

NIGMS Science Advance

Project Title:

Ciliary Central Pair Proteins in Primary Ciliary Dyskinesia

Institution and State:

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PI Name:

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Background:

The objective of this research is to better understand the role of the ciliary central pair in childhood health and disease. Defects in ciliary beating result in a variety of abnormalities, including sinusitis (sinus infection), neonatal respiratory distress, otitis media (ear infection), male infertility, female infertility, hydrocephalus ("water on the brain"), and situs inversus (a reversal of left-right asymmetry). Respiratory and ear infections are common in young children and are usually treated with antibiotics, while neonatal respiratory distress is one of the leading causes of death in newborns. Hydrocephalus is extremely debilitating and potentially fatal if untreated by surgical shunting, and infertility is a major societal concern that impacts families on a regular basis. While all of these disorders are multifactorial, any or all of them can be associated with primary ciliary dyskinesia (PCD), a syndrome that affects approximately one in 16,000 newborn children worldwide and is caused only by defects in motile cilia function. Consequently, this research is of interest to basic scientists, clinicians, and the general public. Although several genes have been implicated in PCD in human patients and mouse models, little is known about how ciliary function is regulated. Mice homozygous for the nm1054 mutation lack primary ciliary dyskinesia protein 1 (Pcdpl), and mice homozygous for the big giant head (bgh) mutation lack sperm flagellar protein 2 (Spf2). Both mutants have PCD, and both proteins localize to the ciliary central pair, enabling further studies focusing on the role of the central pair in ciliary disease. Based on the phenotypes of these mutants, we hypothesize that the central pair regulates the dynein motor force required for proper ciliary beating. We also hypothesize that central pair proteins have a testis-specific function that underlies a distinct pathway required for spermatogenesis. The primary goals of this proposal are to dissect the molecular pathways by which Pcdpl and Spf2 regulate both sperm differentiation and ciliary motility, which will further elucidate the mechanisms perturbed in PCD and its associated disorders.

Advance:

This publication shows that murine PCD models lacking either Pcdp1 or Spf2 have strain-dependent brain defects and suggest the presence of genetic modifiers of PCD-associated hydrocephalus.

How NIGMS Grant Enabled Advance:

The funding provided resources for understanding the role and requirement of ciliary central pair proteins in mouse models of primary ciliary dyskinesia.

Public Health Impact Statement:

PCD is a syndrome comprised of several pediatric disorders, some of which can be devastating and even fatal. Improved treatment of PCD and its associated component disorders will require a better understanding of the mechanisms underlying ciliary and flagellar function. This study employs biochemical and cell biological approaches to elucidate the function of proteins lacking in two mouse models of PCD.

NIH Director's theme(s) relevance*:

Understanding the genetic and molecular basis of syndromic hydrocephalus will ultimately enable improved diagnosis and treatment of this devastating condition.

Grant Support:

5P20GM103620-02

Publication Citation and Link (if applicable):

Finn R, Evans CC, Lee L. Strain-dependent brain defects in mouse models of primary ciliary dyskinesia with mutations in Pcdp1 and Spef2. *Neuroscience*. 2014 Sep 26; 277:552-67.

Key Words:

Cfap221; Pcdp1; Spef2; cilia; hydrocephalus; primary ciliary dyskinesia

NIGMS Point of Contact:

*NIH Director's Themes: *Genomics, Translational Research, Health Care Reform, Global Health, Reinvigorating the Biomedical Community.*

<http://nexus.od.nih.gov/all/2009/09/01/five-themes-for-the-nih-3/>

<http://news.sciencemag.org/funding/2010/02/nih-director-bends-budget-fit-five-themes>