Review of: "Multiple Ciliary Localization Signals Control INPP5E Ciliary Targeting"

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This manuscript focuses on delineating the mechanism by which a Joubert Syndrome associated protein INPP5E (Inositol polyphosphate-5-phosphatase E) localizes to the cilia to carry out its multiple functions, including regulation of ciliary hedgehog signaling, modulating ciliary lipid profile and maintaining ciliary composition. Using in vitro cell culture, immunofluorescence and phosphatase activity assays and 3-D structural modeling, the authors report the identification of at least four different regions in INPP5E that mediate its ciliary localization. They go on to demonstrate that these different regions recruit specific sets of ciliary proteins to carry out their function. Moreover, the ciliary localization signals of INPP5E are also part of its catalytic domain and thus regulate its phosphatase activity as well. However, the ciliary localization regions that are not part of the catalytic domain of INPP5E only modulate its localization.

Although the studies are rigorous, they will benefit from validation in vivo. It would be interesting to correlate the different degrees of ciliary localization of INPP5E to the associated functional manifestations of the cilia in disease-relevant tissues.

A major outcome of this study is the redundancy associated with the mechanisms by which INPP5E is localized to cilia. This may represent evolutionary adaptation so that mutations in INPP5E are not always lethal and may be able to carry out at least partial functions, which may manifest as a spectrum of relatively mild to moderate diseases rather than severe and lethal outcomes. Such mechanisms may also be true for other ciliopathy associated proteins and may shed light on the mechanisms underlying diverse clinical heterogeneity associated with ciliopathies.