

The *Caenorhabditis elegans* PTPN-22 protein tyrosine phosphatase non-receptor type 22 is required for neuronal migration

Mark Yorio¹, Erik Lundquist^{2§}

¹Molecular Biosciences, University of Kansas, Lawrence, KS, United States

²Molecular Biosciences, University of Kansas, Lawrence, Kansas, United States

[§]To whom correspondence should be addressed: erikl@ku.edu

Abstract

PTPN22 is a key negative regulator of T-cell activation in the vertebrate adaptive immune system. [Caenorhabditis elegans ptpn-22](#) encodes a molecule similar to vertebrate PTPN22, is expressed broadly, and regulates the formation of epidermal desmosomal adhesion complexes and cuticular molting. Work here shows that [PTPN-22](#) is required for migration of the AQR and PQR neurons, a novel role for the PTPN22 family of molecules. Our results, along with those reported previously, suggest an ancestral role of the PTPN22 family in cell adhesion and migration, possibly reflected in its role in formation of the immune synapse in vertebrate T cells.

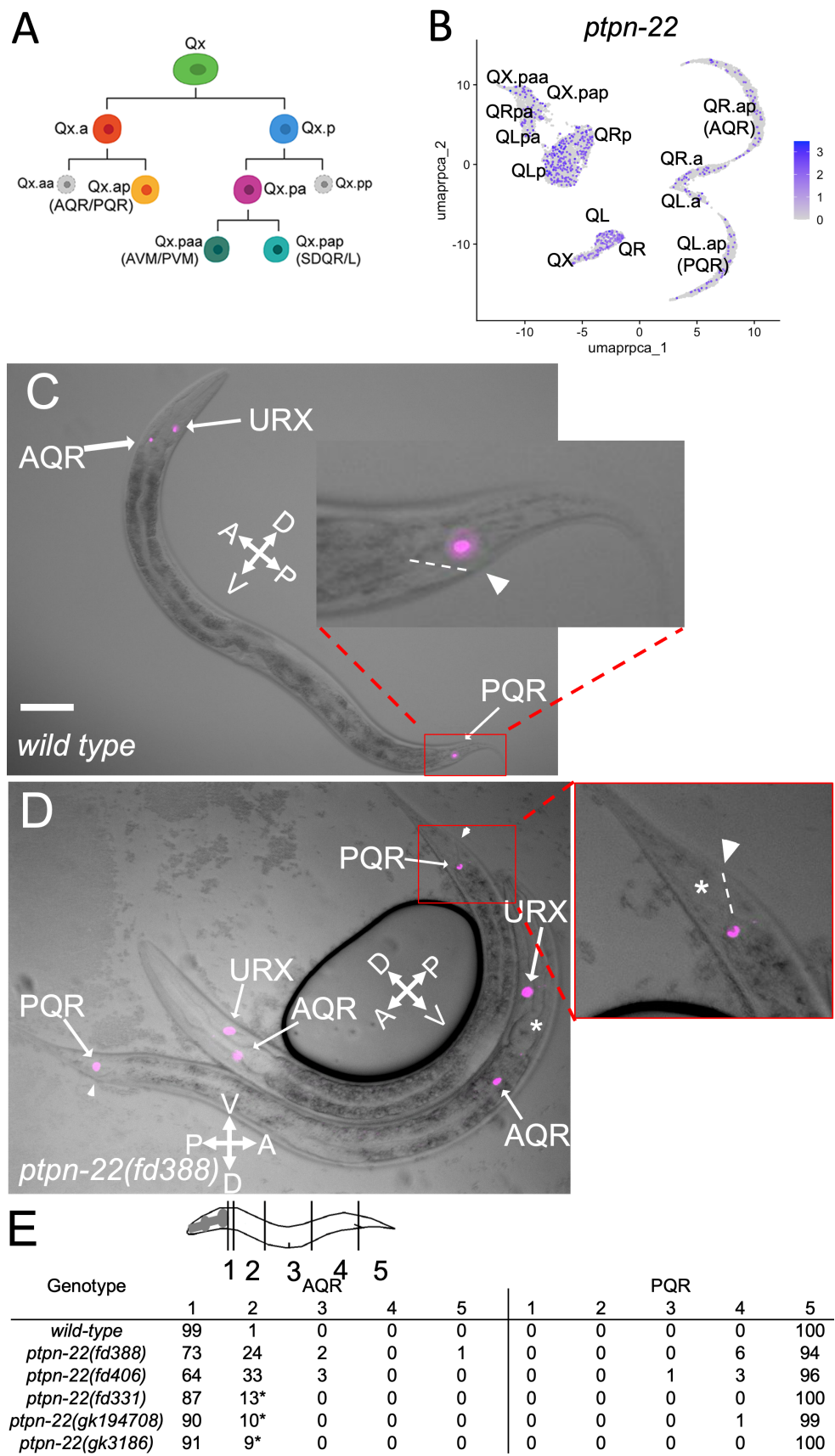


Figure 1. *ptpn-22* mutants displays AQR and PQR migration defects:

Figure 1. AQR and PQR migration defects in *ptpn-22* mutants. A) A schematic of the QR and QL (QX) neuroblast lineage in the early L1 larva. The X axis is anterior to posterior, and the Y axis is time. A small “a” indicates the anterior

daughter of a cell division, and a small “p” indicates the posterior daughter. Small grey circles indicate cells that undergo programmed cell death. B) UMAP coordinates for single-cell RNA-seq of the Q lineage indicating [ptpn-22](#) expression (see Methods). Cells are colored by expression level (purple), with gray indicating undetectable expression. C-D) The [lqls244\[Pgcy-32::cfp\]](#) transgene was used to visualize the URX, AQR and PQR neurons. For each animal, Anterior (A), posterior (P), dorsal (D), and ventral (V) are indicated by arrows. The scale bar in C represents 10µm for both C and D. C) A wild type larva with [lqls244\[gcy-32::cfp\]](#) expression. AQR is located in the anterior deirid ganglion near the posterior pharyngeal bulb (arrow). PQR is located posterior to the anus in the phasmid ganglion (arrow). The red box inset is a magnified view of PQR position posterior to the anus (dashed line and arrowhead). D) [ptpn-22\(fd388\)](#) mutant L4 larvae with [lqls244\[gcy-32::cfp\]](#) expression. In the top animal, PQR has failed to migrate posterior to the anus (arrow). The red box inset is a magnified view of PQR located immediately anterior to the anus (arrowhead and dashed line). The asterisk indicates the normal position of PQR. In the bottom animal, AQR has failed to migrate anteriorly to the anterior deirid and is instead displaced posteriorly behind the posterior pharyngeal bulb. The asterisk indicates the normal position of AQR. E) Quantification of AQR and PQR defects. The table indicates the positions of AQR and PQR in *wild-type* and [ptpn-22](#) mutants. The figure above the table shows the five positions along the anterior-posterior axis of the animal that were used to score AQR and PQR position. For each genotype, 100 animals were scored. The asterisks indicate that the AQR defects in the mutants were significantly less severe than those in [ptpn-22\(fd388\)](#) and [ptpn-22\(fd406\)](#) ($p < 0.03$).

Description

C. elegans [PTPN-22](#) is an ortholog of the vertebrate protein tyrosine phosphatase non-receptor type 22 PTPN22 (Begovich et al., 2004; Binti et al., 2024; Cohen et al., 1999). PTPN22 has been investigated in mammalian systems for its roles in lymphoid and immune function (Bottini & Peterson, 2014; Cohen et al., 1999; Hill et al., 2002), notably suppression of T cell activation (Cloutier & Veillette, 1999) and viral immunity (Bevis et al., 2026; Orozco et al., 2024). In human populations, *Ptpn22* variants are associated with autoimmune disorders (Armitage et al., 2021; Gregersen et al., 2012). In humans, *Ptpn22* is expressed strongly in lymphoid tissues, with lower expression in other tissue types (Thul et al., 2017; Uhlen et al., 2015). In *C. elegans*, mutations in [ptpn-22](#) have been shown to suppress cuticular molting defects due to mutations in NIMA-like kinases [NEKL-2](#) and [NEKL-3](#), and to be associated with hypodermal adhesion complexes including hemidesmosomes (Binti et al., 2024).

Single-cell RNA sequencing of the Q neuroblast lineage shows that [ptpn-22](#) is expressed throughout the Q neuroblast lineages as they develop (Figure 1A and B) (Teixeira et al., 2026). The bilateral Q neuroblasts, are derived embryonically and migrate in the L1 larva after hatching (Chapman et al., 2008; Middelkoop & Korswagen, 2014; Rella et al., 2016; Schild et al., 2023; Sulston & Horvitz, 1977). QR on the right migrates anteriorly over the V4 seam cell, and QL on the left migrates posteriorly over the V5 seam cell (Chapman et al., 2008). A similar pattern of cell division, programmed cell death, and neuronal differentiation results in three neurons on each side: AQR, AVM, and SDQR on the right, and PQR, PVM, and SDQL on the left. The QR descendant AQR migrate farthest anteriorly to the deirid ganglion near the pharynx (Figure 1C). The QL descendant PQR migrates the farthest posteriorly to the phasmid ganglion posterior to the anus (Figure 1C). Mutations that disrupt Q lineage migrations result in misplaced AQR and/or PQR neurons. Directional defects in migration (e.g. anterior PQR migration or posterior AQR migration) result from mutations that affect the first Q cell migration and subsequent Wnt-mediated activation of the Hox transcription factor [MAB-5/Antennapedia](#) (Josephson et al., 2016). Failure of migration (e.g. AQR and PQR migrate in the correct direction but do not complete migration) can result from disruption of the migration substrate such as [epi-1/Laminin-α5](#) mutation (Lang & Lundquist, 2021), or from mutation of downstream target genes of [MAB-5/Antennapedia](#) (Jain et al., 2026; Jain & Lundquist, 2025).

We analyzed AQR and PQR migration in five [ptpn-22](#) alleles (Binti et al., 2024). All five alleles showed failure of complete AQR migration (9-33%) (Figure 1D and E). PQR migration failure was noted in three of the five mutants (0-6%) (Figure 1D and E). No directional migration defects were noted. Rather, AQR and PQR migrated in the correct direction but failed complete migration. Misplaced AQR were displaced posteriorly behind the pharynx, and misplaced PQR were displaced anteriorly, immediately anterior to the anus (Figure 1D). This phenotype is consistent with failure of the third migration of QL.ap/PQR posterior to the anus (Jain et al., 2026; Jain & Lundquist, 2025), and might also represent a late-stage failure of QR.ap/AQR migration (Middelkoop & Korswagen, 2014; Rella et al., 2016). [ptpn-22\(fd388\)](#) introduces a premature stop codon in the second codon exon, and [ptpn-22\(fd406\)](#) is a cysteine to serine missense mutation in the phosphatase catalytic domain (Binti et al., 2024). These two mutants displayed significantly stronger AQR migration defects compared to the other three alleles analyzed ([fd331](#), a frameshift; [gk3186](#), a deletion of the first two coding exons; and [gk194708](#), a premature stop codon in the second to last codon exon) (Binti et al., 2024; Thompson et al., 2013). Each of these is predicted to be a complete loss-of-function, and it is unclear why they have a significantly weaker phenotype than [ptpn-22\(fd388\)](#). This could be due to the genetic background of [ptpn-22\(fd388\)](#), or to retention of some function in [fd331](#), [gk3186](#), and [gk194708](#). The catalytically-dead [ptpn-22\(fd406\)](#) could be significantly stronger because of a potential dominant-negative function (i.e. the molecule might interact with binding partners leading to a non-functional complex). In sum, these results indicate that [PTPN-22](#) is required for migration of the AQR and PQR neurons and defines a new function of the Ptpn22 family. While [ptpn-22](#) expression in the Q lineage is likely not

controlled by [MAB-5](#)/Antennapedia (Paolillo et al., 2024), the evidence here could suggest that [PTPN-22](#) is required for the ability of AQR and PQR to migrate fully.

A balance of tyrosine phosphorylation and dephosphorylation is important in QR lineage migrations (Zhu et al., 2020): the [SRC-1](#)/Src tyrosine kinase phosphorylates the guidance receptor [MIG-13](#) to regulate actin polymerization in the direction of migration, and the receptor tyrosine phosphatase [PTP-3](#)/LAR is responsible for mitigating this in the rear of the migrating cells. Src kinases are key substrates for PTPN22 activity in the immune system (Cloutier & Veillette, 1999; Wu et al., 2006). It is possible that [PTPN-22](#) participates in this tyrosine phosphorylation balance underlying AQR and PQR migration via modulating cytoskeletal or cell adhesion functions. In any case, these results are consistent with an ancestral role of PTPN22 family members in regulating cell adhesion and migration.

Methods

[C. elegans](#) strains were maintained and scored at 20°C. AQR and PQR were visualized using the [Pgcy-32::cfp](#) transgene [lqIs244](#) (Chapman et al., 2008; Josephson et al., 2016) (Chapman et al. 2008; Josephson et al. 2016). AQR and PQR positions along the body were noted using a five-position scale as previously described (Jain et al., 2026; Jain & Lundquist, 2025; Josephson et al., 2016) (See Fig 1E). Statistical significance was determined using Fisher's Exact test.

Reagents

The following [C. elegans](#) mutants and transgenes were used: LGII, [lqIs244\[Pgcy-32::cfp\]](#); LGIV, [ptpn-22\(gk194708\)](#), [ptpn-22\(gk3186\)](#), [ptpn-22\(fd331\)](#), [ptpn-22\(fd388\)](#), [ptpn-22\(fd406\)](#). The [tmC25](#) balancer²⁷ was used to isolate [ptpn-22](#) mutant chromosomes. The presence of [ptpn-22](#) mutations was confirmed by sequencing or PCR genotyping. The following strains were analyzed:

Strain	Genotype	Origin
LE3885	lqIs244 II	(Josephson et al., 2016)
LE8131	ptpn-22(gk194708) IV ; lqIs244 II	(Binti et al., 2024) and this work
LE8130	ptpn-22(gk3186) IV ; lqIs244 II	(Binti et al., 2024) and this work
LE8128	ptpn-22(fd331) IV ; lqIs244 II	(Binti et al., 2024) and this work
LE8127	ptpn-22(fd388) IV ; lqIs244 II	(Binti et al., 2024) and this work
LE8129	ptpn-22(fd406) IV ; lqIs244 II	(Binti et al., 2024) and this work

Acknowledgements: The authors thank D. Fay for sharing the [ptpn-22](#) mutant strains. Some strains were provided by the CGC, which is funded by NIH Office of Research Infrastructure Programs (P40 OD010440).

References

- Armitage LH, Wallet MA, Mathews CE. 2021. Influence of PTPN22 Allotypes on Innate and Adaptive Immune Function in Health and Disease. *Front Immunol.* 12: 636618. 4611. PubMed ID: [33717184](#)
- Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, et al., Gregersen PK. 2004. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet.* 75: 330-7. 4604. PubMed ID: [15208781](#)
- Bevis AM, Rosa K, Schwarting N, Cockerham TR, Kerr CM, More S, Fehr AR, Orozco RC. 2026. An autoimmunity-associated allele of PTPN22 enhances innate antiviral immunity to protect against acute coronavirus infection. *Proc Natl Acad Sci U S A.* 123: e2519903123. 4608. PubMed ID: [41849391](#)
- Binti S, Linder AG, Edeen PT, Fay DS. 2024. A conserved protein tyrosine phosphatase, PTPN-22, functions in diverse developmental processes in *C. elegans*. *PLoS Genet.* 20: e1011219. 4603. PubMed ID: [39173071](#)
- Bottini N, Peterson EJ. 2014. Tyrosine phosphatase PTPN22: multifunctional regulator of immune signaling, development, and disease. *Annu Rev Immunol.* 32: 83-119. 4609. PubMed ID: [24364806](#)

- Chapman JO, Li H, Lundquist EA. 2008. The MIG-15 NIK kinase acts cell-autonomously in neuroblast polarization and migration in *C. elegans*. *Dev Biol.* 324: 245-57. 1311. PubMed ID: [18840424](#)
- Cloutier JF, Veillette A. 1999. Cooperative inhibition of T-cell antigen receptor signaling by a complex between a kinase and a phosphatase. *J Exp Med.* 189: 111-21. 4607. PubMed ID: [9874568](#)
- Cohen S, Dadi H, Shaoul E, Sharfe N, Roifman CM. 1999. Cloning and characterization of a lymphoid-specific, inducible human protein tyrosine phosphatase, Lyp. *Blood.* 93: 2013-24. 4605. PubMed ID: [10068674](#)
- Gregersen PK, Diamond B, Plenge RM. 2012. GWAS implicates a role for quantitative immune traits and threshold effects in risk for human autoimmune disorders. *Curr Opin Immunol.* 24: 538-43. 4610. PubMed ID: [23026397](#)
- Hill RJ, Zozulya S, Lu YL, Ward K, Gishizky M, Jallal B. 2002. The lymphoid protein tyrosine phosphatase Lyp interacts with the adaptor molecule Grb2 and functions as a negative regulator of T-cell activation. *Exp Hematol.* 30: 237-44. 4606. PubMed ID: [11882361](#)
- Jain VD, Johannesen AM, Teixeira FL, Lundquist EA. 2026. EFN-4/Ephrin converges with SAX-3/Robo, UNC-6/Netrin, and Heparan Sulfate Proteoglycan signaling to control MAB-5/Hox-dependent posterior Q neuroblast migration in *Caenorhabditis elegans*. *bioRxiv* 4584. PubMed ID: [41959263](#)
- Jain VD, Lundquist EA. 2025. VAB-8/KIF26, LIN-17/Frizzled, and EFN-4/Ephrin, control distinct stages of posterior neuroblast migration downstream of the MAB-5/Hox transcription factor in *Caenorhabditis elegans*. *PLoS Genet.* 21: e1011906. 4523. PubMed ID: [41071838](#)
- Josephson MP, Chai Y, Ou G, Lundquist EA. 2016. EGL-20/Wnt and MAB-5/Hox Act Sequentially to Inhibit Anterior Migration of Neuroblasts in *C. elegans*. *PLoS One.* 11: e0148658. 3455. PubMed ID: [26863303](#)
- Lang AE, Lundquist EA. 2021. The Collagens DPY-17 and SQT-3 Direct Anterior-Posterior Migration of the Q Neuroblasts in *C. elegans*. *J Dev Biol.* 9 4516. PubMed ID: [33669899](#)
- Middelkoop TC, Korswagen HC. 2014. Development and migration of the *C. elegans* Q neuroblasts and their descendants. *WormBook.* 1-23. 2700. PubMed ID: [25317540](#)
- Orozco RC, Marquardt K, Pratumchai I, Shaikh AF, Mowen K, Domissy A, Teijaro JR, Sherman LA. 2024. Autoimmunity-associated allele of tyrosine phosphatase gene PTPN22 enhances anti-viral immunity. *PLoS Pathog.* 20: e1012095. 4612. PubMed ID: [38512979](#)
- Paolillo VK, Ochs ME, Lundquist EA. 2024. MAB-5/Hox regulates the Q neuroblast transcriptome, including *cwn-1*/Wnt, to mediate posterior migration in *Caenorhabditis elegans*. *Genetics.* 227 4476. PubMed ID: [38652773](#)
- Rella L, Fernandes Pova EE, Korswagen HC. 2016. The *Caenorhabditis elegans* Q neuroblasts: A powerful system to study cell migration at single-cell resolution in vivo. *Genesis.* 54: 198-211. 4432. PubMed ID: [26934462](#)
- Schild ES, Gupta S, Dubois C, Fernandes Pova EE, Felix MA, Mugler A, Korswagen HC. 2023. Precise temporal control of neuroblast migration through combined regulation and feedback of a Wnt receptor. *Elife.* 12 4615. PubMed ID: [37184061](#)
- Sulston JE, Horvitz HR. 1977. Post-embryonic cell lineages of the nematode, *Caenorhabditis elegans*. *Developmental Biology* 56: 110-156. PubMed ID: [838129](#)
- Teixeira FL, Sanderson B, Hackett JL, Lundquist EA. 2026. Single-cell transcriptomic profiling of *C. elegans* Q neuroblast lineage during migration and differentiation. *PLoS One.* 21: e0343734. 4576. PubMed ID: [41774717](#)
- Thompson O, Edgley M, Strasbourger P, Flibotte S, Ewing B, Adair R, et al., Waterston RH. 2013. The million mutation project: a new approach to genetics in *Caenorhabditis elegans*. *Genome Res.* 23: 1749-62. 2613. PubMed ID: [23800452](#)
- Thul PJ, Akesson L, Wiking M, Mahdessian D, Geladaki A, Ait Blal H, et al., Lundberg E. 2017. A subcellular map of the human proteome. *Science.* 356 4613. PubMed ID: [28495876](#)
- Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, et al., Ponten F. 2015. Proteomics. Tissue-based map of the human proteome. *Science.* 347: 1260419. 4614. PubMed ID: [25613900](#)
- Wu J, Katrekar A, Honigberg LA, Smith AM, Conn MT, Tang J, et al., Clark JM. 2006. Identification of substrates of human protein-tyrosine phosphatase PTPN22. *J Biol Chem.* 281: 11002-10. 4617. PubMed ID: [16461343](#)
- Zhu Z, Chai Y, Hu H, Li W, Li WJ, Dong MQ, et al., Ou G. 2020. Spatial confinement of receptor activity by tyrosine phosphatase during directional cell migration. *Proc Natl Acad Sci U S A.* 117: 14270-14279. 4616. PubMed ID: [32513699](#)

Funding:

Supported by National Institute of Neurological Disorders and Stroke (United States) R01-NS115467 to Erik Lundquist.

Conflicts of Interest: The authors declare that there are no conflicts of interest present.

10/31/2026 - Open Access

Author Contributions: Mark Yorio: formal analysis, investigation, visualization, writing - original draft. Erik Lundquist: conceptualization, data curation, funding acquisition, investigation, methodology, formal analysis, project administration, writing - review editing.

Reviewed By: Anonymous

Nomenclature Validated By: Anonymous

WormBase Paper ID: WBPaper00070270

History: **Received** October 12, 2026 **Revision Received** October 17, 2026 **Accepted** October 24, 2026 **Published Online** October 31, 2026 **Indexed** November 14, 2026

Copyright: © 2026 by the authors. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Yorio M, Lundquist E. 2026. The *Caenorhabditis elegans* PTPN-22 protein tyrosine phosphatase non-receptor type 22 is required for neuronal migration. microPublication Biology. [10.17912/micropub.biology.002471](https://doi.org/10.17912/micropub.biology.002471)