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Specific association of particular K2P potassium channels with neurons that have extended longitudinal neurites in *C. elegans* suggests proprioceptive functionality

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Abstract

The nematode *C. elegans* readily adapts its locomotory behaviour to the viscosity of its environment suggesting functional proprioception. Extended Longitudinal neurites (ELNs) elaborated by certain neurons have been speculated to function in this role. Expression data from the CeNGEN database reveals the presence of a conserved sub-set of K2P potassium channels in neurons with ELNs suggesting that these channels are strong candidates for the stretch receptors that confer proprioception functionality to such neurons, including motor neurons of the ventral cord that generate the travelling waves of contraction used for locomotion.

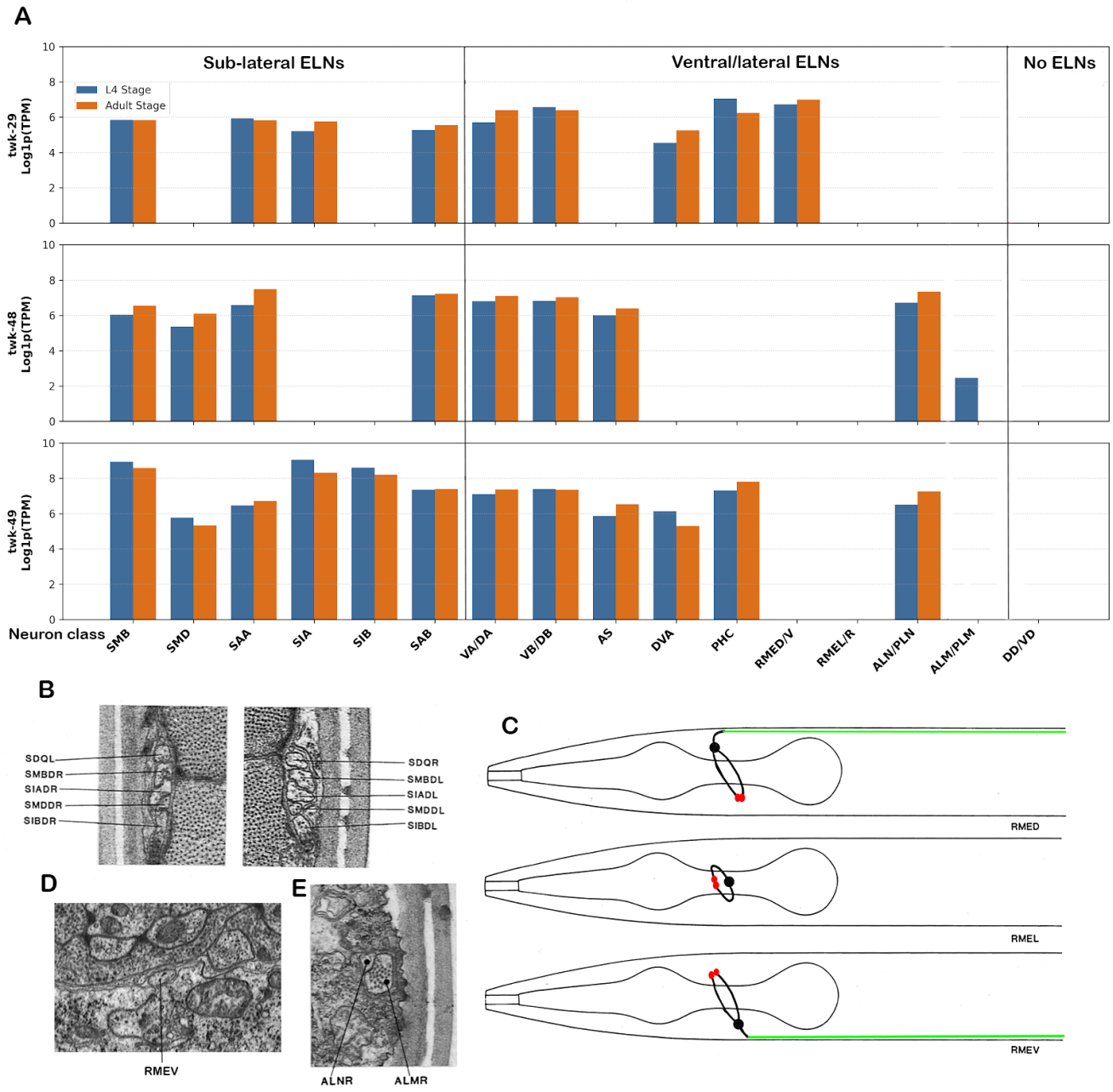


Figure 1. Expression of some highly expressed K2P potassium channels in neurons that have extended longitudinal neurites (ELNs):

(A) Plots of *twk-29*, *twk-48* & *twk-49* expression in neuron classes that have ELNs. A log1p(TPM) scale is used (Taylor et al. 2021). Orange - data from the adult; blue - data from L4. Note similarity between data sets implying consistency in CeNGEN data and similar levels of expression between L4 and adult developmental stages. DD/VD are examples of neuron classes that do not have ELNs. VA/DA, VB/DB & AS are the main excitatory motor neurons innervating body muscles. They use acetylcholine neurotransmitter. VD/DD are cross inhibitors that use the neurotransmitter GABA. SMB & SMD are two classes of cholinergic motor neuron that innervate head muscles and have sub-lateral ELNs. RME is an inhibitory neuron class that innervates head muscles and uses GABA. Note that the RMED/V members of this class have ELNs and have high levels of expression of *twk-29* whereas RMEL/R do not have ELNs and do not express *twk-29* **(C)**. DVA is a stretch receptor that primarily uses (TRP-4) as a stretch receptor (Li et al., 2006) but it also exhibits fairly high levels of expression of *twk-29* & *twk-49*. ALM/PLM are components of the light touch receptors that use MEC-4 as the receptive elements and have little or no levels of K2P channel expression

However, the ALN/PLN neurons which run in close association with the ALM/PLM **(E),** do not express mec genes but have high levels of expression of *twk-48* & *twk-49*. PHC has an ELN that extends into the tail spike.

(B) Sub-lateral bundles of ELNs. Electron micrographs showing small sub-lateral bundles of processes. There are four bundles in the anterior body; only the dorsal left & right are shown. The bundles are situated between the muscles and hypodermis.

(C) Diagrams depicting the trajectory of processes from RME neurons in the head. Black spheres are cell bodies, red dots are neuromuscular junctions, and green lines show the ELNs that project from RMED and RMEV posteriorly down the dorsal and ventral nerve cords. There are no ELNs projecting from RMEL or RMER (not shown).

(D) EM showing the ELN from RMEV running on top of the ventral hypodermal ridge and underneath the neuropil of the ventral ganglion.

(E) EM showing the ELN of ALMR with its distinctive microtubules running in close association with the ELN of ALNR.

Panels B, C, D & E were adapted from White et al., 1986**.**

Description

Caenorhabditis elegans moves with grace and ease over solid substrates in a manner that inspired its name. To do so, it lies on its side and moves forward by propagating backward-directed waves of alternating dorsal/ventral muscle contractions, and backward by propagating forward-directed waves. Both the period and the wavelength of these body waves adapt dynamically to environmental viscosity (Berri et al., 2009, Fang-Yen et al., 2010), implying that motor neuron activation is modulated by sensory awareness of posture and physical forces acting on the body (proprioception).

The elucidation of the connectome (White et al., 1986; Cook et al., 2019; Witvliet et al., 2021) revealed a simple yet enigmatic circuit of motor neurons that innervate the body wall muscles. Observations of ultrastructure combined with laser cell ablation experiments (Chalfie et al., 1985) identified two reciprocal classes of cholinergic excitatory motor neurons: class A neurons mediate backward locomotion and feature long, anteriorly directed axons, whereas class B neurons mediate forward locomotion and feature long, posteriorly directed axons. Cross-inhibiting class D GABAergic motor neurons provide localized coordination between dorsal and ventral muscle regions.

Motor neurons in the ventral cord possess well-defined longitudinal domains where neuromuscular junctions (NMJs) are made. Notably, the A and B classes possess additional extended longitudinal neurites (ELNs) that are devoid of synaptic contacts beyond their NMJ regions. In contrast, the axons of the inhibitory D class terminate soon after their NMJ regions and lack ELNs (White et al., 1986). Other neuron classes in *C. elegans* elaborate ELNs that project along the body with few if any synaptic contacts along the way, including several that run in small sub-lateral nerve cords (Fig. 1B) such as those from SMB and SMD motor neurons which innervate head muscles.

Rhythmic locomotory movements in many animal systems are generated by systems of coupled central pattern generators (CPGs) or intrinsic neural oscillators (Pearson, 1993), and similar oscillator networks have been proposed to operate in *C. elegans* (Gao et al., 2018). An alternative mechanism, originally suggested by R. L. Russell and L. Byerly (personal communication, 1970s), also offered an elegant explanation for the opposing anatomical polarities of the A and B motor neurons. They proposed that the extended distal processes of the A and B neurons act as proprioceptors that measure local body bending in upstream regions and modulate the excitation of adjacent downstream NMJs. Given the structural polarity of the As and Bs, this model requires the putative proprioceptors to exert an inhibitory action—dampening excitation in NMJ regions downstream from the direction of wave propagation, thereby enforcing the direction of wave travel. Experimental observations demonstrating that B-type motor neurons exhibit intrinsic proprioceptive feedback during wave propagation lend direct support to this mechanism (Wen et al., 2012). Anatomical and symmetry comparisons suggest that A-type neurons are also likely to utilize an equivalent mechanism for reverse locomotion. That both A- and B-type neurons possess ELNs upstream to the NMJ region relative to the direction of wave propagation suggests that the proprioceptive region would be in the ELNs.

Several mechanoreceptor systems have been described in *C. elegans*, such as the ALM/PLM touch receptor neurons utilizing MEC-4 ENaC channels (Chalfie et al., 1985; O'Hagan et al., 2005) or the stretch-activated DVA interneuron utilizing TRP-4 channels (Li et al., 2006). In both cases, channel activation causes cation influx and consequent neuronal depolarization (excitation). Some neurons express the ENaC mechanoreceptors along with K2P receptors. Yeon et al. (2018) have reported that the SMD neurons have TRP-1 & TRP-2 channels that are used for steering during forward locomotion. Zhan et al. (2023) have reported that the ASIC-1 and DEL-1 ENaC channels in VA and VB motoneurons facilitate olfactory learning.

Conversely, potassium channels provide hyperpolarizing conductances. *C. elegans* possesses a surprising abundance of two-pore domain potassium (K2P) channels—47 compared to 15 in humans (Bargmann, 1998; Salkoff et al., 2001)—and

essentially all *C. elegans* neurons express one or more (see heat map in Extended Data). Certain mammalian K2P channels are known to be stretch-activated (Nilius & Honoré, 2012; Lengyel et al., 2016), raising the possibility that specific mechanosensitive K2P channels located in ELNs provide the hyperpolarizing drive required for inhibitory proprioception.

Examination of single-cell transcriptomic data from the CeNGEN database (Taylor et al., 2021) reveals high expression of a specific subset of K2P channels (*twk-29*, *twk-48*, and *twk-49*) in the A and B excitatory motor neurons of the ventral cord, as well as in head motor neurons with ELNs (Fig. 1A). Motor neurons that lack ELNs, such as VD/DD and RMEL/R, do not express this channel group (Fig. 1A). Sub-lateral interneurons (SAA, SIB, SAB) also possess ELNs and exhibit high expression of *twk-29*, *twk-48*, or *twk-49*.

This association is particularly striking within the RME class of four GABAergic head motor neurons (Fig. 1C). The dorsal and ventral RMEs (RMED and RMEV) possess long ELNs projecting posteriorly down the dorsal and ventral cords (Fig. 1D) and express high levels of *twk-29*. In contrast, the lateral RMEs (RMEL and RMER) lack ELNs and show zero *twk-29* expression. Furthermore, while the ALM/PLM touch cells show negligible K2P expression, the closely associated ALN/PLN neurons (Fig. 1E)—which run alongside ALM/PLM but lack MEC-4 touch-receptor machinery—exhibit robust expression of *twk-48* and *twk-49*.

In mammalian TREK and TRAAK channels, mechanosensitivity is mediated by the 'force-from-lipids' mechanism, wherein increased lateral membrane tension drives conformational expansion of the channel within the lipid bilayer (Brohawn et al., 2014). Because TWK-29, TWK-48, and TWK-49 possess the canonical two-pore, four-transmembrane (2P/4TM) domain architecture characteristic of K2P channels (Lesage & Lazdunski, 2000; Bargmann, 1998), a similar biophysical mechanism likely allows physical stretch along extended longitudinal neurites (ELNs) to directly open these potassium conductances and hyperpolarize the neuron during body wall flexure. It is probable that a diode blocking mechanism mediated by asymmetric gap junctions prevents back-propagation of this hyperpolarization to the command interneurons (White, 2026).

To evaluate whether expression of the three K2P channels (*twk-29*, *twk-48*, and *twk-49*) is significantly enriched in neurons possessing extended longitudinal neurites (sublateral motor neurons SAA, SAB, SIA, SIB, SMB, SMD, interneurons SDQ, and VC motor neurons), we performed a 2x2 contingency analysis across all 118 neuronal classes in the CeNGEN dataset. Neurons with ELNs were significantly more likely to express at least one of these three K2P channels compared to non-ELN neurons (8/10 ELN classes vs. 15/108 non-ELN classes; Fisher's exact test, $p = 2.3 \times 10^{-5}$ Odds Ratio 28.4; Extended Data 1). Notably, the only two ELN-bearing classes that do not express this K2P channel set are the primary touch receptor neurons ALM and PLM. Because these MEC-4-expressing neurons rely on DEG/ENaC sodium channels for mechanical gating rather than K2P-mediated resting conductance tuning, their exclusion reinforces the specific association of *twk-29*/*-48*/*-49* with non-canonical, proprioception-dedicated longitudinal neurites.

Many of the 47 K2P channel genes are probably not involved in proprioception; for example, *unc-58*, *twk-43* & *twk-7* are expressed in all ventral cord neurons including DD/VD which do not have ELNs. Behavioural phenotyping is challenging because of functional redundancy among the 47 K2P genes (Zhou et al., 2022); phenotyping of forward locomotion is particularly challenging because the head neuromuscular circuitry entrains the body; however, reverse locomotion is generated solely by the ventral cord motor system. The specific association of *twk-29*, *twk-48*, and *twk-49* with ELN-bearing neurons therefore identifies this channel trio as a prime target for gene knockouts to dissect proprioceptive-driven wave propagation during *C. elegans* reverse locomotion.

Methods

Single-cell transcriptomic expression levels for *Caenorhabditis elegans* two-pore domain potassium K2P channel genes (*twk-29*, *twk-48*, *twk-49*, *unc-58*, *twk-7*, and *twk-43*) were mined from the public CeNGEN dataset (Taylor et al., 2021; www.cengen.org). Gene expression values were retrieved as transcripts per million (TPM) and visualized using a log1p(TPM) scale across L4 larval and young adult hermaphrodite dataset collections. Anatomical classifications of extended longitudinal neurites (ELNs) and synaptic connectivity patterns were cross-referenced against original electron micrograph reconstructions (White et al., 1986) and WormAtlas anatomical descriptors.

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Extended Data

Description: Extended data 1. Heatmap of K2P gene expression in adult C. elegans. Resource Type: Image. File: Heatmap of K2P gene expression in adult.png. DOI: 10.22002/gdev1-29r59

Description: Extended data 2 Contingency table. Resource Type: Text. File: Extended data 2.docx. DOI: 10.22002/yzxsb-q9f07

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