Mutation of two central pair apparatus genes results in severe primary ciliary dyskinesia in mice

Casey W. McKenzie[1] and Lance Lee[1,2]

[1]Pediatrics and Rare Diseases Group, Sanford Research, Sioux Falls, SD
[2]Department of Pediatrics, Sanford School of Medicine of the University of South Dakota, Sioux Falls, SD

Introduction: Defects in motile cilia and flagella typically result in primary ciliary dyskinesia (PCD), a genetically and phenotypically heterogeneous syndrome resulting from a wide range of genes in human patients and animal models. The ciliary axoneme has a 9 + 2 microtubule structure that is comprised of nine outer doublets and a central pair apparatus (CPA) that plays a critical role in regulating proper ciliary function. We previously showed that mutations in CPA genes *CFAP221*, *CFAP54*, and *SPEF2* result in a PCD phenotype with ciliary motility defects in mouse models. Here, we have investigated how loss of multiple CPA genes affects ciliary function and PCD pathogenesis.

Methods: Each combination of double heterozygous and double homozygous mutants was generated by crossing the individual mouse lines with mutations in *CFAP221*, *CFAP54*, and *SPEF2*. The effects of double mutations on PCD pathogenesis were assessed by histological analysis, while cilia morphology was assessed by immunohistochemistry.

Results: While there were no detectable phenotypes in double heterozygotes, all three double homozygous mutant lines exhibited early mortality and PCD-associated phenotypes of hydrocephalus and sinusitis that are generally more severe than those previously observed for each single mutant line. The morphology and distribution of double mutant cilia appears normal, but spermiogenesis is aborted, and severe defects in sperm flagellar assembly were observed.

Conclusions: Severe phenotypes in double homozygotes indicate genetic interactions between CPA genes and demonstrate the importance of the CPA in regulating proper ciliary function. Further, the severity of the spermatogenic defects compared to the morphology of motile cilia underscores fundamental mechanistic differences between ciliary and flagellar biogenesis.