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Cos2/Kif7 and OSM-3/Kif17 Regulate Onset of Outer Segment Development in Zebrafish Photoreceptors Through Distinct Mechanisms

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Abstract

Zebrafish morphants of *osm-3/kif17*, a kinesin-2 family member and intraflagellar transport motor, have photoreceptor outer segments that are dramatically reduced in number and size. However, two genetic mutant lines, *osm-3/kif17*^{sa0119} and *osm-3/kif17*^{sa18340}, reportedly lack any observable morphological outer segment defects. In this work, we use TALENs to generate an independent allele, *osm-3/kif17*^{mw405}, and show that both *osm-3/kif17*^{sa0119} and *osm-3/kif17*^{mw405} have an outer segment developmental delay in both size and density that is fully recovered by 6 days post-fertilization. Additionally, we use CRISPRs to generate *cos2/kif7*^{mw406}, a mutation in the kinesin-4 family member *cos2/kif7* that has been implicated in controlling ciliary architecture and Hedgehog signaling to test whether it may be functioning redundantly with *osm-3/kif17*. We show that *cos2/kif7*^{mw406} has an outer segment developmental delay similar to the *osm-3/kif17* mutants. Using a three-dimensional mathematical model of outer segments, we show that while *cos2/kif7*^{mw406} and *osm-3/kif17*^{mw405} outer segments are smaller throughout the first 6 days of development, the volumetric rates of outer segment morphogenesis are not different among wild-type, *cos2/kif7*^{mw406}, and *osm-3/kif17*^{mw405} after 60hpf. Instead, our model suggests that *cos2/kif7*^{mw406} and *osm-3/kif17*^{mw405} impact outer segment morphogenesis through upstream events that are different for each motor. In the case of *cos2/kif7*^{mw406} mutants, we show that early defects in Hedgehog signaling lead to a general, non-photoreceptor-specific delay of retinal neurogenesis, which in turn causes the secondary phenotype of delayed outer segment morphogenesis. In contrast, the *osm-3/kif17*^{mw405} outer segment morphogenesis delays are linked specifically to initial disc morphogenesis of photoreceptors rather than an upstream event. Further, we show that *osm-3/kif17* mutant mice also exhibit a similarly delayed outer segment

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