

# POTASSIUM CHANNELS

Almost a decade ago, a standardised nomenclature for the six-transmembrane domain (TM), voltage-gated K<sup>+</sup> channel genes – the K<sub>V</sub> naming system – was widely adopted<sup>1,2</sup>. This nomenclature was based on deduced phylogenetic relationships; channels that shared 65% sequence identity being assigned to one subfamily. A parallel nomenclature – KCN – was developed by the Human Genome Organisation (HUGO)<sup>3</sup>. Since then, the K<sup>+</sup> channel superfamily of genes has greatly expanded, requiring an update of the naming system.

### Structural characteristics

Several structural classes of the potassium channels are now known, as illustrated by the transmembrane folding diagrams for this section of the compendium, and most of these classes have multiple members.

The 6TM proteins include the K<sub>V</sub> channels, and the related small-conductance and intermediate-conductance, Ca<sup>2+</sup>-activated K<sup>+</sup> channels (K<sub>Ca</sub>). Both the N- and C-termini of these proteins are located intracellularly and the region between the fifth and sixth transmembrane domains (the

P-region) forms the ion conduction pathway. The functional channel is formed by the tetrameric association of these 6TM/1P subunits.

The second class of 2TM proteins includes the inward rectifiers, the K<sub>ATP</sub> channels and the G protein-coupled channels<sup>4</sup>. The N- and C-termini of these channels are also located cytoplasmically, the P-region between the two transmembrane domains forms the pore, and the functional channel is a tetramer of these 2TM/1P subunits.

A third class has 7TM and encodes the large-conductance channel, Slo. There is a P-region between TMVI and TMVII and the channel functions as a tetramer, but unlike the other channels, Slo has its N-terminus located extracellularly.

A fourth class of proteins has a 6TM/1P segment linked in tandem to a 2TM/1P segment, and the functional channel in this case is formed from the dimeric association of the 8TM/2P subunit.

Yet another class of channels, the K<sub>2P</sub> family, contains two 2TM/1P region-containing subunits linked in tandem, and the functional channel is a dimer of the 4TM/2P subunits.

Table 1. **The KCN classification system.**

Name	Protein
KCNA1–KCNA7	6TM/1P K <sub>V</sub> channel (Shaker-related)
KCNB1, KCNB2	6TM/1P K <sub>V</sub> channel (Shab-related)
KCNC1–KCNC4	6TM/1P K <sub>V</sub> channel (Shaw-related)
KCND1–KCND3	6TM/1P K <sub>V</sub> channel (Shal-related)
KCNE1–KCNE3	1TM ISK accessory subunit
KCNF1	6TM/1P K <sub>V</sub> channel (modulatory)
KCNG1–KCNG2	6TM/1P K <sub>V</sub> channel (modulatory)
KCNH1–KCNH5	6TM/1P K <sub>V</sub> channel (EAG, ERG, ELK)
KCNI1	–
KCNJ1–KCNJ15	2TM/1P K <sub>ir</sub> channel
KCNK1–KCNK9	4TM/2P (TWIK, TASK, TREK)
KCNL	–
KCNMA1	7TM/1P maxi-K <sub>Ca</sub> channel
KCNMB1	β subunit of maxi-K <sub>Ca</sub> channel
KCNN1–KCNN4	6TM/1P SK <sub>Ca</sub> and IK <sub>Ca</sub> channel
KCNO	–
KCNP	–
KCNQ1–KCNQ4	6TM/1P K <sub>V</sub> channel
KCNR	–
KCNS1–KCNS3	6TM/1P K <sub>V</sub> channel (modulatory)

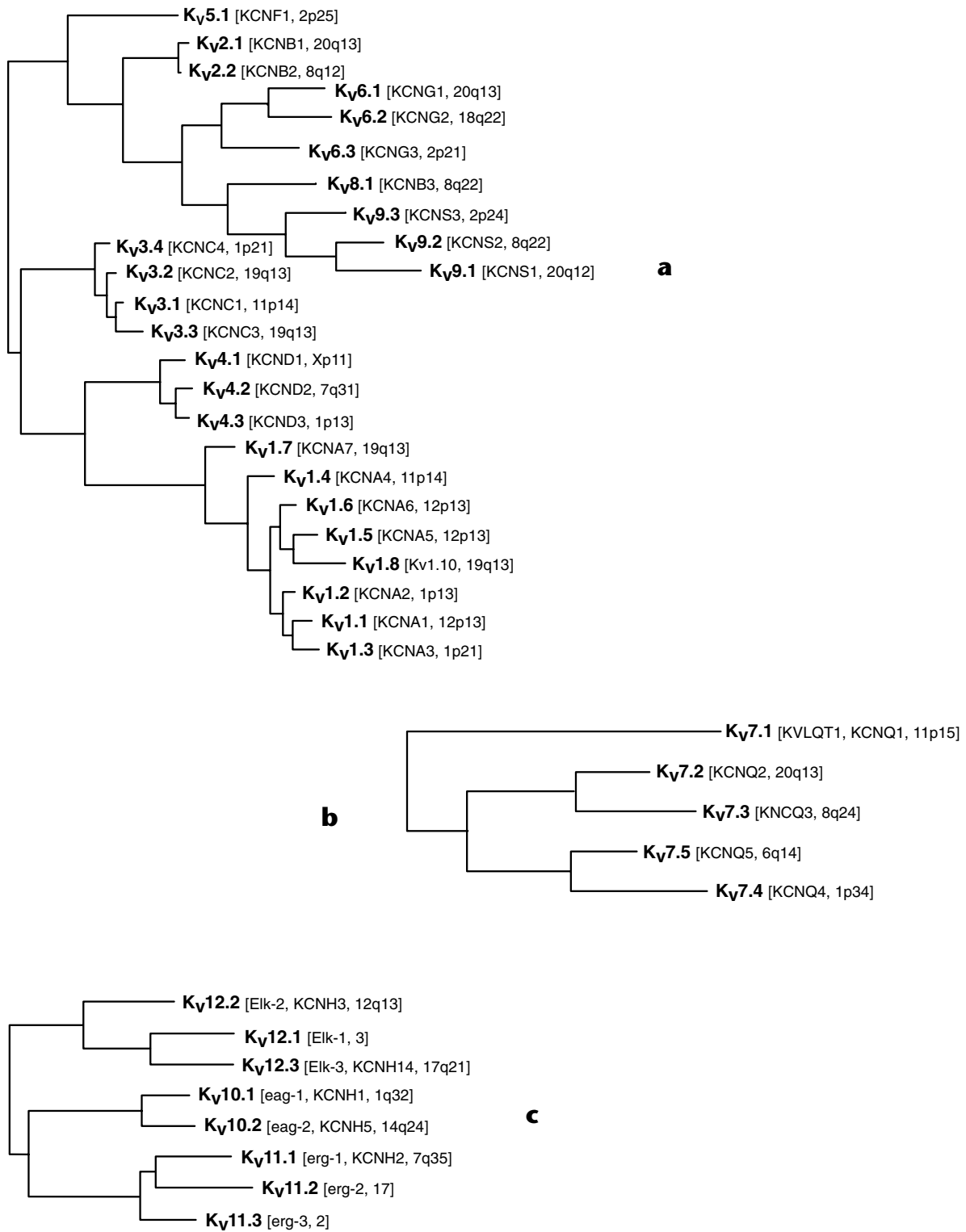


Figure 1. **Phylogenetic trees of the K<sub>v</sub> channels.** a, the K<sub>v</sub>1–K<sub>v</sub>6 and K<sub>v</sub>8–K<sub>v</sub>9 families; b, the K<sub>v</sub>7 family; c, the K<sub>v</sub>10–K<sub>v</sub>12 families. An amino acid sequence alignment made using CLUSTALW was subjected to analysis by maximum parsimony (PAUP\*). Only the hydrophobic core region of the alignment was used for analysis.

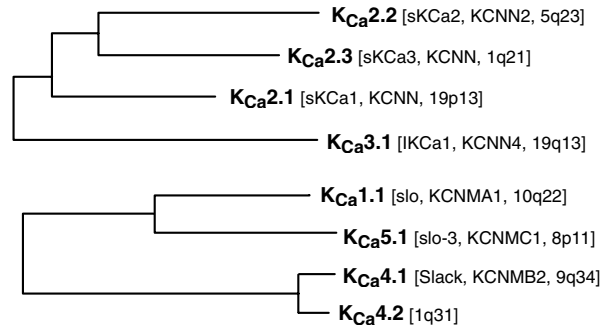


Figure 2. **Two phylogenetic trees showing the K<sub>Ca</sub>1–K<sub>Ca</sub>5 families.** See Figure 1 for details of analysis.

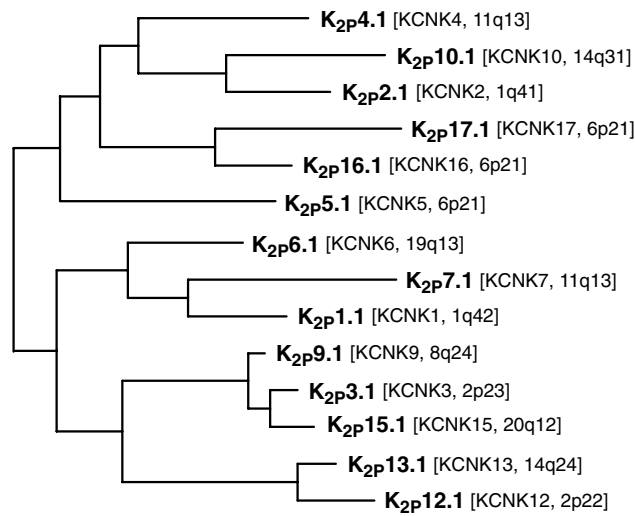


Figure 3. **Phylogenetic tree showing the K<sub>2p</sub> families.** See Figure 1 for details of analysis.

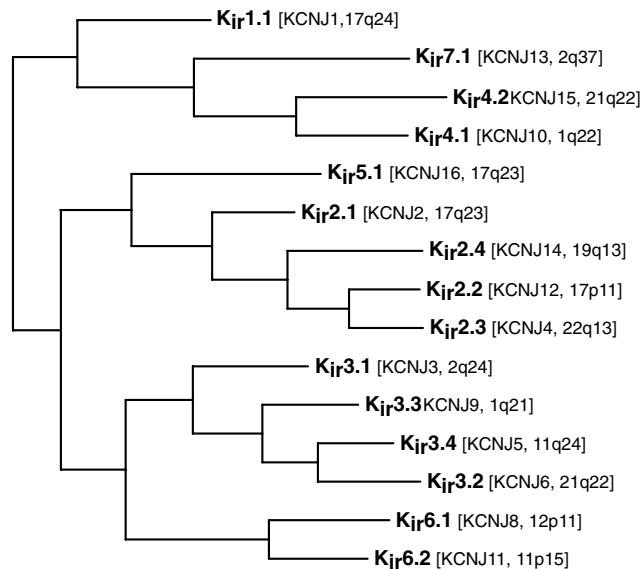


Figure 4. **Phylogenetic tree showing the K<sub>ir</sub> families.** See Figure 1 for details of analysis.

### Human gene nomenclature committee system

The KCN system established by the Human Gene Nomenclature Committee (HGNC) of HUGO (Table 1) suffers from a lack of any rational basis for nomenclature, and in particular ignores the structural and phylogenetic relationships of these proteins. For example, the KCNA–KCND subfamilies refer to 6TM/1P proteins, whereas the KCNE subfamily corresponds to an unrelated protein that functions as an accessory subunit to some families of K<sup>+</sup> channels. Subfamilies encoding other 6TM/1P proteins include KCNF, KCNG, KCNH, KCNN, KCNQ and KCNS, while KCNJ contains the 2TM/1P proteins, the KCNK subfamily corresponds to the 4TM/2P proteins, and the 7TM/1P is subfamily KCNMA1. Even though the Eag, Erg and Elk channels are very different in their sequences, they are grouped together as KCNH; several members of this group, namely Elk1, Erg2 and Erg3, have not yet been assigned HGNC names. Similarly, the small-conductance (SKCa1–SKCa3) and intermediate-conductance (IKCa1) Ca<sup>2+</sup>-activated K<sup>+</sup> channels are grouped together in the KCNN subfamily even though they share only ~45% amino acid sequence identity and therefore are best considered as belonging to distinct subfamilies.

### The standardised K<sup>+</sup> channel nomenclature system

The original K<sub>v</sub> nomenclature that created subfamilies K<sub>v</sub>1–K<sub>v</sub>6 has not been updated for several years. As new genes were discovered the name K<sub>v</sub>7 was skipped, and these new genes were instead assigned to subfamilies K<sub>v</sub>8 and K<sub>v</sub>9. Also, the more recently discovered KCNH (Eag, Erg, Elk) and KCNQ ('KVLQT') subfamilies have not been included in the K<sub>v</sub> classification. A standardised nomenclature has been adopted in the case of the 2TM/1P channels, and subfamilies defined in this K<sub>ir</sub> family determined by the degree of sequence relatedness.

### Formulation of a rational classification

With the impending completion of the mapping of the human genome, the time may be ripe for a re-evaluation of these issues, and the development of a uniform and rational nomenclature for all K<sup>+</sup>-selective channels. Such a naming system could incorporate the architectural similarities between different channel families, as well as

their phylogenetic relationships. For example, the numerous 6TM/1P proteins and the sole 7TM/1P channel listed in Table 1 could be grouped into a single large family comprising multiple subfamilies defined according to their phylogenetic relatedness. Similarly, the 2TM/1P channels the 2P channels could each be clustered into a separate family containing multiple subfamilies.

The standardised nomenclature for potassium channels presented in this compendium is shown in the phylogenetic trees of Figures 1–4. The 6TM/1P channels have been organised into two distinct groups based on their structural relatedness and predominant functional characteristics, namely the voltage-gated (K<sub>v</sub>) and calcium-activated (K<sub>ca</sub>) channels. The two-pore (K<sub>2p</sub>) and inward rectifier (K<sub>ir</sub>) channels likewise form two additional groups. Figure 1a shows the voltage-gated K<sup>+</sup> channels of families K<sub>v</sub>1–K<sub>v</sub>6 and K<sub>v</sub>8–K<sub>v</sub>9, in a phylogenetic reconstruction using maximum parsimony based on an amino acid sequence alignment. Among this group, only K<sub>v</sub>1.8 currently lacks an HGNC name. The five members of a second K<sub>v</sub> group, the K<sub>v</sub>7 family (KCNQ1–KCNQ5), cannot readily be aligned with other K<sub>v</sub> channel proteins, and are therefore shown in a separate tree in Figure 1b. The three remaining K<sub>v</sub> families, K<sub>v</sub>10, K<sub>v</sub>11 and K<sub>v</sub>12, are closely enough related to each other to be shown in the single tree of Figure 1c.

The five families comprising the calcium-sensitive potassium channels, K<sub>ca</sub>1–K<sub>ca</sub>5, numbered according to the order of their discovery, are shown in the two trees of Figure 2. The phylogenetic relationship between the K<sub>ca</sub>1, K<sub>ca</sub>4, K<sub>ca</sub>5 group on the one hand, and the K<sub>ca</sub>2, K<sub>ca</sub>3 group on the other, is insufficiently clear at this time to readily connect them into a single tree.

The two-pore or K<sub>2p</sub> potassium channels are shown in the tree of Figure 3. The numbers have been taken from the HGNC 'KCNK' numbering, without re-sequencing around the missing numbers (namely 8, 11 and 14), and without consolidating clearly related channels into subfamilies. A consensus among researchers in the field will hopefully establish a more rational nomenclature in the future.

The last remaining group of potassium channels, the 'inward rectifier' or K<sub>ir</sub> channels, is represented in the tree of Figure 4, using the previously established nomenclature and subfamily groupings.

## REFERENCES

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