25339223]
 10. Bang H, Kim Y and Kim D. (2000) TREK-2, a new member of the mechanosensitive tandem-pore K⁺ channel family. *J Biol Chem* **275**: 17412-9 [PMID:10747911]
 11. Barel O, Shalev SA, Ofir R, Cohen A, Zlotogora J, Shorer Z, Mazor G, Finer G, Khateeb S and Zilberberg N *et al.* (2008) Maternally inherited Birk Barel mental retardation dysmorphism syndrome caused by a mutation in the genomically imprinted potassium channel KCNK9. *Am J Hum Genet* **83**: 193-9 [PMID:18678320]
 12. Barriere H, Belfodil R, Rubera I, Tauc M, Lesage F, Poujeol C, Guy N, Barhanin J and Poujeol P. (2003) Role of TASK2 potassium channels regarding volume regulation in primary cultures of mouse proximal tubules. *J Gen Physiol* **122**: 177-90 [PMID:12860925]
 13. Bautista DM, Sigal YM, Milstein AD, Garrison JL, Zorn JA, Tsuruda PR, Nicoll RA and Julius D. (2008) Pungent agents from Szechuan peppers excite sensory neurons by inhibiting two-pore potassium channels. *Nat Neurosci* **11**: 772-9 [PMID:18568022]
 14. Benson MD, Li QJ, Kieckhafer K, Dudek D, Whorton MR, Sunahara RK, Iñiguez-Lluhí JA and Martens JR. (2007) SUMO modification regulates inactivation of the voltage-gated potassium channel Kv1.5. *Proc Natl Acad Sci U S A* **104**: 1805-10 [PMID:17261810]
 15. Berg AP, Talley EM, Manger JP and Bayliss DA. (2004) Motoneurons express heteromeric TWIK-related acid-sensitive K⁺ (TASK) channels containing TASK-1 (KCNK3) and TASK-3 (KCNK9) subunits. *J Neurosci* **24**: 6693-702 [PMID:15282272]
 16. Bichet D, Blin S, Feliciangeli S, Chatelain FC, Bobak N and Lesage F. (2015) Silent but not dumb: how cellular trafficking and pore gating modulate expression of TWIK1 and THIK2. *Pflugers Arch* **467**: 1121-31 [PMID:25339226]
 17. Blin S, Ben Soussia I, Kim EJ, Brau F, Kang D, Lesage F and Bichet D. (2016) Mixing and matching TREK/TRAAK subunits generate heterodimeric K2P channels with unique properties. *Proc Natl Acad Sci USA* **113**: 4200-5 [PMID:27035965]
 18. Blin S, Chatelain FC, Feliciangeli S, Kang D, Lesage F and Bichet D. (2014) Tandem pore domain halothane-inhibited K⁺ channel subunits THIK1 and THIK2 assemble and form active channels. *J Biol Chem* **289**: 28202-12 [PMID:25148687]
 19. Bockenhauer D, Nimmakayalu MA, Ward DC, Goldstein SA and Gallagher PG. (2000) Genomic organization and chromosomal localization of the murine 2 P domain potassium channel gene *Kcnk8*: conservation of gene structure in 2 P domain potassium channels. *Gene* **261**: 365-72 [PMID:11167025]
 20. Bockenhauer D, Zilberberg N and Goldstein SA. (2001) KCNK2: reversible conversion of a hippocampal potassium leak into a voltage-dependent channel. *Nat Neurosci* **4**: 486-91 [PMID:11319556]
 21. Brohawn SG, Campbell EB and MacKinnon R. (2013) Domain-swapped chain connectivity and gated membrane access in a Fab-mediated crystal of the human TRAAK K⁺ channel. *Proc Natl Acad Sci U S A* **110**: 2129-34 [PMID:23341632]
 22. Brohawn SG, Campbell EB and MacKinnon R. (2014) Physical mechanism for gating and mechanosensitivity of the human TRAAK K⁺ channel. *Nature* **516**: 126-30 [PMID:25471887]
 23. Brohawn SG, del Mármol J and MacKinnon R. (2012) Crystal structure of the human K2P TRAAK, a lipid- and mechano-sensitive K⁺ ion channel. *Science* **335**: 436-41 [PMID:22282805]
 24. Brohawn SG, Su Z and MacKinnon R. (2014) Mechanosensitivity is mediated directly by the lipid membrane in TRAAK and TREK1 K⁺ channels. *Proc Natl Acad Sci U S A* **111**: 3614-9 [PMID:24550493]
 25. Buckler KJ, Williams BA and Honore E. (2000) An oxygen-, acid- and anaesthetic-sensitive TASK-like background potassium channel in rat arterial chemoreceptor cells. *J Physiol (Lond.)* **525 Pt 1**: 135-42 [PMID:10811732]
 26. 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]
 27. Cazals Y, Bévingut M, Zanella S, Brocard F, Barhanin J and Gestreau C. (2015) KCNK5 channels mostly expressed in cochlear outer sulcus cells are indispensable for hearing. *Nat Commun* **6**: 8780

[PMID:26549439]

28. Chapman CG, Meadows HJ, Godden RJ, Campbell DA, Duckworth M, Kellsell RE, Murdock PR, Randall AD, Rennie GI and Gloger IS. (2000) Cloning, localisation and functional expression of a novel human, cerebellum specific, two pore domain potassium channel. *Brain Res Mol Brain Res* **82**: 74-83
[PMID:11042359]
29. Chatelain FC, Bichet D, Douguet D, Feliciangeli S, Bendahhou S, Reichold M, Warth R, Barhanin J and Lesage F. (2012) TWIK1, a unique background channel with variable ion selectivity. *Proc Natl Acad Sci U S A* **109**: 5499-504 [PMID:22431633]
30. Chatelain FC, Bichet D, Feliciangeli S, Larroque MM, Braud VM, Douguet D and Lesage F. (2013) Silencing of the tandem pore domain halothane-inhibited K⁺ channel 2 (THIK2) relies on combined intracellular retention and low intrinsic activity at the plasma membrane. *J Biol Chem* **288**: 35081-92
[PMID:24163367]
31. Chavez RA, Gray AT, Zhao BB, Kindler CH, Mazurek MJ, Mehta Y, Forsayeth JR and Yost CS. (1999) TWIK-2, a new weak inward rectifying member of the tandem pore domain potassium channel family. *J Biol Chem* **274**: 7887-92 [PMID:10075682]
32. Chemin J, Patel AJ, Duprat F, Lauritzen I, Lazdunski M and Honoré E. (2005) A phospholipid sensor controls mechanogating of the K⁺ channel TREK-1. *EMBO J* **24**: 44-53 [PMID:15577940]
33. Chemin J, Patel AJ, Duprat F, Sachs F, Lazdunski M and Honore E. (2007) Up- and down-regulation of the mechano-gated K(2P) channel TREK-1 by PIP (2) and other membrane phospholipids. *Pflugers Arch* **455**: 97-103 [PMID:17384962]
34. Christensen AH, Chatelain FC, Huttner IG, Olesen MS, Soka M, Feliciangeli S, Horvat C, Santiago CF, Vandenberg JI and Schmitt N *et al.*. (2016) The two-pore domain potassium channel, TWIK-1, has a role in the regulation of heart rate and atrial size. *J Mol Cell Cardiol* **97**: 24-35 [PMID:27103460]
35. Cohen A, Ben-Abu Y, Hen S and Zilberberg N. (2008) A novel mechanism for human K2P2.1 channel gating. Facilitation of C-type gating by protonation of extracellular histidine residues. *J Biol Chem* **283**: 19448-55 [PMID:18474599]
36. Comoglio Y, Levitz J, Kienzler MA, Lesage F, Isacoff EY and Sandoz G. (2014) Phospholipase D2 specifically regulates TREK potassium channels via direct interaction and local production of phosphatidic acid. *Proc Natl Acad Sci USA* **111**: 13547-52 [PMID:25197053]
37. Conway KE and Cotten JF. (2012) Covalent modification of a volatile anesthetic regulatory site activates TASK-3 (KCNK9) tandem-pore potassium channels. *Mol Pharmacol* **81**: 393-400 [PMID:22147752]
38. Cooper BY, Johnson RD and Rau KK. (2004) Characterization and function of TWIK-related acid sensing K⁺ channels in a rat nociceptive cell. *Neuroscience* **129**: 209-24 [PMID:15489043]
39. Czirják G and Enyedi P. (2002) Formation of functional heterodimers between the TASK-1 and TASK-3 two-pore domain potassium channel subunits. *J Biol Chem* **277**: 5426-32 [PMID:11733509]
40. Czirják G and Enyedi P. (2014) The LQLP calcineurin docking site is a major determinant of the calcium-dependent activation of human TRESK background K⁺ channel. *J Biol Chem* **289**: 29506-18
[PMID:25202008]
41. Czirják G and Enyedi P. (2006) Targeting of calcineurin to an NFAT-like docking site is required for the calcium-dependent activation of the background K⁺ channel, TRESK. *J Biol Chem* **281**: 14677-82
[PMID:16569637]
42. Czirják G, Fischer T, Spät A, Lesage F and Enyedi P. (2000) TASK (TWIK-related acid-sensitive K⁺ channel) is expressed in glomerulosa cells of rat adrenal cortex and inhibited by angiotensin II. *Mol Endocrinol* **14**: 863-74 [PMID:10847588]
43. Czirják G, Tóth ZE and Enyedi P. (2004) The two-pore domain K⁺ channel, TRESK, is activated by the cytoplasmic calcium signal through calcineurin. *J Biol Chem* **279**: 18550-8 [PMID:14981085]
44. Czirják G, Vuity D and Enyedi P. (2008) Phosphorylation-dependent binding of 14-3-3 proteins controls TRESK regulation. *J Biol Chem* **283**: 15672-80 [PMID:18397886]
45. Dai XQ, Kolic J, Marchi P, Sipione S and Macdonald PE. (2009) SUMOylation regulates Kv2.1 and modulates pancreatic beta-cell excitability. *J Cell Sci* **122**: 775-9 [PMID:19223394]
46. Decher N, Maier M, Dittrich W, Gassenhuber J, Brüggemann A, Busch AE and Steinmeyer K. (2001) Characterization of TASK-4, a novel member of the pH-sensitive, two-pore domain potassium channel family. *FEBS Lett* **492**: 84-9 [PMID:11248242]
47. Decher N, Wemhöner K, Rinné S, Netter MF, Zuzarte M, Aller MI, Kaufmann SG, Li XT, Meuth SG and Daut J *et al.*. (2011) Knock-out of the potassium channel TASK-1 leads to a prolonged QT interval and a

- disturbed QRS complex. *Cell Physiol Biochem* **28**: 77-86 [PMID:21865850]
48. Decressac S, Franco M, Bendahhou S, Warth R, Knauer S, Barhanin J, Lazdunski M and Lesage F. (2004) ARF6-dependent interaction of the TWIK1 K⁺ channel with EFA6, a GDP/GTP exchange factor for ARF6. *EMBO Rep* **5**: 1171-5 [PMID:15540117]
 49. Dobler T, Springauf A, Tovornik S, Weber M, Schmitt A, Sedlmeier R, Wischmeyer E and Döring F. (2007) TRESK two-pore-domain K⁺ channels constitute a significant component of background potassium currents in murine dorsal root ganglion neurones. *J Physiol* **585**: 867-79 [PMID:17962323]
 50. Dong YY, Pike AC, Mackenzie A, McClenaghan C, Aryal P, Dong L, Quigley A, Grieben M, Goubin S and Mukhopadhyay S *et al.*. (2015) K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac. *Science* **347**: 1256-9 [PMID:25766236]
 51. Du Y, Kiyoshi CM, Wang Q, Wang W, Ma B, Alford CC, Zhong S, Wan Q, Chen H and Lloyd EE *et al.*. (2016) Genetic Deletion of TREK-1 or TWIK-1/TREK-1 Potassium Channels does not Alter the Basic Electrophysiological Properties of Mature Hippocampal Astrocytes In Situ. *Front Cell Neurosci* **10**: 13 [PMID:26869883]
 52. Duprat F, Girard C, Jarretou G and Lazdunski M. (2005) Pancreatic two P domain K⁺ channels TALK-1 and TALK-2 are activated by nitric oxide and reactive oxygen species. *J Physiol (Lond.)* **562**: 235-44 [PMID:15513946]
 53. Duprat F, Lesage F, Fink M, Reyes R, Heurteaux C and Lazdunski M. (1997) TASK, a human background K⁺ channel to sense external pH variations near physiological pH. *EMBO J* **16**: 5464-71 [PMID:9312005]
 54. Duprat F, Lesage F, Patel AJ, Fink M, Romey G and Lazdunski M. (2000) The neuroprotective agent riluzole activates the two P domain K⁽⁺⁾ channels TREK-1 and TRAAK. *Mol Pharmacol* **57**: 906-12 [PMID:10779373]
 55. Enyedi P and Czirják G. (2010) Molecular background of leak K⁺ currents: two-pore domain potassium channels. *Physiol Rev* **90**: 559-605 [PMID:20393194]
 56. Enyedi P, Veres I, Braun G and Czirják G. (2014) Tubulin binds to the cytoplasmic loop of TRESK background K⁺ channel in vitro. *PLoS ONE* **9**: e97854 [PMID:24830385]
 57. Feliciangeli S, Bendahhou S, Sandoz G, Gounon P, Reichold M, Warth R, Lazdunski M, Barhanin J and Lesage F. (2007) Does sumoylation control K2P1/TWIK1 background K⁺ channels? *Cell* **130**: 563-9 [PMID:17693262]
 58. Feliciangeli S, Chatelain FC, Bichet D and Lesage F. (2015) The family of K2P channels: salient structural and functional properties. *J Physiol (Lond.)* **593**: 2587-603 [PMID:25530075]
 59. Feliciangeli S, Tardy MP, Sandoz G, Chatelain FC, Warth R, Barhanin J, Bendahhou S and Lesage F. (2010) Potassium channel silencing by constitutive endocytosis and intracellular sequestration. *J Biol Chem* **285**: 4798-805 [PMID:19959478]
 60. Fink M, Duprat F, Lesage F, Reyes R, Romey G, Heurteaux C and Lazdunski M. (1996) Cloning, functional expression and brain localization of a novel unconventional outward rectifier K⁺ channel. *EMBO J* **15**: 6854-62 [PMID:9003761]
 61. Fink M, Lesage F, Duprat F, Heurteaux C, Reyes R, Fosset M and Lazdunski M. (1998) A neuronal two P domain K⁺ channel stimulated by arachidonic acid and polyunsaturated fatty acids. *EMBO J* **17**: 3297-308 [PMID:9628867]
 62. Fong P, Argent BE, Guggino WB and Gray MA. (2003) Characterization of vectorial chloride transport pathways in the human pancreatic duct adenocarcinoma cell line HPAF. *Am J Physiol Cell Physiol* **285**: C433-45 [PMID:12711595]
 63. Friedrich C, Rinné S, Zumhagen S, Kiper AK, Silbernagel N, Netter MF, Stallmeyer B, Schulze-Bahr E and Decher N. (2014) Gain-of-function mutation in TASK-4 channels and severe cardiac conduction disorder. *EMBO Mol Med* **6**: 937-51 [PMID:24972929]
 64. Gaborit N, Le Bouter S, Szuts V, Varro A, Escande D, Nattel S and Demolombe S. (2007) Regional and tissue specific transcript signatures of ion channel genes in the non-diseased human heart. *J Physiol* **582**: 675-93 [PMID:17478540]
 65. Gabriel A, Abdallah M, Yost CS, Winegar BD and Kindler CH. (2002) Localization of the tandem pore domain K⁺ channel KCNK5 (TASK-2) in the rat central nervous system. *Brain Res Mol Brain Res* **98**: 153-63 [PMID:11834308]
 66. Gestreau C, Heitzmann D, Thomas J, Dubreuil V, Bandulik S, Reichold M, Bendahhou S, Pierson P, Sterner C and Peyronnet-Roux J *et al.*. (2010) Task2 potassium channels set central respiratory CO₂ and O₂ sensitivity. *Proc Natl Acad Sci U S A* **107**: 2325-30 [PMID:20133877]

67. Girard C, Duprat F, Terrenoire C, Tinel N, Fosset M, Romey G, Lazdunski M and Lesage F. (2001) Genomic and functional characteristics of novel human pancreatic 2P domain K(+) channels. *Biochem Biophys Res Commun* **282**: 249-56 [PMID:11263999]
68. Girard C, Tinel N, Terrenoire C, Romey G, Lazdunski M and Borsotto M. (2002) p11, an annexin II subunit, an auxiliary protein associated with the background K+ channel, TASK-1. *EMBO J* **21**: 4439-48 [PMID:12198146]
69. Goldstein SA. (2011) K2P potassium channels, mysterious and paradoxically exciting. *Sci Signal* **4**: pe35 [PMID:21868351]
70. Goldstein SA, Bayliss DA, Kim D, Lesage F, Plant LD and Rajan S. (2005) International Union of Pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. *Pharmacol Rev* **57**: 527-40 [PMID:16382106]
71. Goldstein SA, Bockenhauer D, O'Kelly I and Zilberberg N. (2001) Potassium leak channels and the KCNK family of two-P-domain subunits. *Nat Rev Neurosci* **2**: 175-84 [PMID:11256078]
72. Goldstein SA, Price LA, Rosenthal DN and Pausch MH. (1996) ORK1, a potassium-selective leak channel with two pore domains cloned from *Drosophila melanogaster* by expression in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* **93**: 13256-61 [PMID:8917578]
73. Goldstein SA, Wang KW, Ilan N and Pausch MH. (1998) Sequence and function of the two P domain potassium channels: implications of an emerging superfamily. *J Mol Med* **76**: 13-20 [PMID:9462864]
74. Gomes AQ, Correia DV, Grosso AR, Lança T, Ferreira C, Lacerda JF, Barata JT, Silva MG and Silva-Santos B. (2010) Identification of a panel of ten cell surface protein antigens associated with immunotargeting of leukemias and lymphomas by peripheral blood gamma delta T cells. *Haematologica* **95**: 1397-404 [PMID:20220060]
75. Gray AT, Kindler CH, Sampson ER and Yost CS. (1999) Assignment of KCNK6 encoding the human weak inward rectifier potassium channel TWIK-2 to chromosome band 19q13.1 by radiation hybrid mapping. *Cytogenet Cell Genet* **84**: 190-1 [PMID:10393428]
76. Gray AT, Zhao BB, Kindler CH, Winegar BD, Mazurek MJ, Xu J, Chavez RA, Forsayeth JR and Yost CS. (2000) Volatile anesthetics activate the human tandem pore domain baseline K+ channel KCNK5. *Anesthesiology* **92**: 1722-30 [PMID:10839924]
77. Gu W, Schlichthörl G, Hirsch JR, Engels H, Karschin C, Karschin A, Derst C, Steinlein OK and Daut J. (2002) Expression pattern and functional characteristics of two novel splice variants of the two-pore-domain potassium channel TREK-2. *J Physiol (Lond.)* **539**: 657-68 [PMID:11897838]
78. Han J, Kang D and Kim D. (2003) Functional properties of four splice variants of a human pancreatic tandem-pore K+ channel, TALK-1. *Am J Physiol, Cell Physiol* **285**: C529-38 [PMID:12724142]
79. Han J, Truell J, Gnatenco C and Kim D. (2002) Characterization of four types of background potassium channels in rat cerebellar granule neurons. *J Physiol (Lond.)* **542**: 431-44 [PMID:12122143]
80. Hay RT. (2005) SUMO: a history of modification. *Mol Cell* **18**: 1-12 [PMID:15808504]
81. Heitzmann D, Derand R, Jungbauer S, Bandulik S, Sterner C, Schweda F, El Wakil A, Lalli E, Guy N and Mengual R *et al.*. (2008) Invalidation of TASK1 potassium channels disrupts adrenal gland zonation and mineralocorticoid homeostasis. *EMBO J* **27**: 179-87 [PMID:18034154]
82. Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M, Lang-Lazdunski L, Widmann C, Zanzouri M and Romey G *et al.*. (2004) TREK-1, a K+ channel involved in neuroprotection and general anesthesia. *EMBO J* **23**: 2684-95 [PMID:15175651]
83. HODGKIN AL and HUXLEY AF. (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol (Lond.)* **117**: 500-44 [PMID:12991237]
84. Honoré E. (2007) The neuronal background K2P channels: focus on TREK1. *Nat Rev Neurosci* **8**: 251-61 [PMID:17375039]
85. Hsu K, Seharaseyon J, Dong P, Bour S and Marbán E. (2004) Mutual functional destruction of HIV-1 Vpu and host TASK-1 channel. *Mol Cell* **14**: 259-67 [PMID:15099524]
86. Hwang EM, Kim E, Yarishkin O, Woo DH, Han KS, Park N, Bae Y, Woo J, Kim D and Park M *et al.*. (2014) A disulphide-linked heterodimer of TWIK-1 and TREK-1 mediates passive conductance in astrocytes. *Nat Commun* **5**: 3227 [PMID:24496152]
87. Ilan N and Goldstein SA. (2001) Kcnkø: single, cloned potassium leak channels are multi-ion pores. *Biophys J* **80**: 241-53 [PMID:11159398]
88. Kang D, Choe C and Kim D. (2005) Thermosensitivity of the two-pore domain K+ channels TREK-2 and TRAAK. *J Physiol (Lond.)* **564**: 103-16 [PMID:15677687]

89. Kang D, Choe C and Kim D. (2004) Functional expression of TREK-2 in insulin-secreting MIN6 cells. *Biochem Biophys Res Commun* **323**: 323-31 [PMID:15351740]
90. Kang D, Han J, Talley EM, Bayliss DA and Kim D. (2004) Functional expression of TASK-1/TASK-3 heteromers in cerebellar granule cells. *J Physiol (Lond.)* **554**: 64-77 [PMID:14678492]
91. Kang D and Kim D. (2004) Single-channel properties and pH sensitivity of two-pore domain K⁺ channels of the TALK family. *Biochem Biophys Res Commun* **315**: 836-44 [PMID:14985088]
92. Kang D and Kim D. (2006) TREK-2 (K2P10.1) and TRESK (K2P18.1) are major background K⁺ channels in dorsal root ganglion neurons. *Am J Physiol Cell Physiol* **291**: C138-46 [PMID:16495368]
93. Kennard LE, Chumbley JR, Ranatunga KM, Armstrong SJ, Veale EL and Mathie A. (2005) Inhibition of the human two-pore domain potassium channel, TREK-1, by fluoxetine and its metabolite norfluoxetine. *Br J Pharmacol* **144**: 821-9 [PMID:15685212]
94. Keshavaprasad B, Liu C, Au JD, Kindler CH, Cotten JF and Yost CS. (2005) Species-specific differences in response to anesthetics and other modulators by the K2P channel TRESK. *Anesth Analg* **101**: 1042-9, table of contents [PMID:16192517]
95. Ketchum KA, Joiner WJ, Sellers AJ, Kaczmarek LK and Goldstein SA. (1995) A new family of outwardly rectifying potassium channel proteins with two pore domains in tandem. *Nature* **376**: 690-5 [PMID:7651518]
96. Kim D, Cavanaugh EJ, Kim I and Carroll JL. (2009) Heteromeric TASK-1/TASK-3 is the major oxygen-sensitive background K⁺ channel in rat carotid body glomus cells. *J Physiol (Lond.)* **587**: 2963-75 [PMID:19403596]
97. Kim D, Fujita A, Horio Y and Kurachi Y. (1998) Cloning and functional expression of a novel cardiac two-pore background K⁺ channel (cTBAK-1). *Circ Res* **82**: 513-8 [PMID:9506712]
98. Kim D and Gnatenco C. (2001) TASK-5, a new member of the tandem-pore K(+) channel family. *Biochem Biophys Res Commun* **284**: 923-30 [PMID:11409881]
99. Kim D, Sladek CD, Aguado-Velasco C and Mathiasen JR. (1995) Arachidonic acid activation of a new family of K⁺ channels in cultured rat neuronal cells. *J Physiol (Lond.)* **484 (Pt 3)**: 643-60 [PMID:7623282]
100. Kim E, Hwang EM, Yarishkin O, Yoo JC, Kim D, Park N, Cho M, Lee YS, Sun CH and Yi GS *et al.* (2010) Enhancement of TREK1 channel surface expression by protein-protein interaction with beta-COP. *Biochem Biophys Res Commun* **395**: 244-50 [PMID:20362547]
101. Kim SJ, Sohn I, Do IG, Jung SH, Ko YH, Yoo HY, Paik S and Kim WS. (2014) Gene expression profiles for the prediction of progression-free survival in diffuse large B cell lymphoma: results of a DASL assay. *Ann Hematol* **93**: 437-47 [PMID:23975159]
102. Kim Y, Bang H and Kim D. (1999) TBAK-1 and TASK-1, two-pore K(+) channel subunits: kinetic properties and expression in rat heart. *Am J Physiol* **277**: H1669-78 [PMID:10564119]
103. Kim Y, Bang H and Kim D. (2000) TASK-3, a new member of the tandem pore K(+) channel family. *J Biol Chem* **275**: 9340-7 [PMID:10734076]
104. Kindler CH, Yost CS and Gray AT. (1999) Local anesthetic inhibition of baseline potassium channels with two pore domains in tandem. *Anesthesiology* **90**: 1092-102 [PMID:10201682]
105. Kollwe A, Lau AY, Sullivan A, Roux B and Goldstein SA. (2009) A structural model for K2P potassium channels based on 23 pairs of interacting sites and continuum electrostatics. *J Gen Physiol* **134**: 53-68 [PMID:19564427]
106. Kruse M, Schulze-Bahr E, Corfield V, Beckmann A, Stallmeyer B, Kurtbay G, Ohmert I, Schulze-Bahr E, Brink P and Pongs O. (2009) Impaired endocytosis of the ion channel TRPM4 is associated with human progressive familial heart block type I. *J Clin Invest* **119**: 2737-44 [PMID:19726882]
107. Lafrenière RG, Cader MZ, Poulin JF, Andres-Enguix I, Simoneau M, Gupta N, Boisvert K, Lafrenière F, McLaughlan S and Dubé MP *et al.* (2010) A dominant-negative mutation in the TRESK potassium channel is linked to familial migraine with aura. *Nat Med* **16**: 1157-60 [PMID:20871611]
108. Lauritzen I, Zanzouri M, Honoré E, Duprat F, Ehrengruber MU, Lazdunski M and Patel AJ. (2003) K⁺-dependent cerebellar granule neuron apoptosis. Role of task leak K⁺ channels. *J Biol Chem* **278**: 32068-76 [PMID:12783883]
109. Lazarenko RM, Willcox SC, Shu S, Berg AP, Jevtovic-Todorovic V, Talley EM, Chen X and Bayliss DA. (2010) Motoneuronal TASK channels contribute to immobilizing effects of inhalational general anesthetics. *J Neurosci* **30**: 7691-704 [PMID:20519544]
110. Lengyel M, Czirják G and Enyedi P. (2016) Formation of Functional Heterodimers by TREK-1 and TREK-2 Two-pore Domain Potassium Channel Subunits. *J Biol Chem* **291**: 13649-61 [PMID:27129242]

111. Leonoudakis D, Gray AT, Winegar BD, Kindler CH, Harada M, Taylor DM, Chavez RA, Forsayeth JR and Yost CS. (1998) An open rectifier potassium channel with two pore domains in tandem cloned from rat cerebellum. *J Neurosci* **18**: 868-77 [PMID:9437008]
112. Lesage F, Guillemare E, Fink M, Duprat F, Lazdunski M, Romey G and Barhanin J. (1996) TWIK-1, a ubiquitous human weakly inward rectifying K⁺ channel with a novel structure. *EMBO J* **15**: 1004-11 [PMID:8605869]
113. Lesage F, Lauritzen I, Duprat F, Reyes R, Fink M, Heurteaux C and Lazdunski M. (1997) The structure, function and distribution of the mouse TWIK-1 K⁺ channel. *FEBS Lett* **402**: 28-32 [PMID:9013852]
114. Lesage F, Maingret F and Lazdunski M. (2000) Cloning and expression of human TRAAK, a polyunsaturated fatty acids-activated and mechano-sensitive K⁽⁺⁾ channel. *FEBS Lett* **471**: 137-40 [PMID:10767409]
115. Lesage F, Mattéi M, Fink M, Barhanin J and Lazdunski M. (1996) Assignment of the human weak inward rectifier K⁺ channel TWIK-1 gene to chromosome 1q42-q43. *Genomics* **34**: 153-5 [PMID:8661042]
116. Lesage F, Terrenoire C, Romey G and Lazdunski M. (2000) Human TREK2, a 2P domain mechano-sensitive K⁺ channel with multiple regulations by polyunsaturated fatty acids, lysophospholipids, and Gs, Gi, and Gq protein-coupled receptors. *J Biol Chem* **275**: 28398-405 [PMID:10880510]
117. Levitz J, Royal P, Comoglio Y, Wdziekonski B, Schaub S, Clemens DM, Isacoff EY and Sandoz G. (2016) Heterodimerization within the TREK channel subfamily produces a diverse family of highly regulated potassium channels. *Proc Natl Acad Sci USA* **113**: 4194-9 [PMID:27035963]
118. Lloyd EE, Crossland RF, Phillips SC, Marrelli SP, Reddy AK, Taffet GE, Hartley CJ and Bryan Jr RM. (2011) Disruption of K(2P)6.1 produces vascular dysfunction and hypertension in mice. *Hypertension* **58**: 672-8 [PMID:21876070]
119. Lolicato M, Riegelhaupt PM, Arrigoni C, Clark KA and Minor Jr DL. (2014) Transmembrane helix straightening and buckling underlies activation of mechanosensitive and thermosensitive K(2P) channels. *Neuron* **84**: 1198-212 [PMID:25500157]
120. Lopes CM, Gallagher PG, Buck ME, Butler MH and Goldstein SA. (2000) Proton block and voltage gating are potassium-dependent in the cardiac leak channel Kcnk3. *J Biol Chem* **275**: 16969-78 [PMID:10748056]
121. Lopes CM, Rohács T, Czirják G, Balla T, Enyedi P and Logothetis DE. (2005) PIP2 hydrolysis underlies agonist-induced inhibition and regulates voltage gating of two-pore domain K⁺ channels. *J Physiol* **564**: 117-29 [PMID:15677683]
122. Lopes CM, Zilberberg N and Goldstein SA. (2001) Block of Kcnk3 by protons. Evidence that 2-P-domain potassium channel subunits function as homodimers. *J Biol Chem* **276**: 24449-52 [PMID:11358956]
123. Lotshaw DP. (2007) Biophysical, pharmacological, and functional characteristics of cloned and native mammalian two-pore domain K⁺ channels. *Cell Biochem Biophys* **47**: 209-56 [PMID:17652773]
124. Loucif AJC, Saintot PP, Liu J, Antonio BM, Zellmer SG, Yoger K, Veale EL, Wilbrey A, Omoto K and Cao L *et al.*. (2018) GI-530159, a novel, selective, mechanosensitive two-pore-domain potassium (K_{2P}) channel opener, reduces rat dorsal root ganglion neuron excitability. *Br J Pharmacol* **175**: 2272-2283 [PMID:29150838]
125. Ma L, Zhang X, Zhou M and Chen H. (2012) Acid-sensitive TWIK and TASK two-pore domain potassium channels change ion selectivity and become permeable to sodium in extracellular acidification. *J Biol Chem* **287**: 37145-53 [PMID:22948150]
126. Maingret F, Fosset M, Lesage F, Lazdunski M and Honoré E. (1999) TRAAK is a mammalian neuronal mechano-gated K⁺ channel. *J Biol Chem* **274**: 1381-7 [PMID:9880510]
127. Maingret F, Lauritzen I, Patel AJ, Heurteaux C, Reyes R, Lesage F, Lazdunski M and Honoré E. (2000) TREK-1 is a heat-activated background K⁽⁺⁾ channel. *EMBO J* **19**: 2483-91 [PMID:10835347]
128. Maingret F, Patel AJ, Lazdunski M and Honoré E. (2001) The endocannabinoid anandamide is a direct and selective blocker of the background K⁽⁺⁾ channel TASK-1. *EMBO J* **20**: 47-54 [PMID:11226154]
129. Maingret F, Patel AJ, Lesage F, Lazdunski M and Honoré E. (1999) Mechano- or acid stimulation, two interactive modes of activation of the TREK-1 potassium channel. *J Biol Chem* **274**: 26691-6 [PMID:10480871]
130. Maingret F, Patel AJ, Lesage F, Lazdunski M and Honoré E. (2000) Lysophospholipids open the two-pore domain mechano-gated K⁽⁺⁾ channels TREK-1 and TRAAK. *J Biol Chem* **275**: 10128-33 [PMID:10744694]
131. Manjunath NA, Bray-Ward P, Goldstein SA and Gallagher PG. (1999) Assignment of the 2P domain, acid-sensitive potassium channel OAT1 gene KCN3 to human chromosome bands 2p24.1-->p23.3 and

- murine 5B by in situ hybridization. *Cytogenet Cell Genet* **86**: 242-3 [PMID:10575216]
132. Martin S, Nishimune A, Mellor JR and Henley JM. (2007) SUMOylation regulates kainate-receptor-mediated synaptic transmission. *Nature* **447**: 321-5 [PMID:17486098]
 133. Mazella J, Pétrault O, Lucas G, Deval E, Béraud-Dufour S, Gandin C, El-Yacoubi M, Widmann C, Guyon A and Chevet E *et al.*. (2010) Spadin, a sortilin-derived peptide, targeting rodent TREK-1 channels: a new concept in the antidepressant drug design. *PLoS Biol* **8**: e1000355 [PMID:20405001]
 134. McClenaghan C, Schewe M, Aryal P, Carpenter EP, Baukrowitz T and Tucker SJ. (2016) Polymodal activation of the TREK-2 K2P channel produces structurally distinct open states. *J Gen Physiol* **147**: 497-505 [PMID:27241700]
 135. Meadows HJ, Benham CD, Cairns W, Gloger I, Jennings C, Medhurst AD, Murdock P and Chapman CG. (2000) Cloning, localisation and functional expression of the human orthologue of the TREK-1 potassium channel. *Pflugers Arch* **439**: 714-22 [PMID:10784345]
 136. Medhurst AD, Rennie G, Chapman CG, Meadows H, Duckworth MD, Kelsell RE, Gloger II and Pangalos MN. (2001) Distribution analysis of human two pore domain potassium channels in tissues of the central nervous system and periphery. *Brain Res Mol Brain Res* **86**: 101-14 [PMID:11165377]
 137. Millar JA, Barratt L, Southan AP, Page KM, Fyffe RE, Robertson B and Mathie A. (2000) A functional role for the two-pore domain potassium channel TASK-1 in cerebellar granule neurons. *Proc Natl Acad Sci USA* **97**: 3614-8 [PMID:10725353]
 138. Miller AN and Long SB. (2012) Crystal structure of the human two-pore domain potassium channel K2P1. *Science* **335**: 432-6 [PMID:22282804]
 139. Morton MJ, Chipperfield S, Abohamed A, Sivaprasadarao A and Hunter M. (2005) Na(+)-induced inward rectification in the two-pore domain K(+) channel, TASK-2. *Am J Physiol Renal Physiol* **288**: F162-9 [PMID:15328068]
 140. Mu D, Chen L, Zhang X, See LH, Koch CM, Yen C, Tong JJ, Spiegel L, Nguyen KC and Servoss A *et al.*. (2003) Genomic amplification and oncogenic properties of the KCNK9 potassium channel gene. *Cancer Cell* **3**: 297-302 [PMID:12676587]
 141. Nie X, Arrighi I, Kaissling B, Pfaff I, Mann J, Barhanin J and Vallon V. (2005) Expression and insights on function of potassium channel TWIK-1 in mouse kidney. *Pflugers Arch* **451**: 479-88 [PMID:16025300]
 142. Niemeyer MI, Cid LP, Barros LF and Sepúlveda FV. (2001) Modulation of the two-pore domain acid-sensitive K⁺ channel TASK-2 (KCNK5) by changes in cell volume. *J Biol Chem* **276**: 43166-74 [PMID:11560934]
 143. Niemeyer MI, Cid LP, González W and Sepúlveda FV. (2016) Gating, Regulation, and Structure in K2P K⁺ Channels: In Varietate Concordia? *Mol Pharmacol* **90**: 309-17 [PMID:27268784]
 144. Niemeyer MI, González-Nilo FD, Zúñiga L, González W, Cid LP and Sepúlveda FV. (2007) Neutralization of a single arginine residue gates open a two-pore domain, alkali-activated K⁺ channel. *Proc Natl Acad Sci U S A* **104**: 666-71 [PMID:17197424]
 145. Noël J, Zimmermann K, Busserolles J, Deval E, Alloui A, Diochot S, Guy N, Borsotto M, Reeh P and Eschalier A *et al.*. (2009) The mechano-activated K⁺ channels TRAAK and TREK-1 control both warm and cold perception. *EMBO J* **28**: 1308-18 [PMID:19279663]
 146. O'Kelly I. (2015) Endocytosis as a mode to regulate functional expression of two-pore domain potassium (K_{2p}) channels. *Pflugers Arch* **467**: 1133-42 [PMID:25413469]
 147. O'Kelly I, Butler MH, Zilberberg N and Goldstein SA. (2002) Forward transport. 14-3-3 binding overcomes retention in endoplasmic reticulum by dibasic signals. *Cell* **111**: 577-88 [PMID:12437930]
 148. O'Kelly I and Goldstein SA. (2008) Forward Transport of K2p3.1: mediation by 14-3-3 and COPI, modulation by p11. *Traffic* **9**: 72-8 [PMID:17908283]
 149. Orias M, Velázquez H, Tung F, Lee G and Desir GV. (1997) Cloning and localization of a double-pore K channel, KCNK1: exclusive expression in distal nephron segments. *Am J Physiol* **273**: F663-6 [PMID:9362344]
 150. Ozaita A and Vega-Saenz de Miera E. (2002) Cloning of two transcripts, HKT4.1a and HKT4.1b, from the human two-pore K⁺ channel gene KCNK4. Chromosomal localization, tissue distribution and functional expression. *Brain Res Mol Brain Res* **102**: 18-27 [PMID:12191490]
 151. Patel AJ, Honoré E, Lesage F, Fink M, Romey G and Lazdunski M. (1999) Inhalational anesthetics activate two-pore-domain background K⁺ channels. *Nat Neurosci* **2**: 422-6 [PMID:10321245]
 152. Patel AJ, Honoré E, Maingret F, Lesage F, Fink M, Duprat F and Lazdunski M. (1998) A mammalian two pore domain mechano-gated S-like K⁺ channel. *EMBO J* **17**: 4283-90 [PMID:9687497]

153. Patel AJ, Maingret F, Magnone V, Fosset M, Lazdunski M and Honoré E. (2000) TWIK-2, an inactivating 2P domain K⁺ channel. *J Biol Chem* **275**: 28722-30 [PMID:10887187]
154. Pei L, Wisner O, Slavin A, Mu D, Powers S, Jan LY and Hoey T. (2003) Oncogenic potential of TASK3 (Kcnk9) depends on K⁺ channel function. *Proc Natl Acad Sci USA* **100**: 7803-7 [PMID:12782791]
155. Pereira V, Busserolles J, Christin M, Devilliers M, Poupon L, Legha W, Alloui A, Aissouni Y, Bourinet E and Lesage F *et al.*. (2014) Role of the TREK2 potassium channel in cold and warm thermosensation and in pain perception. *Pain* **155**: 2534-2544 [PMID:25239074]
156. Piechotta PL, Rapedius M, Stansfeld PJ, Bolleballi MK, Ehrlich G, Erlich G, Andres-Enguix I, Fritzenschaft H, Decher N and Sansom MS *et al.*. (2011) The pore structure and gating mechanism of K2P channels. *EMBO J* **30**: 3607-19 [PMID:21822218]
157. Plant LD & Goldstein SA. (2015) Two-Pore Domain Potassium Channels *In Handbook of Ion Channels* Edited by Zheng J, Trudeau MC: CRC Press: 261-274 [ISBN: 9781138198845]
158. Plant LD, Dementieva IS, Kollwe A, Olikara S, Marks JD and Goldstein SA. (2010) One SUMO is sufficient to silence the dimeric potassium channel K2P1. *Proc Natl Acad Sci USA* **107**: 10743-8 [PMID:20498050]
159. Plant LD, Dowdell EJ, Dementieva IS, Marks JD and Goldstein SA. (2011) SUMO modification of cell surface Kv2.1 potassium channels regulates the activity of rat hippocampal neurons. *J Gen Physiol* **137**: 441-54 [PMID:21518833]
160. Plant LD, Kemp PJ, Peers C, Henderson Z and Pearson HA. (2002) Hypoxic depolarization of cerebellar granule neurons by specific inhibition of TASK-1. *Stroke* **33**: 2324-8 [PMID:12215606]
161. Plant LD, Rajan S and Goldstein SA. (2005) K2P channels and their protein partners. *Curr Opin Neurobiol* **15**: 326-33 [PMID:15922586]
162. Plant LD, Zuniga L, Araki D, Marks JD and Goldstein SA. (2012) SUMOylation silences heterodimeric TASK potassium channels containing K2P1 subunits in cerebellar granule neurons. *Sci Signal* **5**: ra84 [PMID:23169818]
163. Plant LD, Zúñiga L, Olikara S, Marks JD and Goldstein SAN. (2010) K2P1 Assembles with K2P3 or K2P9 to Form Sumo-Regulated Task Background Channels *Biophysical Journal* **98**: 710a
164. Pope L, Arrigoni C, Lou H, Bryant C, Gallardo-Godoy A, Renslo AR and Minor Jr DL. (2018) Protein and Chemical Determinants of BL-1249 Action and Selectivity for K_{2p} Channels. *ACS Chem Neurosci* **9**: 3153-3165 [PMID:30089357]
165. Pountney DJ, Gulkarov I, Vega-Saenz de Miera E, Holmes D, Saganich M, Rudy B, Artman M and Coetzee WA. (1999) Identification and cloning of TWIK-originated similarity sequence (TOSS): a novel human 2-pore K⁺ channel principal subunit. *FEBS Lett* **450**: 191-6 [PMID:10359073]
166. Rajan S, Plant LD, Rabin ML, Butler MH and Goldstein SA. (2005) Sumoylation silences the plasma membrane leak K⁺ channel K2P1. *Cell* **121**: 37-47 [PMID:15820677]
167. Rajan S, Wischmeyer E, Karschin C, Preisig-Müller R, Grzeschik KH, Daut J, Karschin A and Derst C. (2001) THIK-1 and THIK-2, a novel subfamily of tandem pore domain K⁺ channels. *J Biol Chem* **276**: 7302-11 [PMID:11060316]
168. Rajan S, Wischmeyer E, Xin Liu G, Preisig-Müller R, Daut J, Karschin A and Derst C. (2000) TASK-3, a novel tandem pore domain acid-sensitive K⁺ channel. An extracellular histiding as pH sensor. *J Biol Chem* **275**: 16650-7 [PMID:10747866]
169. Rapedius M, Schmidt MR, Sharma C, Stansfeld PJ, Sansom MS, Baukowitz T and Tucker SJ. (2012) State-independent intracellular access of quaternary ammonium blockers to the pore of TREK-1. *Channels (Austin)* **6**: 473-8 [PMID:22991046]
170. Reed AP, Bucci G, Abd-Wahab F and Tucker SJ. (2016) Dominant-Negative Effect of a Missense Variant in the TASK-2 (KCNK5) K⁺ Channel Associated with Balkan Endemic Nephropathy. *PLoS One* **11**: e0156456 [PMID:27228168]
171. Renigunta V, Fischer T, Zuzarte M, Kling S, Zou X, Siebert K, Limberg MM, Rinné S, Decher N and Schlichthörl G *et al.*. (2014) Cooperative endocytosis of the endosomal SNARE protein syntaxin-8 and the potassium channel TASK-1. *Mol Biol Cell* **25**: 1877-91 [PMID:24743596]
172. Renigunta V, Zou X, Kling S, Schlichthörl G and Daut J. (2014) Breaking the silence: functional expression of the two-pore-domain potassium channel THIK-2. *Pflugers Arch* **466**: 1735-45 [PMID:24297522]
173. Reyes R, Duprat F, Lesage F, Fink M, Salinas M, Farman N and Lazdunski M. (1998) Cloning and expression of a novel pH-sensitive two pore domain K⁺ channel from human kidney. *J Biol Chem* **273**:

- 30863-9 [PMID:9812978]
174. Reyes R, Lauritzen I, Lesage F, Ettaiche M, Fosset M and Lazdunski M. (2000) Immunolocalization of the arachidonic acid and mechanosensitive baseline traak potassium channel in the nervous system. *Neuroscience* **95**: 893-901 [PMID:10670456]
 175. Salinas M, Reyes R, Lesage F, Fosset M, Heurteaux C, Romey G and Lazdunski M. (1999) Cloning of a new mouse two-P domain channel subunit and a human homologue with a unique pore structure. *J Biol Chem* **274**: 11751-60 [PMID:10206991]
 176. Sandoz G, Tardy MP, Thümmeler S, Feliciangeli S, Lazdunski M and Lesage F. (2008) Mtap2 is a constituent of the protein network that regulates twik-related K⁺ channel expression and trafficking. *J Neurosci* **28**: 8545-52 [PMID:18716213]
 177. Sandoz G, Thümmeler S, Duprat F, Feliciangeli S, Vinh J, Escoubas P, Guy N, Lazdunski M and Lesage F. (2006) AKAP150, a switch to convert mechano-, pH- and arachidonic acid-sensitive TREK K(+) channels into open leak channels. *EMBO J* **25**: 5864-72 [PMID:17110924]
 178. Sano Y, Inamura K, Miyake A, Mochizuki S, Kitada C, Yokoi H, Nozawa K, Okada H, Matsushime H and Furuichi K. (2003) A novel two-pore domain K⁺ channel, TRESK, is localized in the spinal cord. *J Biol Chem* **278**: 27406-12 [PMID:12754259]
 179. Schewe M, Nematian-Ardestani E, Sun H, Musinszki M, Cordeiro S, Bucci G, de Groot BL, Tucker SJ, Rapedius M and Baukowitz T. (2016) A Non-canonical Voltage-Sensing Mechanism Controls Gating in K2P K(+) Channels. *Cell* **164**: 937-49 [PMID:26919430]
 180. Schmidt C, Wiedmann F, Voigt N, Zhou XB, Heijman J, Lang S, Albert V, Kallenberger S, Ruhparwar A and Szabó G *et al.*. (2015) Upregulation of K(2P)3.1 K⁺ Current Causes Action Potential Shortening in Patients With Chronic Atrial Fibrillation. *Circulation* **132**: 82-92 [PMID:25951834]
 181. Simkin D, Cavanaugh EJ and Kim D. (2008) Control of the single channel conductance of K2P10.1 (TREK-2) by the amino-terminus: role of alternative translation initiation. *J Physiol* **586**: 5651-63 [PMID:18845607]
 182. Sirois JE, Lei Q, Talley EM, Lynch 3rd C and Bayliss DA. (2000) The TASK-1 two-pore domain K⁺ channel is a molecular substrate for neuronal effects of inhalation anesthetics. *J Neurosci* **20**: 6347-54 [PMID:10964940]
 183. Streit AK, Netter MF, Kempf F, Walecki M, Rinné S, Bollepalli MK, Preisig-Müller R, Renigunta V, Daut J and Baukowitz T *et al.*. (2011) A specific two-pore domain potassium channel blocker defines the structure of the TASK-1 open pore. *J Biol Chem* **286**: 13977-84 [PMID:21362619]
 184. Su Z, Brown EC, Wang W and MacKinnon R. (2016) Novel cell-free high-throughput screening method for pharmacological tools targeting K⁺ channels. *Proc Natl Acad Sci U S A* **113**: 5748-53 [PMID:27091997]
 185. Talley EM and Bayliss DA. (2002) Modulation of TASK-1 (Kcnk3) and TASK-3 (Kcnk9) potassium channels: volatile anesthetics and neurotransmitters share a molecular site of action. *J Biol Chem* **277**: 17733-42 [PMID:11886861]
 186. Talley EM, Lei Q, Sirois JE and Bayliss DA. (2000) TASK-1, a two-pore domain K⁺ channel, is modulated by multiple neurotransmitters in motoneurons. *Neuron* **25**: 399-410 [PMID:10719894]
 187. Talley EM, Solorzano G, Lei Q, Kim D and Bayliss DA. (2001) Cns distribution of members of the two-pore-domain (KCNK) potassium channel family. *J Neurosci* **21**: 7491-505 [PMID:11567039]
 188. Terrenoire C, Lauritzen I, Lesage F, Romey G and Lazdunski M. (2001) A TREK-1-like potassium channel in atrial cells inhibited by beta-adrenergic stimulation and activated by volatile anesthetics. *Circ Res* **89**: 336-42 [PMID:11509450]
 189. Theilig F, Goranova I, Hirsch JR, Wieske M, Unsal S, Bachmann S, Veh RW and Derst C. (2008) Cellular localization of THIK-1 (K(2P)13.1) and THIK-2 (K(2P)12.1) K channels in the mammalian kidney. *Cell Physiol Biochem* **21**: 63-74 [PMID:18209473]
 190. Thomas D, Plant LD, Wilkens CM, McCrossan ZA and Goldstein SA. (2008) Alternative translation initiation in rat brain yields K2P2.1 potassium channels permeable to sodium. *Neuron* **58**: 859-70 [PMID:18579077]
 191. Toncheva D, Mihailova-Hristova M, Vazharova R, Staneva R, Karachanak S, Dimitrov P, Simeonov V, Ivanov S, Balabanski L and Serbezov D *et al.*. (2014) NGS nominated CELA1, HSPG2, and KCNK5 as candidate genes for predisposition to Balkan endemic nephropathy. *Biomed Res Int* **2014**: 920723 [PMID:24949484]
 192. Tulleuda A, Cokic B, Callejo G, Saiani B, Serra J and Gasull X. (2011) TRESK channel contribution to nociceptive sensory neurons excitability: modulation by nerve injury. *Mol Pain* **7**: 30 [PMID:21527011]

193. Veale EL, Al-Moubarak E, Bajaria N, Omoto K, Cao L, Tucker SJ, Stevens EB and Mathie A. (2014) Influence of the N terminus on the biophysical properties and pharmacology of TREK1 potassium channels. *Mol Pharmacol* **85**: 671-81 [PMID:24509840]
194. Veale EL and Mathie A. (2016) Aristolochic acid, a plant extract used in the treatment of pain and linked to Balkan endemic nephropathy, is a regulator of K2P channels. *Br J Pharmacol* **173**: 1639-52 [PMID:26914156]
195. Vivier D, Bennis K, Lesage F and Ducki S. (2016) Perspectives on the Two-Pore Domain Potassium Channel TREK-1 (TWIK-Related K(+) Channel 1). A Novel Therapeutic Target? *J Med Chem* **59**: 5149-57 [PMID:26588045]
196. Wang S, Benamer N, Zanella S, Kumar NN, Shi Y, Bévangut M, Penton D, Guyenet PG, Lesage F and Gestreau C *et al.* (2013) TASK-2 channels contribute to pH sensitivity of retrotrapezoid nucleus chemoreceptor neurons. *J Neurosci* **33**: 16033-44 [PMID:24107938]
197. Wang W, Kiyoshi CM, Du Y, Ma B, Alford CC, Chen H and Zhou M. (2016) mGluR3 Activation Recruits Cytoplasmic TWIK-1 Channels to Membrane that Enhances Ammonium Uptake in Hippocampal Astrocytes. *Mol Neurobiol* **53**: 6169-6182 [PMID:26553349]
198. Wang W, Putra A, Schools GP, Ma B, Chen H, Kaczmarek LK, Barhanin J, Lesage F and Zhou M. (2013) The contribution of TWIK-1 channels to astrocyte K(+) current is limited by retention in intracellular compartments. *Front Cell Neurosci* **7**: 246 [PMID:24368895]
199. Warth R, Barrière H, Meneton P, Bloch M, Thomas J, Tauc M, Heitzmann D, Romeo E, Verrey F and Mengual R *et al.* (2004) Proximal renal tubular acidosis in TASK2 K+ channel-deficient mice reveals a mechanism for stabilizing bicarbonate transport. *Proc Natl Acad Sci USA* **101**: 8215-20 [PMID:15141089]
200. Washburn CP, Sirois JE, Talley EM, Guyenet PG and Bayliss DA. (2002) Serotonergic raphe neurons express TASK channel transcripts and a TASK-like pH- and halothane-sensitive K+ conductance. *J Neurosci* **22**: 1256-65 [PMID:11850453]
201. Wiedmann F, Kiper AK, Bedoya M, Ratte A, Rinné S, Kraft M, Waibel M, Anad P, Wenzel W and González W *et al.* (2019) Identification of the A293 (AVE1231) Binding Site in the Cardiac Two-Pore-Domain Potassium Channel TASK-1: a Common Low Affinity Antiarrhythmic Drug Binding Site. *Cell Physiol Biochem* **52**: 1223-1235 [PMID:31001961]
202. Woo DH, Han KS, Shim JW, Yoon BE, Kim E, Bae JY, Oh SJ, Hwang EM, Marmorstein AD and Bae YC *et al.* (2012) TREK-1 and Best1 channels mediate fast and slow glutamate release in astrocytes upon GPCR activation. *Cell* **151**: 25-40 [PMID:23021213]
203. Yamamoto Y, Hatakeyama T and Taniguchi K. (2009) Immunohistochemical colocalization of TREK-1, TREK-2 and TRAAK with TRP channels in the trigeminal ganglion cells. *Neurosci Lett* **454**: 129-33 [PMID:19429069]
204. Yellen G. (1998) The moving parts of voltage-gated ion channels. *Q Rev Biophys* **31**: 239-95 [PMID:10384687]
205. Zilberberg N, Ilan N and Goldstein SA. (2001) KCNKØ: opening and closing the 2-P-domain potassium leak channel entails "C-type" gating of the outer pore. *Neuron* **32**: 635-48 [PMID:11719204]
206. Zilberberg N, Ilan N, Gonzalez-Colaso R and Goldstein SA. (2000) Opening and closing of KCNKØ potassium leak channels is tightly regulated. *J Gen Physiol* **116**: 721-34 [PMID:11055999]
207. Zuzarte M, Heusser K, Renigunta V, Schlichthörl G, Rinné S, Wischmeyer E, Daut J, Schwappach B and Preisig-Müller R. (2009) Intracellular traffic of the K+ channels TASK-1 and TASK-3: role of N- and C-terminal sorting signals and interaction with 14-3-3 proteins. *J Physiol* **587**: 929-52 [PMID:19139046]