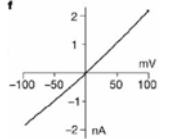
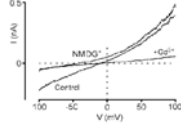
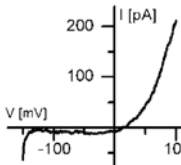
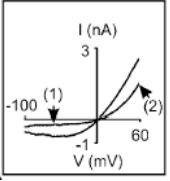
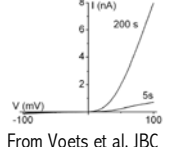
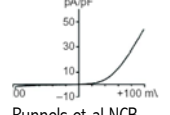
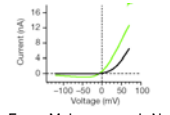


The TRPM Melastatin Subfamily

Clapham Lab 1/20/2007

TRP Subtype Unigene	M1 (MLSN) Hs.43265 Splice variants	M2 (hTRPC7, LTRPC2) Mm.133517 Splice variants	M3 (MLSN2, LTRPC3) Hs.288911 96 splice variants (m)	M4 (LTRPC4, MLS2s, CAN [4b]) Hs.31608 Splice variants	M5 (Mtr1, LTRPC5) Hs.272287 Splice variants	M6 (CHAK2) Hs.272225 Splice variants	M7 (CHAK1, TRP- PLIK, LTRPC7) Hs.33819	M8 (Trp-p8, CMR1) Hs.366053
# Amino acids	H 1533 R 1628 M 1506	H 1503 R 1508 M 1506	H 1325-1732 R N.D. M 1325-1721	1214 M4b/1040M4a R 1208 M 1213	H 1165 R M 1158	H 2022 R 2020 M 2028	H 1864 R 1862 M 1862	H 1104 R 1104 M 1104
Accession # Human Rat Mouse	075660 Q2WEA5 Q2TV84	094759 Q2PH54 Q91YD4	Q9HCF6 (long) N.D. Q5F4S9 (long)	Q8TD43 Q9ESQ5 Q7TN37	Q52LU2 Q9JJH7	Q9BX84 XB219747 Q8CIR4	Hs 512894 Rn86991 Mm.244705	Q722W7 Q8R455 Q84RD5
Splice variants and other accession #s	Q7Z4N2 Hs 1533 BAC80204 Hs 1527 BAC80202 Hs 230 070334 Mm 542 Q5U4B3 Mm 426 Q640P5 Mm 443	094759 Hs 1503 Q5KTC2ii Hs 1503 Q5KTC1 Hs 1289 NP_001001188 Hs 846 Q91YD4 Mm 1507 Q5KTC0 Mm 1506 Q8BNJ4 Mm 328	Q9HCF6 Hs 1732 NP001007472Hs 1707 AAO49153Hs1554 3a AAO49154Hs1566 3b AAO49155Hs1566 3c AAO49156Hs1544 3d NP_996827iiHs544 3d AAO49157Hs1556 3e AAO49158Hs1579 3f BAC80203 Hs1533 BAC80204 Hs1527 BAC55106 Hs1526 CAD43605 Hs1325 BAB13442 Hs1017 BAC80202 Hs230 Q5F4T0 Mm1721 α1 Q5F4S8 Mm1711 α2 Q5F4S9 Mm1721 α3 Q5F4S7 Mm1709 α4 Q5F4S6 Mm 1699 α5	Q96L84 Hs 1040 a Q7Z5D9 Hs 1069 c Q7TN37 Mm 1213 NP_780339 Mm 945 AAH58632 Mm 872 AAH46472 Mm 793 AAH49993 Mm 510 BAC81770 Mm 488 BAC81769 Mm 422 b	Q9NZQ8 Hs 1165iv Q9JJH7 Mm 1158 Q99NF9 Mm 1148 Q9EPM3 Mm 1116 Q7TPL4 Mm 1000	AAR03490 Hs 1943 a AAR03488 Hs 2017 b AAR03489 Hs 2017 c Q8CIR4 Mm 2028	Q96QT4 Hs 1865 Q923J1 Mm 1863	Q7Z2W7 Hs 1104v NP_076985vi Hs 1104 Q8R4D5 Mm 1104
OMIM gene map H, R, M	15q13-q14 rat 1q22 mouse 7c	21q22.3 20p12 10C1	9q21.11 N.D. 19 B	19q13.33 1q22 7	11p15.5 7E5	9q21.13 1q43 19B	15q21 3 2F2	2q37.1 9q35 2 H1
Genetic model or disease mutation		Bipolar disorder BP-I, II, nonsyndromic hereditary deafness	Candidate gene for ALS with frontotemporal dementia (OMIM 105550), early-onset pulverulent cataract (OMIM 605749), hemophagocytic lymphohistiocytosis (HLH, OMIM 603552), infantile nephronophthisis (OMIM 602088)		Mouse TRPM5-/- Candidate gene for rhabdomyosarcomas, Wilms tumor, Beckwith-Widemann	Human hypomagnesemia with secondary hypocalcemia (HGH)	TRPM7-/- A variant form of TRPM7 has been detected in patients with Guamanian amyotrophic lateral sclerosis (ALS-G) and Parkinsonism dementia (PD- G)	
Known Functions		Oxidant stress sensor in immune cells, glia in brain, T- dependent, Ca entry pancreatic beta cells		endogenous calcium- activated cation (CAN) channels, negative feedback regulator of Ca ²⁺ entry,	Taste (Sweet, Bitter, Umami) via T1R, T2R and PLCb	Renal and gastrointestinal tract Mg ²⁺ uptake		Cold sensing

Likely role in	Melanoma invasiveness	Oxidant stress response in immune and other cells (microglia in brain, respiratory burst in neutrophils?)	Probable role in osmosensation and renal Ca ²⁺ homeostasis, mechanosensor, cation homeostasis in cerebrospinal fluid	Ca oscillations in activated T cells Myogenic cerebral artery constriction Bayliss effect in smooth muscle Spreading depression hypoxic depolarisation, stroke, heart hypertrophy and arrhythmia	Perhaps temperature	Magnesium absorption in kidney	Cellular Mg homeostasis proposed. Potential other trace metals, such as Zn, Mn. Oxygen-glucose deprivation-induced calcium influx and neuronal death	Pain pathways (present in Ad fibers), presynaptic potentiation in DRG neurons Present in various adenocarcinomas
N or C terminal domain modules	N-700 a.a. TRPM domain, W/FIX ₃ - (F/I/I)XK(R/K)EC(V/I/S)X ₁₂₋₂₄ CXCG C-TRP (VWKFQR) box C-PolyP C-coiled coil	N-700 a.a. TRPM domain, W/FIX ₃ - (F/I/I)XK(R/K)EC(V/I/S)X ₁₂₋₂₄ CXCG [VIYFL]WK[FAY][QN]R; C-NUDT9 ADP-ribose hydrolase (NUDT9-H) C-TRP (IWKFQR) box C-PolyP;C-coiled coil	4 CaM binding domains N-700 a.a. TRPM domain, W/FIX ₃ - (F/I/I)XK(R/K)EC(V/I/S)X ₁₂₋₂₄ CXCG C-TRP (VWKFQR) box [VIYFL]WK[FAY][QN]R; C-PolyP C-coiled coil	N-700 a.a. TRPM domain, W/FIX ₃ - (F/I/I)XK(R/K)EC(V/I/S)X ₁₂₋₂₄ CXCG C-TRP (YWKAQR) box [VIYFL]WK[FAY][QN]R; C-PolyP; C-coiled coil	C-TRP (FWKFQR) box [VIYFL]WK[FAY][QN]R; C-PolyP C-coiled coil	N-700 a.a. TRPM domain, W/FIX ₃ - (F/I/I)XK(R/K)EC(V/I/S)X ₁₂₋₂₄ CXCG C-TRP (LWKYNR) box [VIYFL]WK[FAY][QN]R; C-PolyP C-coiled coil C-Atypical protein kinase	N-700 a.a. TRPM domain, W/FIX ₃ - (F/I/I)XK(R/K)EC(V/I/S)X ₁₂₋₂₄ CXCG C-TRP (VWKYQR) box [VIYFL]WK[FAY][QN]R; C-PolyP C-coiled coil	N-700 a.a. TRPM domain, W/FIX ₃ - (F/I/I)XK(R/K)EC(V/I/S)X ₁₂₋₂₄ CXCG-TRP (VWKFQR) box [VIYFL]WK[FAY][QN]R; C-PolyP C-coiled coil
Reported Interacting Proteins	Short transcript of M1 (MLSN-S).	N- CaM C-ADP-ribose hydrolase Sir2(sirtuin) , a NAD ⁺ dependent deacetylases, binds to TRPM2	N.D.	Calmodulin Probably SUR1	N.D.	TRPM7	PLCβ1,2,3, PLCγ1, snapin TRPM6, myosin IIA heavy chain	
Activation	N.D. Microphthalmia-associated transcription factor (MITF) induces expression Ca ²⁺ entry channel, whose membrane insertion is regulated by a short isoform,(MLSN-S, 500 AA) (disputed).	~100 μM ADPR, NAD, NAADP, 700 μM cADPR oxidative stress, PARP-1, heat potentiates cysteines C996, C1008 are essential for pore function	Constitutive, V _{0.5} =-61 mV Enhanced by hypoosmolarity Activated by sphingolipids (10 mM D-erythrospingosine)	M4b:K _{act} : 300-500 nM [Ca ²⁺] _i ; >1 μM (Nilius)5μM PIP ₂ ; V _{0.5} =-20to+60mV Decavanadate; BTP2 or YM-58483 Ca ²⁺ affinity depends on range of voltage activation; depends on PIP ₂ , PKC phosphorylation, decreased Ca ²⁺ affinity during desensitization; U73122 prevents TRPM4 desensitization	GPCR (T1R, T2R) Ggus-PLCb2 [Ca ²⁺] _i , 20-30 μM PIP2 Heat activation of TRPM5 results from marked leftward shift of the voltage dependence of activation (-7.0 mV °C)	Low pH 2-APB (200 μM)	PIP ₂ Tyrosine phosphorylation, Activation upon oxidative stress and cAmp proposed, PKA No V dependence Low pH increases inward current	T<25°C (80 μM menthol, icilin potentiate) Cold-induced activation via leftward shift of voltage dependence of activation (7.3mV/C)
Direct Agonist (bind channel protein to activate)	N.D.		D-erythrospingosine, steroids					Menthol (40 μM) Icilin (280 nM) Eucalyptol (5 mM) FrescolatMAG (5 μM)
~P_{Ca}/P_{Na}	N.D.	~1 (estimated) reported ~6 at 35C	< 0.1 TRPM3a1-no divalents, perm to Na, K, Cs, NMDG	M4b: <0.05 (monovalent selective) Na>K>Cs>Li	<0.05 (Monovalent nonselective)	<1 Zn>Ba>Mg>Ca>Mn>Sr >Cd>Ni	0.3 monovalent s outward inward – Zn~Ni>Ba>Co>Mg~Mn~Sr~Cd~Ca	1-3 Cs>K>Na
Blockers and inhibitors	N.D.	No pore block by lanthanides and heavy metal ions 2 μM N-ACA econazole, miconazole,	Mg _i for M3a1, 3a2 (9 mM comp. block) 100 μM Gd, La	M4a: 80 μM La, Gd M4b: intracellular free ATP ⁺ , 1.7μM Polyamines, spermine	Sensitive to pH below 7.0 with complete block around 6	Ruthenium Red Mgi (0.5 mM)	La (2 mM), Mgi (0.6 mM) PIP ₂ hydrolysis by GPCR (M1,	BCTC (1 μM) Capsazepine (18 μM) 2-APB (10 μM)

		clotrimazole, 2-APB, flufenamic acid	extracell Na>K decreases outward currents in M3a2 2-APB (100 μM)	30-60μM) Pore mutation D984A results in a non-functional channel with a dominant negative phenotype			LPAR/EDG-7R)-Gq-PLCβ and TK(EGF)-PLCγ hydrolyzes PIP ₂ to turn off channel.	
Single channel conductance (γ) in pS.	N.D.	60 pS (140 Na/140 Na)	TRPM3 ¹³²⁵ 83 (140 Na/140 Na) 133 pS (140 Cs, -60 mV); 83 pS (-60 mV, 140 Na), 73 pS physiological cond.	M4b:25 pS (isotonic monovalents)	23 pS (isotonic monovalents)	84 pS	105 pS (+ voltages)	83 pS (+ voltages)
I-V shape	N.D.	 Instantaneous I/V is linear From Perraud et al. Nature	 From Grimm et al. JBC	M4b:  Instantaneous I/V is linear Nilius et al, 2003	 Hofmann	 From Voets et al. JBC	 Runnels et al NCB	 From Mckemy et al. Nature
Tissue Expression	Skin; Melanocytes and retinal pigmented epithelium	Brain; microglia, cerebellum, cortex, medulla oblongata, hippocampus, striatum, pancreatic b-cells, immune cells, PMNs, thymocytes, vascular endothelium	Kidney, pulmonary endothelium, cultured trigeminal neurons, liver, pancreas, ovary, testis, spinal cord Brain: dentate gyrus, lateral septal nuclei, indusium griseum, tenia tecti, epithelial cells of choroid plexus, human iris, retinal pigmented cells	stomach aorta endothelium esophagus, pancreas kidney,glom., PCT, MTAL, DCT, CCD brain: widely expressed smooth muscle cerebral arteries	Tonge, taste tissue stomach intestines uterus testis	Small intestine, kidney	Ubiquitous	DRG, Trigem ganglia, Testis, prostate, bladder
Comments	Decrease in M1 RNA with melanoma progression. loss of melastatin expression correlates with the thickness of the melanomas	Increased [Ca ²⁺] _i potentiates (EC ₅₀ 340 nM) Regulated by [Ca ²⁺] _i , probably via CaM, sensitizes TRPM2 to activation by ADPR, PARP-1 inhibitors (SB750139>PJ34>DPQ) decrease activation of TRPM2 by oxidative stress. Catalase, dimethylthiourea, mannitol inhibit TRPM2 activation by oxidative stress.	Independent of [Ca ²⁺] _i Insensitive to 1 μM RuR	Probably ubiquitous Voltage-modulated calcium-activated Decavanadate (2μM) inhibits V dependence; Human: long variant TRPM4b 1214 AA, AF497623; short variant TRPM4a 1040 AA, first 174 AA lacking, AY046396; short splice variant TRPMc, 537 AA N-terminal lacking, AX443225 mouse: two short splice variants from brain AB112658, AB112657	Voltage-modulated Calcium-activated	Contains a protein kinase on its C terminus as part of the protein (Chanzyme) Currently difficult to separate from TRPM7 current measurements	Contains a protein kinase on its C terminus as part of the protein (Chanzyme). The kinase activity is not required for channel conduction. Overexpression results in cell death. Deletion also results in cell death in DT40 cells. Kinase domain phosphorylates Annexin 1	Correlated with trkA NGF receptors trp-p8 mRNA also expressed in primary tumors of prostate, breast, colon, lung, and skin. Loss of prostate trp-p8 mRNA e associated with shorter survival. trp-p8 may be androgen- regulated.

