Table S1. Aligned sequences of L45, S5, P-loop, and S6 segments in P-loop channels

Channel	L45-S5	k1	k11	o1	o11	o21	Sequence identity/similarity (%)			
							Kv1.2	NavAb	NavMs	NavRh
K_v1.2		SKGLQILGQT	LK	ASMRELGLLI	FFLFIGVILF	SSAVYFAE				
NavAb		VPQMRKIVSA	LI	SVIPGMLSVI	ALMTLFFYIF	AIMATQLF	8 / 28			
NavMs		IPTMRRVVQG	ML	LALPGVGSVA	ALLTVVFYIA	AVMATNLY	8 / 35	48 / 80		
NavRh		IPELKQIIEA	IL	ESVRRVFFVS	LLLFIILYIY	ATMGAILF	15 / 48	28 / 55	30 / 58	
Nav1.4	I	IPGLKTIVGA	LI	QSVKKLSDVM	ILTVFCLSVF	ALVGLQLF	15 / 38	32 / 50	18 / 48	38 / 66
	II	WPTLNMLIKI	IG	NSVGALGNLT	LVLAIIVFIF	AVVGMQLF	25 / 45	18 / 55	20 / 60	38 / 66
	III	FEGMRVVVNA	LL	GAIPSIMNVL	LVCLIFWLIF	SIMGVNLF	13 / 43	38 / 65	30 / 62	25 / 50
	IV	AKGIRTLLFA	LM	MSLPALFNIG	LLLFLVMFIY	SIFGMSNF	22 / 45	22 / 50	18 / 52	28 / 58
Cav1.2	I	VPSLQVVLNS	II	KAMVPLLHIA	LLVLFVIIIY	AIIGLELF	12 / 55	25 / 50	22 / 58	28 / 55
	II	WNSLSNLVAS	LL	NSVRSIASLL	LLLFLFIIIF	SLLGMQLF	28 / 55	28 / 50	18 / 50	32 / 58
	III	AKGLKHVVQC	VF	VAIRTIGNIV	IVTTLLQFMF	ACIGVQLF	18 / 48	22 / 55	20 / 60	18 / 55
	IV	GEGIRTLLWT	FI	KSFQALPYVA	LLIVMLFFIY	AVIGMQVF	12 / 40	22 / 50	20 / 55	22 / 56

	P-loop	p38	p41	p51	p60				
K_v1.2		DAF	WWAVVSMTTV	GYGDMVPTT	---				
NavAb		ESF	YTLFQVMTLE	SWSMGIVRP	LME	12 / 32			
NavMs		ISL	YTLFQVMTLE	SWSMGIVRP	VMN	8 / 24	84 / 92		
NavRh		ISL	ITLFQVLTLS	SWETVML-P	MQE	4 / 12	48 / 60	52 / 68	
Nav1.4	I	WAF	LALFRLMTQD	YW-ENLFQL	TLR	16 / 32	24 / 40	20 / 32	16 / 32
	II	HSF	LIVFRILCGE	–WIETMWDC	MEV	4 / 24	20 / 36	16 / 32	24 / 52
	III	LGY	LSLLQVATFK	GW-MDIMYA	AVD	8 / 36	28 / 48	28 / 48	20 / 48
	IV	NSI	ICLFEITTSA	GW-DGLLNP	ILN	12 / 40	28 / 56	32 / 60	32 / 60
Cav1.2	I	FAM	LTVFQCITME	GWTDVLYWM	QDA	16 / 28	24 / 40	24 / 40	24 / 44
	II	QSL	LTVFQILTGE	DWNSVMYDG	IMA	4 / 16	32 / 56	36 / 56	40 / 68
	III	AAM	MALFTVSTFE	GWPELLYRS	IDS	12 / 32	28 / 40	28 / 44	20 / 36
	IV	QAV	LLLFRCATGE	AWQDIMLAC	MPG	12 / 28	20 / 36	20 / 36	28 / 56

Channel	S6	i2	i11	i21	Sequence identity/similarity (%)			
					Kv1.2	NavAb	NavMs	NavRh
K_v1.2		GGKIVGSLC	AIAGVLTIAL	PVPVIVSNFN				
NavAb		YAWVFFIPF	IFVVTFVMIN	LVVAICVDAM	7 / 34			
NavMs		NAWVFFIPF	IMLTTFTVLN	LFIGIIVDAM	7 / 38	62 / 76		
NavRh		WSWVYFFSF	IIICSITILN	LVIAILVDVV	17 / 44	41 / 66	45 / 69	
Nav1.4	I	TYMIFFVVI	IFLGSFYLIN	LILAVVAMAY	10 / 38	34 / 66	28 / 62	21 / 59
	II	MCLTVFLMV	MVIGNLVVLN	LFLALLLSSF	10 / 34	17 / 41	21 / 45	24 / 45
	III	YMYLYFVIF	IIFGSFFTLN	LFIGVIIDNF	7 / 34	28 / 66	41 / 66	38 / 62
	IV	IGICFFCSY	IIISFLIVVN	MYIAIILENF	14 / 41	21 / 48	28 / 59	31 / 59
Cav1.2	I	IPWVYFVSL	VIFGSFFVLN	LVLGVLSGEF	14 / 41	24 / 55	31 / 55	41 / 59
	II	LVCIYFIIL	FISPNYILLN	LFLAIADDNL	10 / 38	24 / 48	28 / 55	31 / 48
	III	EISIFFIIY	IIIIAFFMMN	IFVGFVIVTF	10 / 34	28 / 55	28 / 59	17 / 45
	IV	FAVFYFISF	YMLCAFLIIN	LFVAVIMDNF	3 / 31	38 / 55	41 / 62	34 / 55

Highlighted are small-size residues in positions *o21* and *o23* of S5 helices (Tikhonov et al. 2015. *Pflugers Arch.* 467:253–266), conserved tryptophans in positions *p52* of P-loops (Tikhonov and Zhorov. 2012. *Mol. Pharmacol.* 82:97–104) and conserved asparagines in positions *i20* of S6 helices (Tikhonov et al. 2015. *Pflugers Arch*. 467:253–266).

Sequence identities and similarities were calculated using server “http://www.bioinformatics.org/sms2/ident_sim.html” and the following groups of similar residues: GAVLI, FYW, CM, ST, KRH, DENQ, P