Worms, genetics and healthy kidneys: the candidate PKD-2 localization factor, *papl*, may play a role in polycystic kidney disease.

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Background

Polycystic Kidney Disease (PKD) causes cysts to form within the kidneys, leading ultimately to renal failure. Prior research in our lab demonstrated that expression of the *papl* gene is downregulated in a zebrafish model of cystic kidney disease. We asked whether the *papl* gene has a direct effect on proper localization of PKD2, one of the proteins known to be involved in cyst formation, and whether the *papl* gene influences cilia structure.

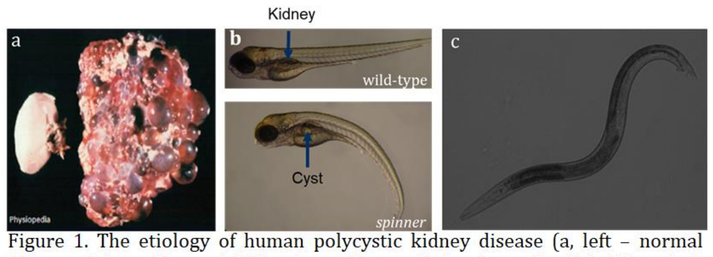

Figure 1. The etiology of human polycystic kidney disease (a, left – normal kidney, right – diseased kidney) can be studied using zebrafish (b) and *C. elegans* (c), not to scale.

papl-1, not previously associated with PKD, belongs to a gene family associated with human disorders.

Neither the human ortholog (ACP7) nor the zebrafish ortholog (*acp7/papl-1)* has been associated with a specific function or organelle. *papl* encodes an acid phosphatase with putative hydrolase activity and a metal ion binding domain. Acid phosphatases have been associated with a number of human disorders, including prostate cancer (Araujo and Vihko 2013). Zebrafish *papl* ESTs have been identified in the kidney, olfactory rosettes and reproductive system.

RNA interference reduces *papl-1*

Reducing *papl-1* expression allows us to examine its effects on PKD-2 localization.

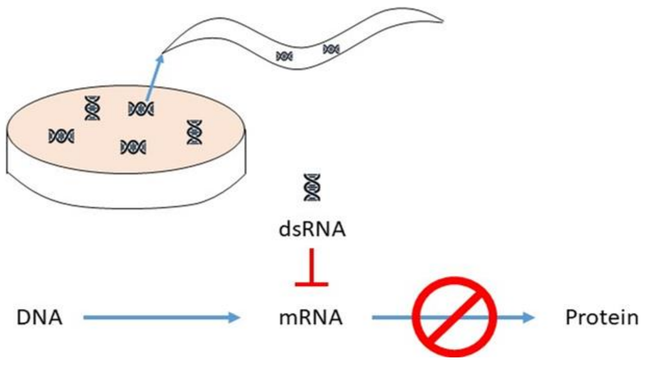

Figure 2. RNA interference (RNAi) downregulates *papl-1* transcript. When bacteria produce dsRNA, *C. elegans* ingest the bacteria and degredation of *C. elegans* papl-1 RNA is triggered.

Assessment of neuron integrity by dye-filling demonstrates that downregulation of *papl-1* does not affect cilia integrity.

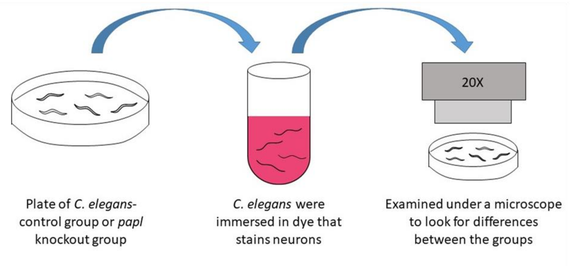

Figure 3 (left). Cilia Structure is unaffected by knockdown of *papl-1* expression. Wild type neurons exposed to DiI (a and c) appeared similar to neurons after *papl-1* RNAi treatment (b and d).

papl-1 plays a role in PKD-2 localization in cilia.

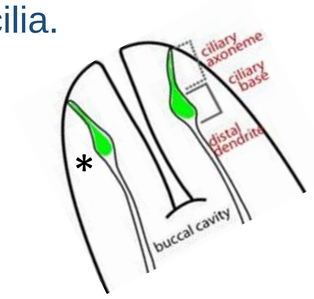

Figure 4 (left). The green shaded region shows the PKD-2 expression (*) in the cilia structure of the head of a wild-type *C. elegans* (Bae, 2006).

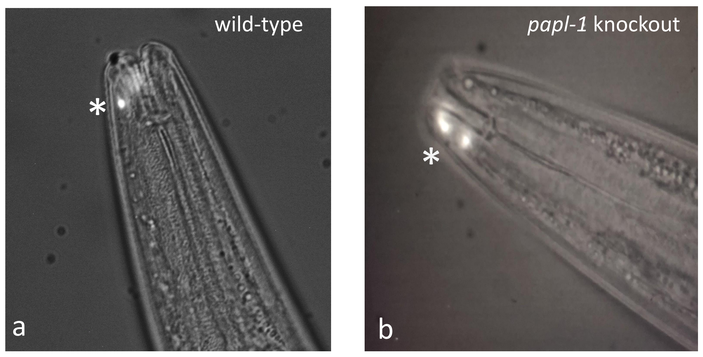

Figure 5. PKD-2::GFP localization (*), in male-specific cilia of the head, differs when *papl-1* gene expression is down-regulated. In wild-type *C. elegans*, localization is symmetric (a) while after RNAi treatment, localization is asymmetric (b). Anterior to left.

papl-1 knockout leads to altered expression of PKD-2 in cilia.

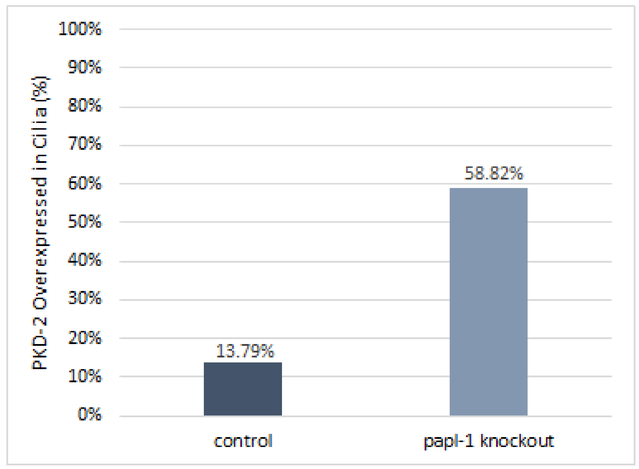

Figure 6. *papl-1* knockdown resulted in abnormal PKD-2::GFP localization in cilia. Abnormal localization included asymmetric expression (left versus right) and increased localization compared to wild type. (Control n=29; Papl RNAi n=51)

Conclusions

- Downregulation of *papl* does not affect all cilia equally. *papl-1* knockout leads to overexpression of PKD-2::GFP in cilia in male specific neurons
- This suggests that *papl* is either specifically affecting PKD2::GFP localization in male specific neurons, structure of male specific, neurons or asymmetry of neurons.

Discussion and Future Research

Our results suggest the *papl-1* gene may play a role in the proper localization of PKD-2 in cilia in *C. elegans.* Thus, *papl-1* may be involved in cyst formation and might play a role in PKD.

Future research includes confirming that *papl-1* expression is downregulated after RNAi using RT-PCR and examining whether zebrafish lacking *papl-1* develop cystic kidneys.

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