Review of: "Myosin phosphatase target subunit 1 governs integrity of the embryonic gut epithelium to circumvent atresia development in medaka, Oryzias latipes"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

This is a well-written paper reporting the discovery of a recessive MYPT1 mutation that results in partial penetrance intestinal atresia in the fish Medaka. The work appears scientifically accurate, the imaging data are of high quality. In particular, the fact that the phenotype was reproduced by gene editing/deletion of MYP1 supports the conclusion that MYPT1 mutation is causative in this model. The involvement of MYPT1 leading to enhanced myosin light chain phosphorylation and actin redistribution in the areas of atresia is also supportive. Furthermore, the fact that a relatively brief treatment of the fish with blebbistatin (inhibiting myosin activity) reduced the penetrance of intestinal atresia to zero is also supportive of the conclusion that enhanced myosin II – mediated contractility is causative for the defect.

The main limitation of this study is that the activity of the MYPT protein with the 1-4 mutation (the PRGK1 binding site) was not further studied. Given that most of the molecule, except for its C-terminus is intact, it seems possible that it could still function as a myosin phosphatase. The work presented here does not allow us to know whether this mutant still binds its catalytic phosphatase subunit, whether that subunit is active or inactive, and it does not tell us whether this MYPT1 mutation alters interaction with MLC2. That MYPT1 activity is reduced is only inferred from increased pMLC2 staining in the affected fish. Another significant limitation is that gene editing produced a completely different mutation - expected to delete one MYPT1 allele entirely. Why the investigators did not try to reproduce the original mutation is unclear.

Suggestions for revision of text:

1. Although the first sentence in the results section stipulates that the MYPT1 mutation is a recessive lethal – The point that it is the mutant haplotype which results in intestinal atresia with partial penetrance needs to be reiterated in subsequent reporting of the results and needs to be made more clearly in the discussion.
2. In the results and discussion sections, the nature of the original mutation and the mutation introduced by gene editing need to be better described, and limitation due to their differences need to be made

more clearly.