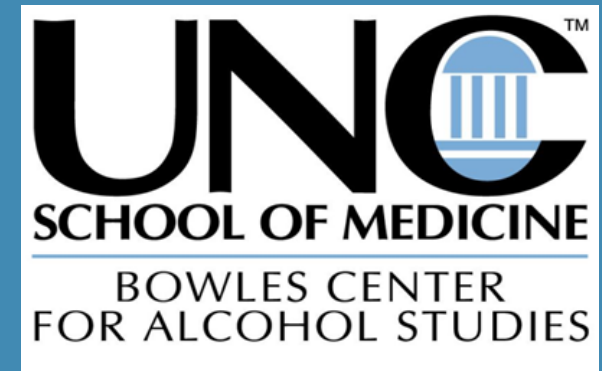


# Primary cilia dysfunction as a novel pathogenic mechanism of birth defects in FASD

Karen Boschen, PhD

Parnell Lab

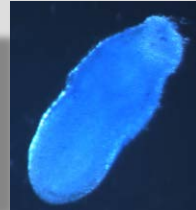
March 7, 2019



## CONFLICT OF INTEREST STATEMENT

- Karen Boschen has no conflicts of interest to report.

# A MOUSE MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS (FASD)



Gastrulation

Gestational Week in Humans

2

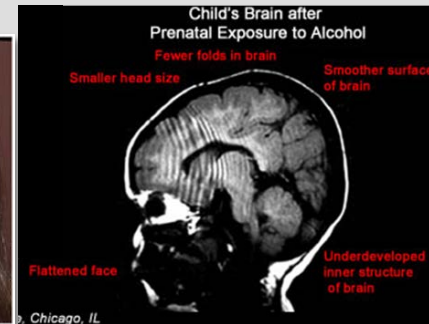
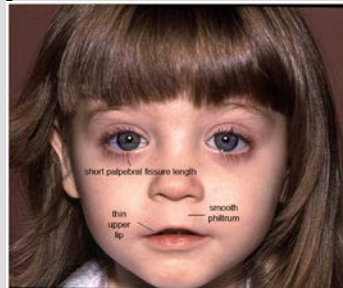
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Gestational Day in Mice

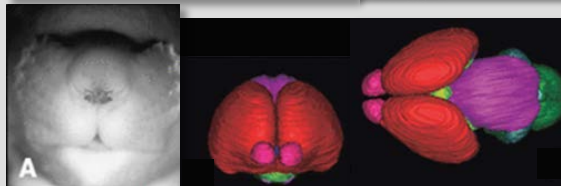
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7

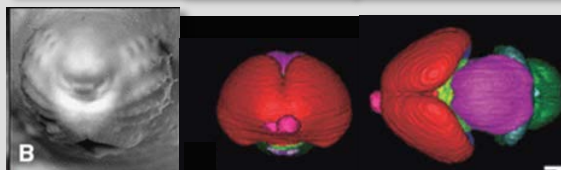
FAS



Control



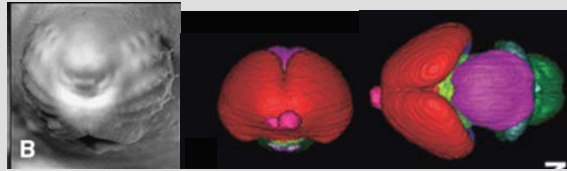
PAE



# HOW DOES ALCOHOL AFFECT FACE AND BRAIN DEVELOPMENT?

## Gastrulation

PAE

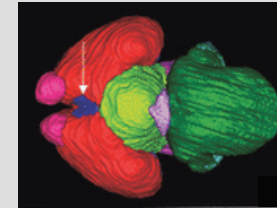


Sonic hedgehog pathway: ↓

Cell death: ↑

## Neurulation

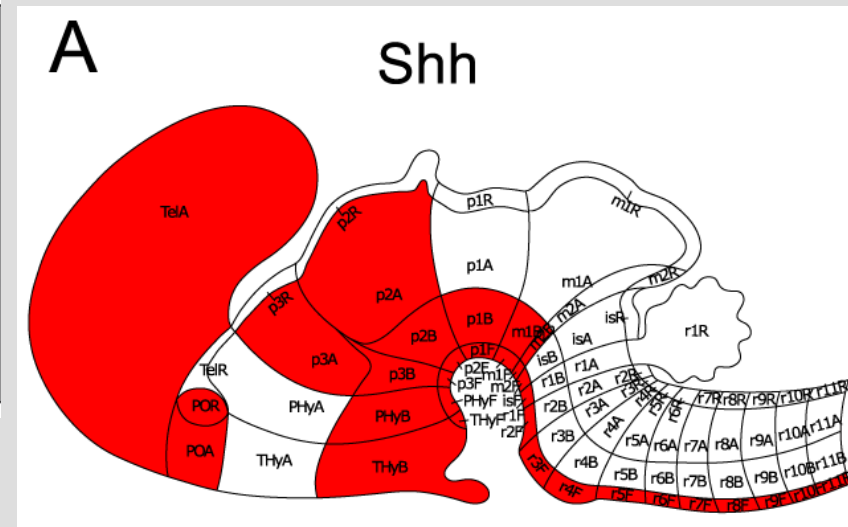
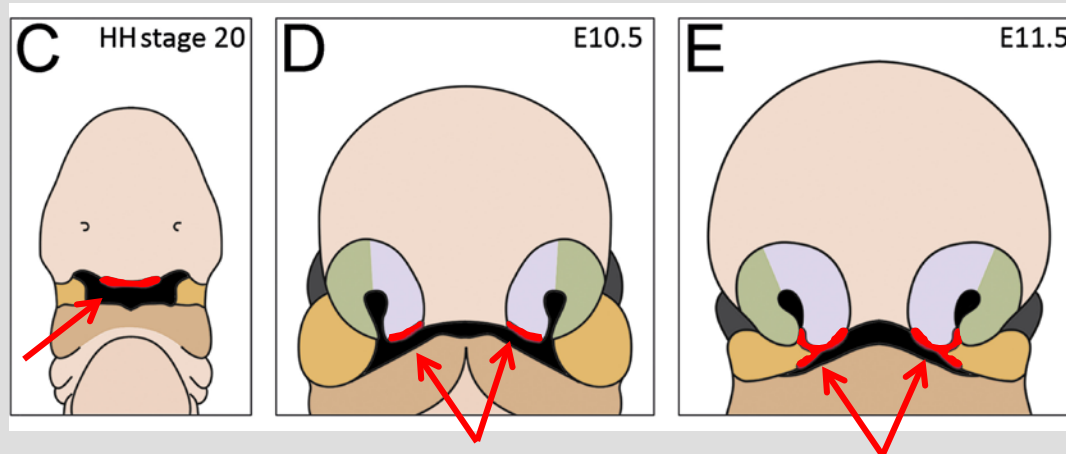
PAE



Sonic hedgehog pathway: ?

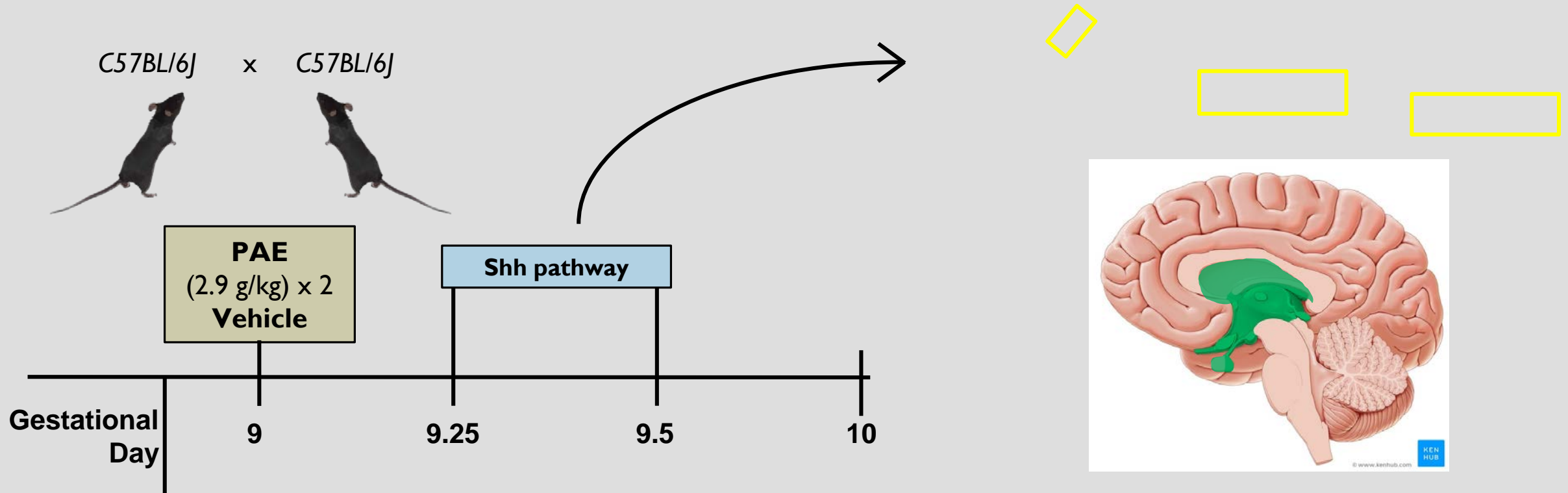
Cell death: —

Sonic hedgehog (Shh): protein critical for face and brain development, particularly along the ventral midline

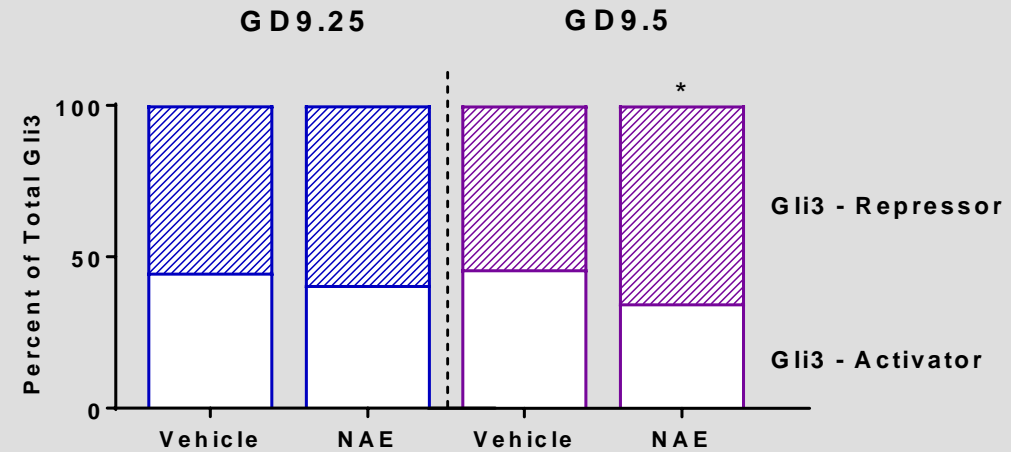
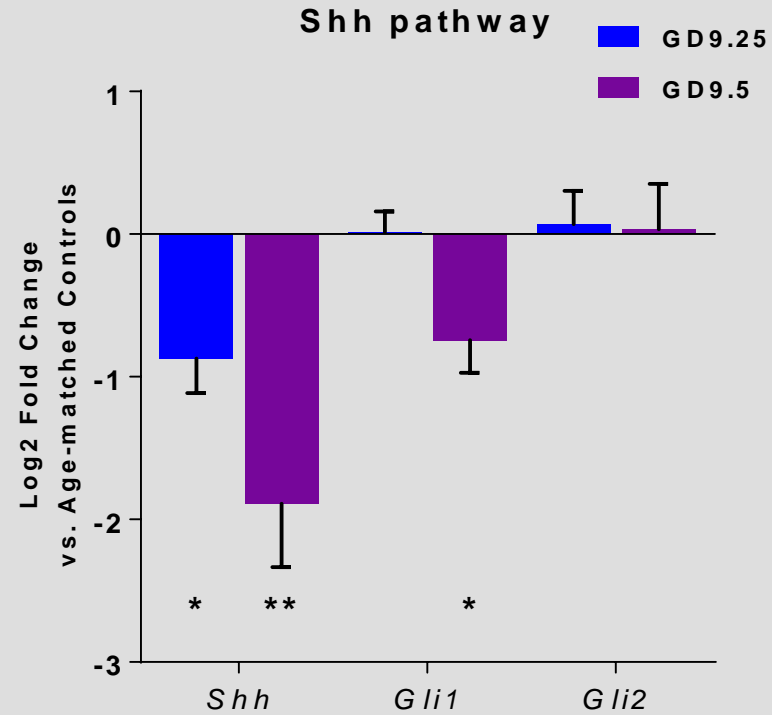
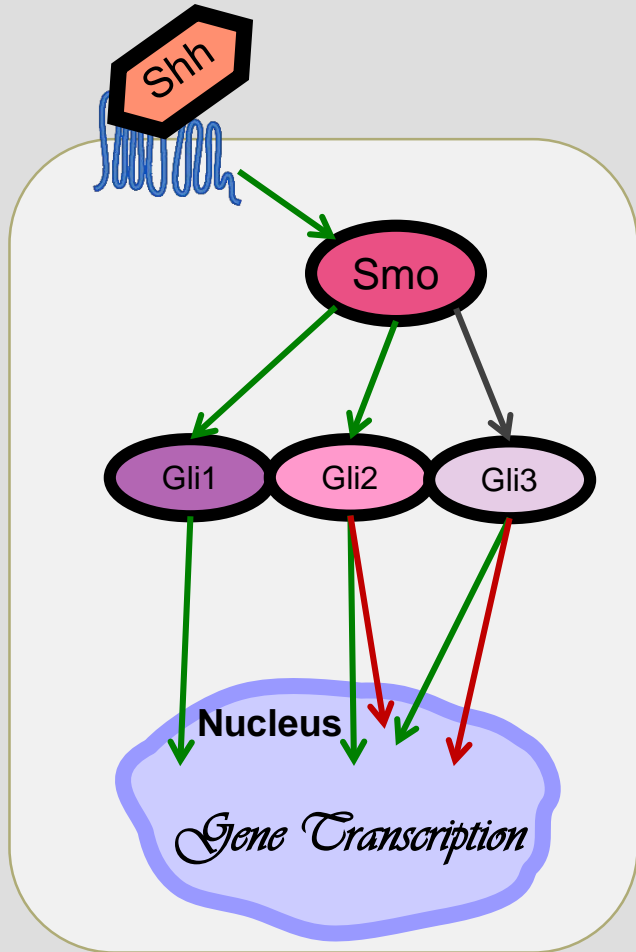


# SONIC HEDGEHOG (SHH) PATHWAY IN THE ROSTROVENTRAL NEURAL TUBE (RVNT)

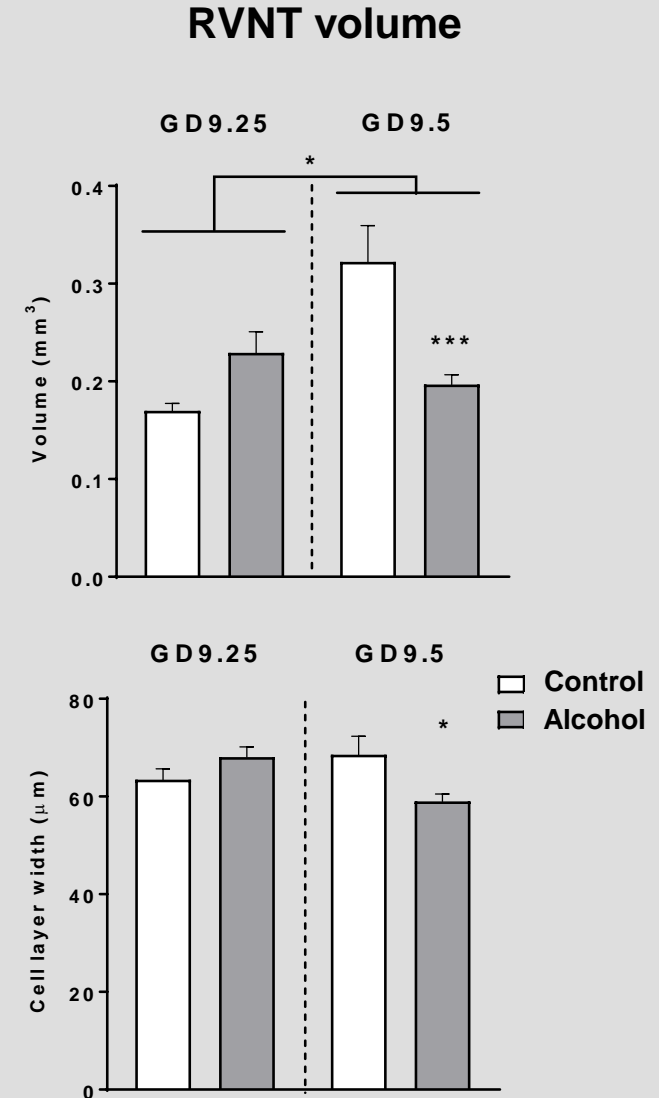
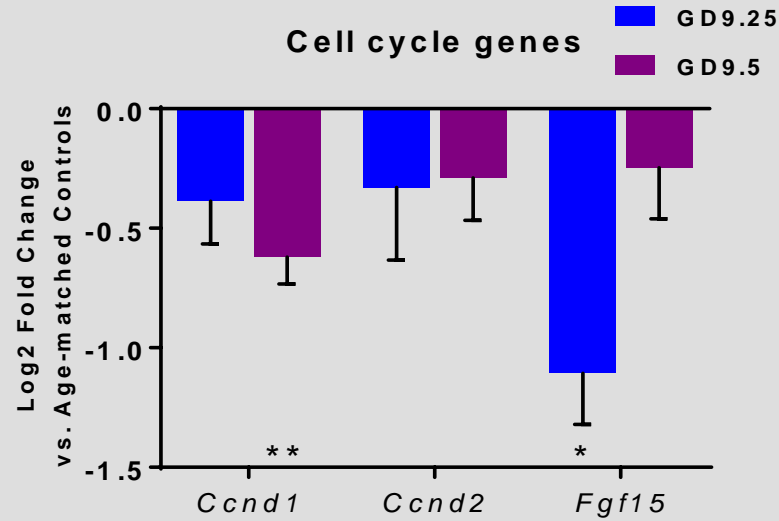
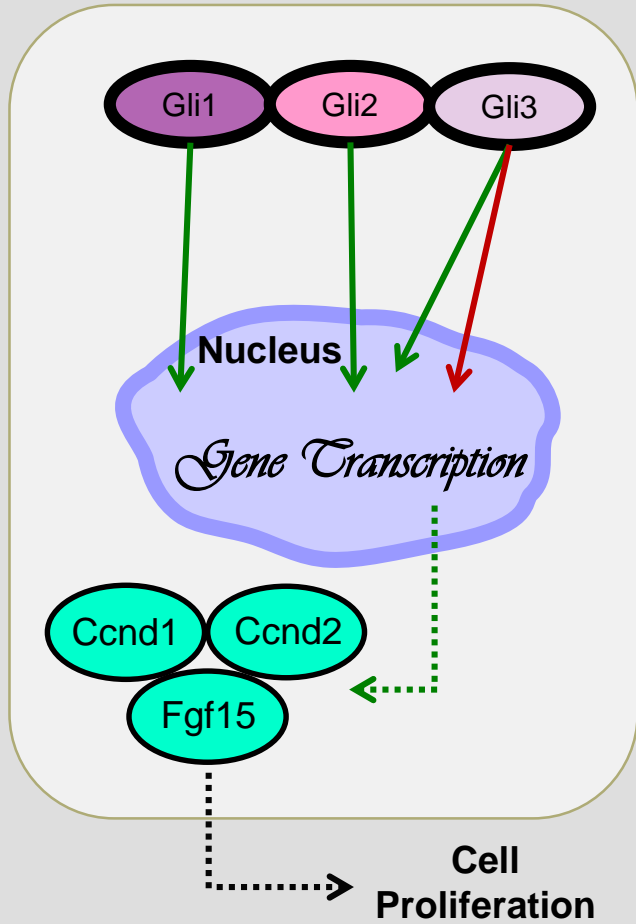
Does neurulation-stage alcohol exposure affect the Shh pathway in the RVNT?



# SHH PATHWAY IS DOWNREGULATED 6-12 HR AFTER PAE

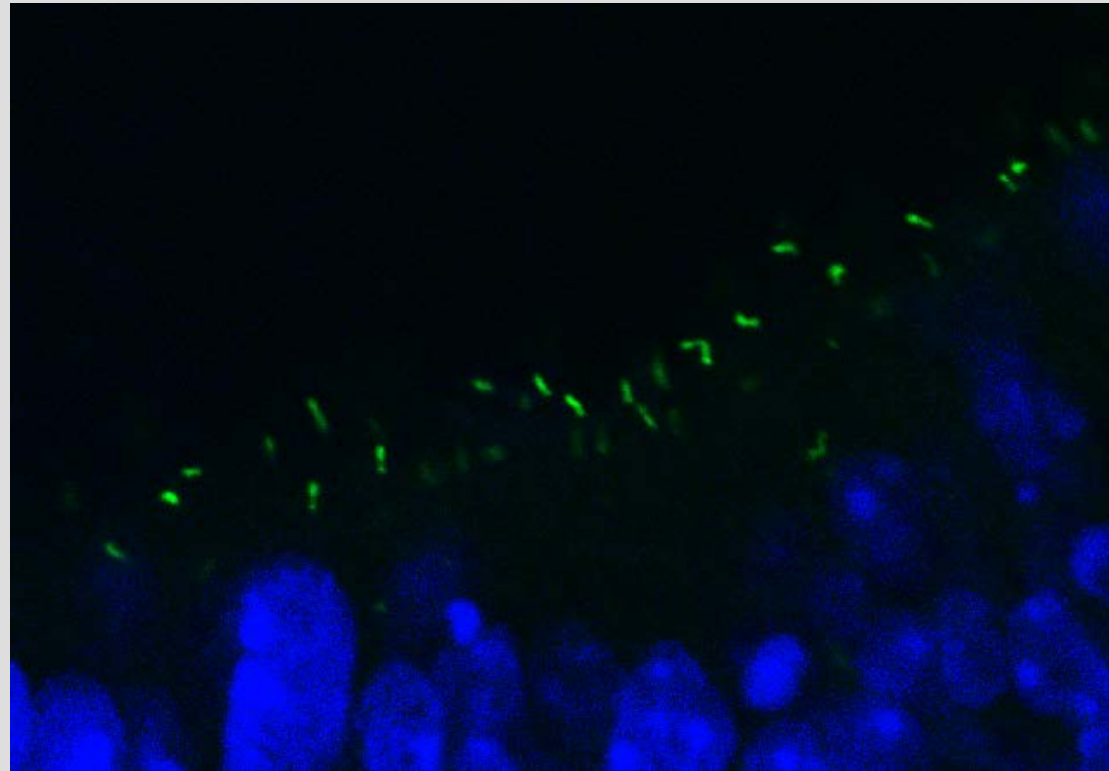
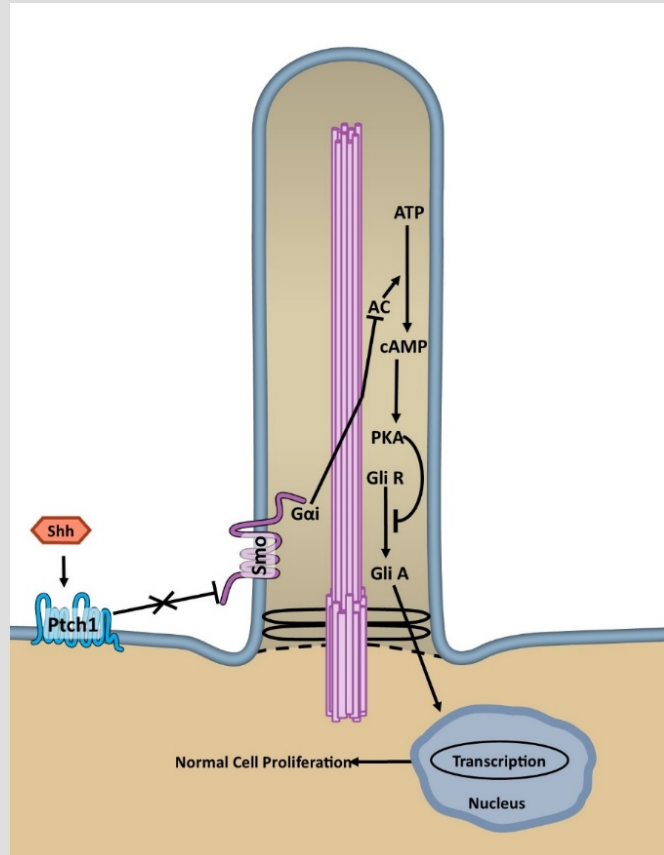


# REDUCED SHH-MEDIATED CELL CYCLE GENES AND RVNT VOLUME 6-12 HR AFTER PAE



# SHH TRANSDUCTION REQUIRES PRIMARY CILIA

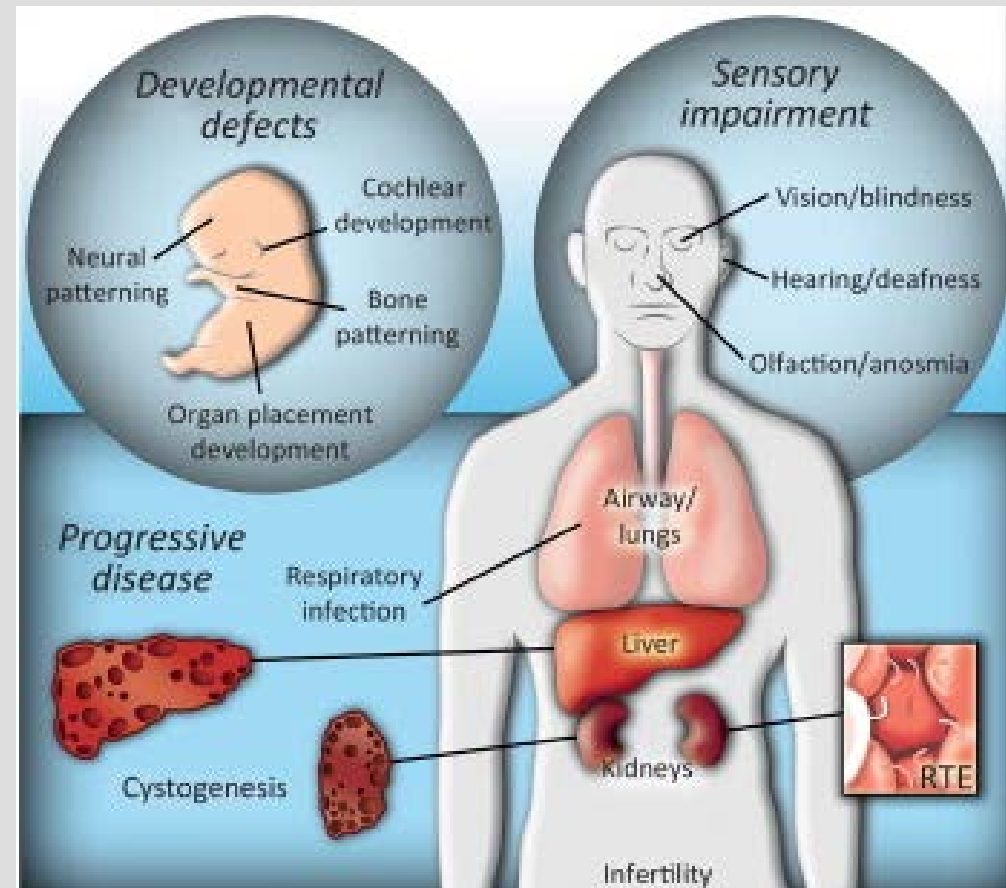
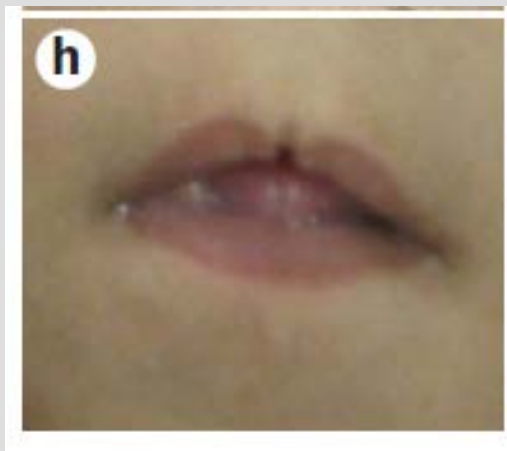
- Shh pathway requires functioning primary cilia: hair-like sensory organelles that protrude from most cells
- Important for developmental processes, e.g. organogenesis, limb development, neural patterning





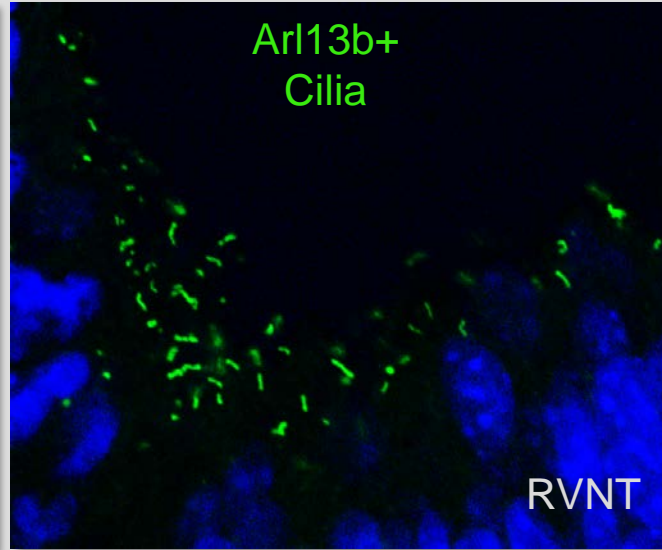
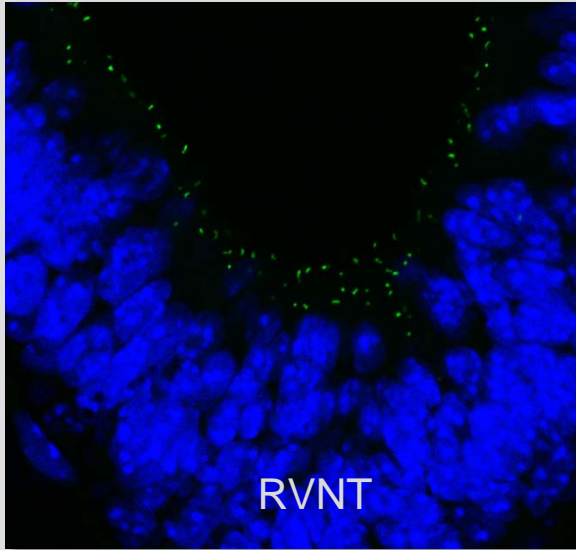
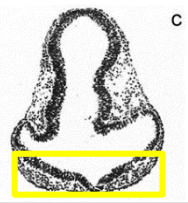
# GENETIC CILIOPATHIES

- Genetic ciliopathies affect primary cilia structure, function, or cilia-anchoring proteins
- Ciliopathies affect many organ systems, including development of the brain, orofacial region, and digits
  - Eye defects (e.g. coloboma)
  - Cleft palates, lips
  - Polydactyly
- Associated with Shh pathway dysregulation

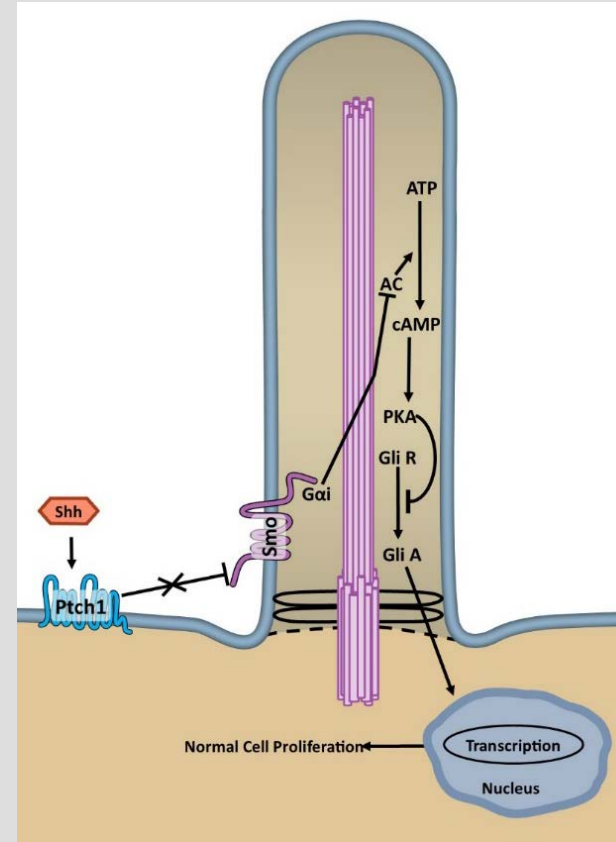




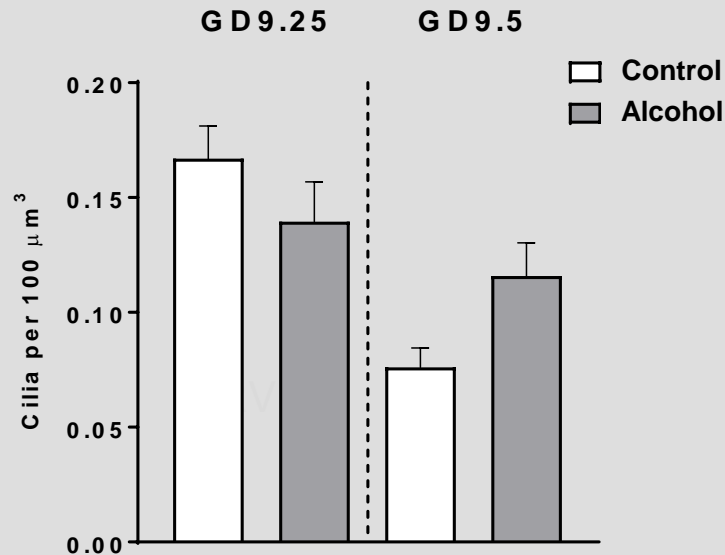
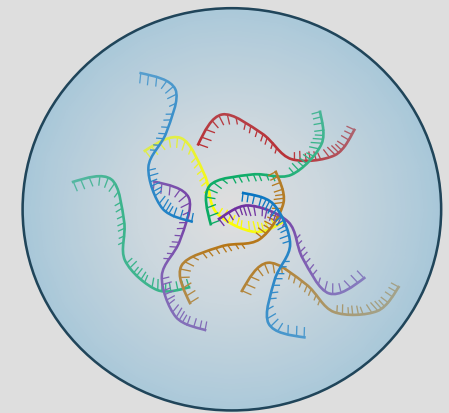
# PRIMARY CILIA DENSITY WAS NOT AFFECTED BY PAE



What about primary cilia function?



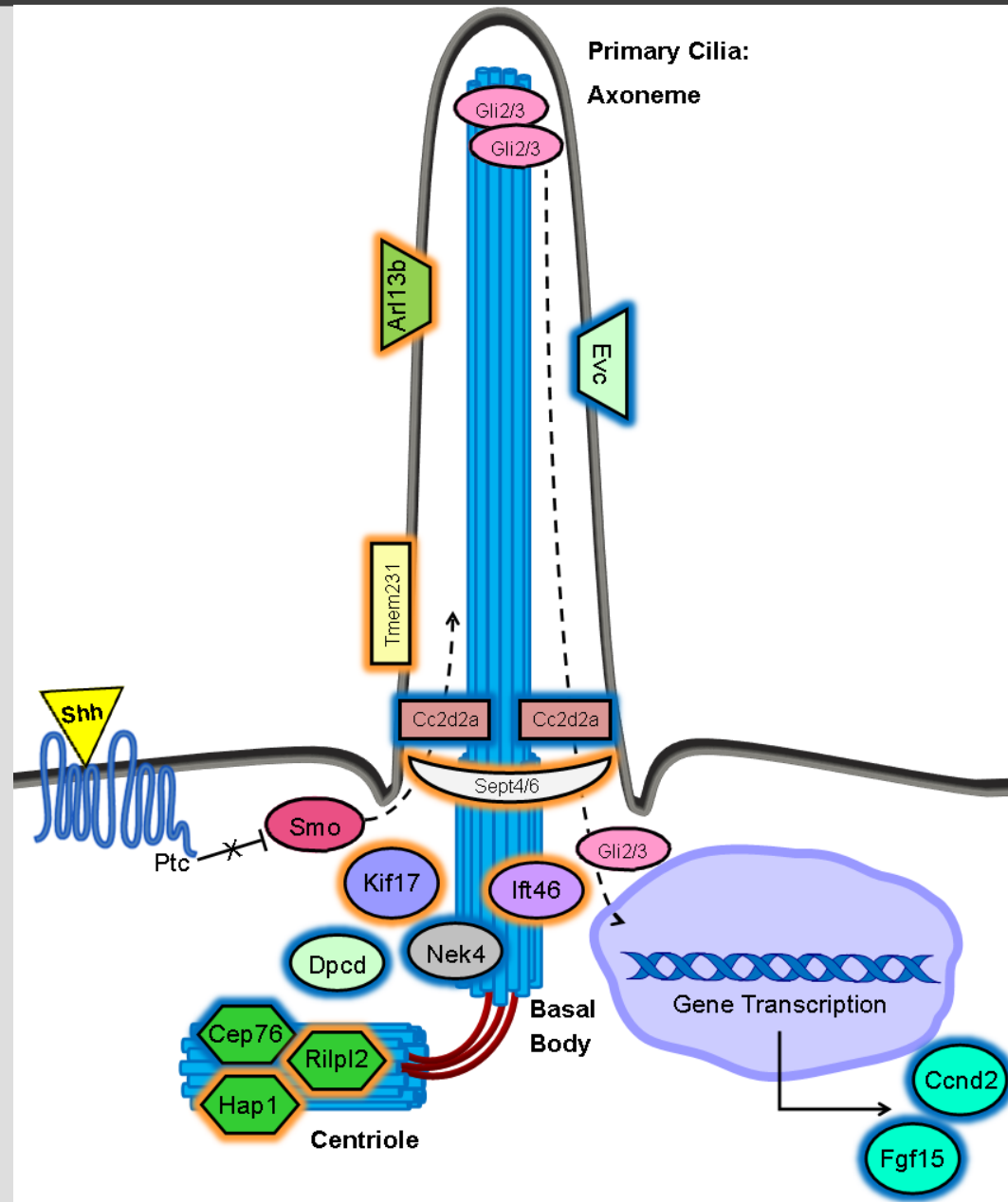
Whole transcriptome analysis



# PAE ALTERS CILIA-RELATED GENE EXPRESSION IN THE RVNT

Upregulated

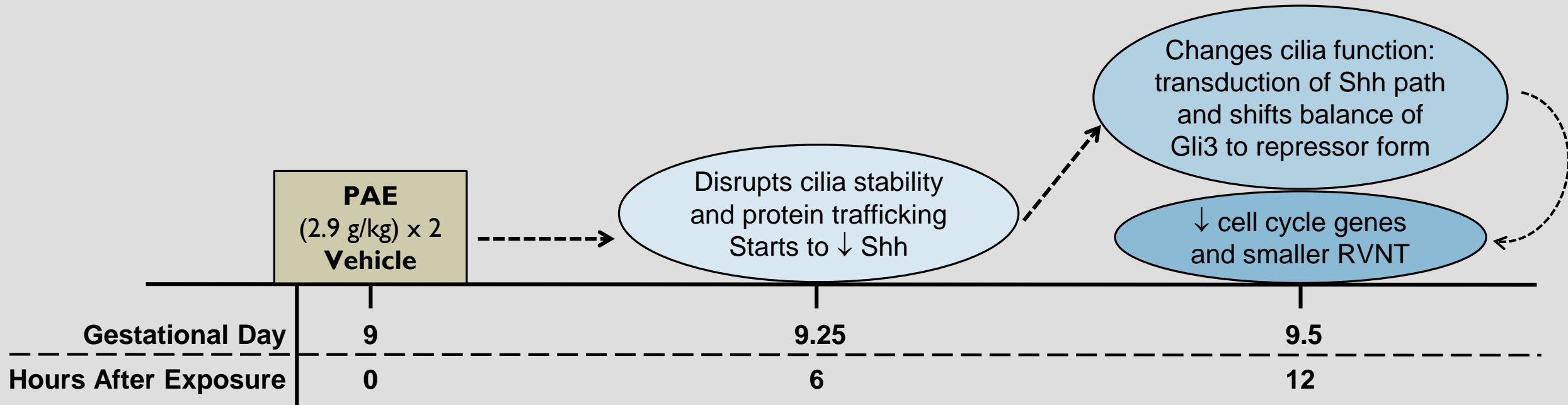
Downregulated



Genes related to:

- Ciliogenesis
- Cilia structure
- Protein trafficking
- Shh signaling
- Cell cycle
- Genetic ciliopathies

# SUMMARY



1. Dysregulation of Shh pathway in regions of the neural tube that give rise to ventral midline brain structures could disturb the growth trajectory of these areas, resulting in both physical malformations and perturbed cognitive-behavioral function.
2. Based on the changes in expression of Gli3 and genes related to cilia function and stability, we hypothesize that neurulation-stage alcohol induces a "transient" ciliopathy in the embryo, leading to the shared phenotype between ciliopathies and prenatal alcohol exposure.



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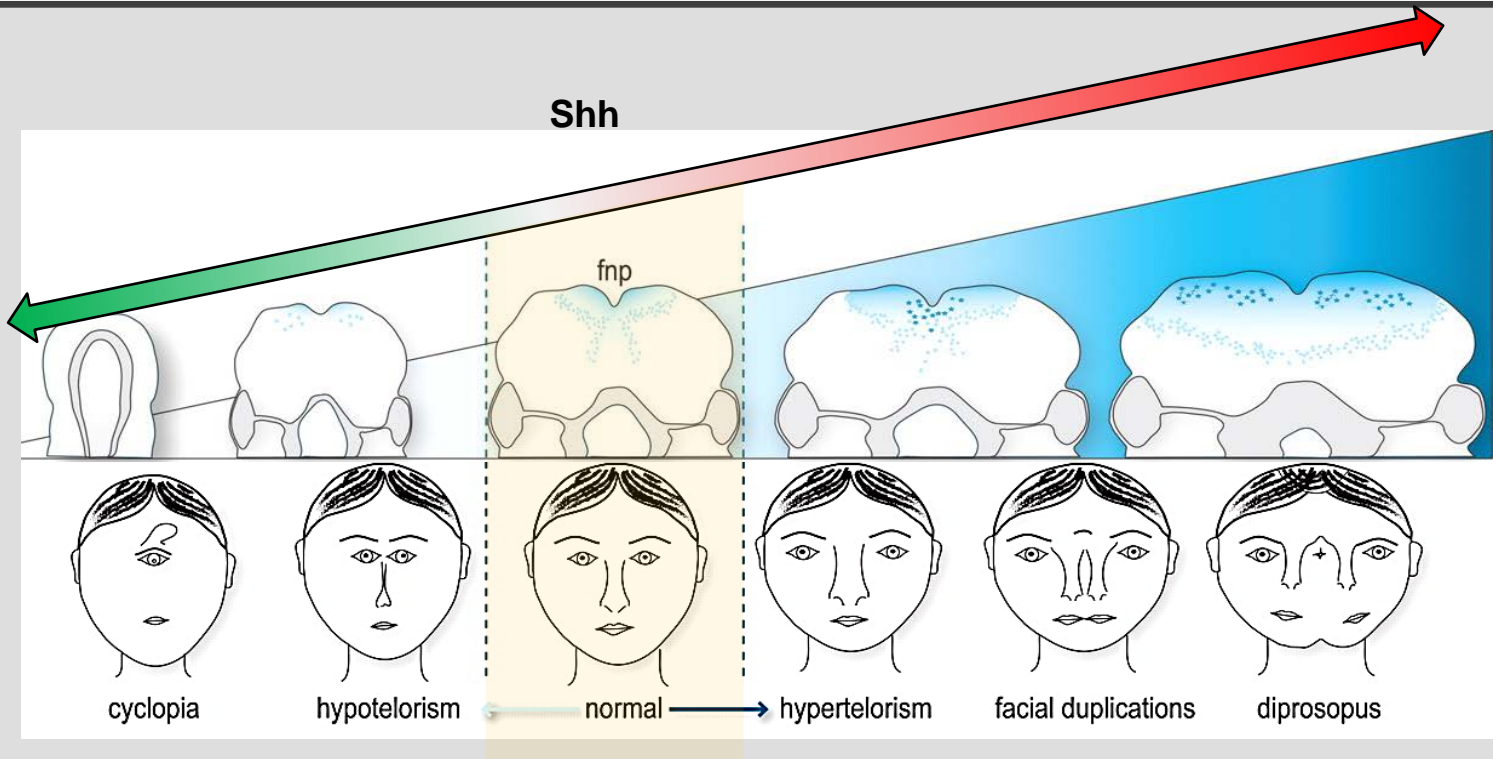


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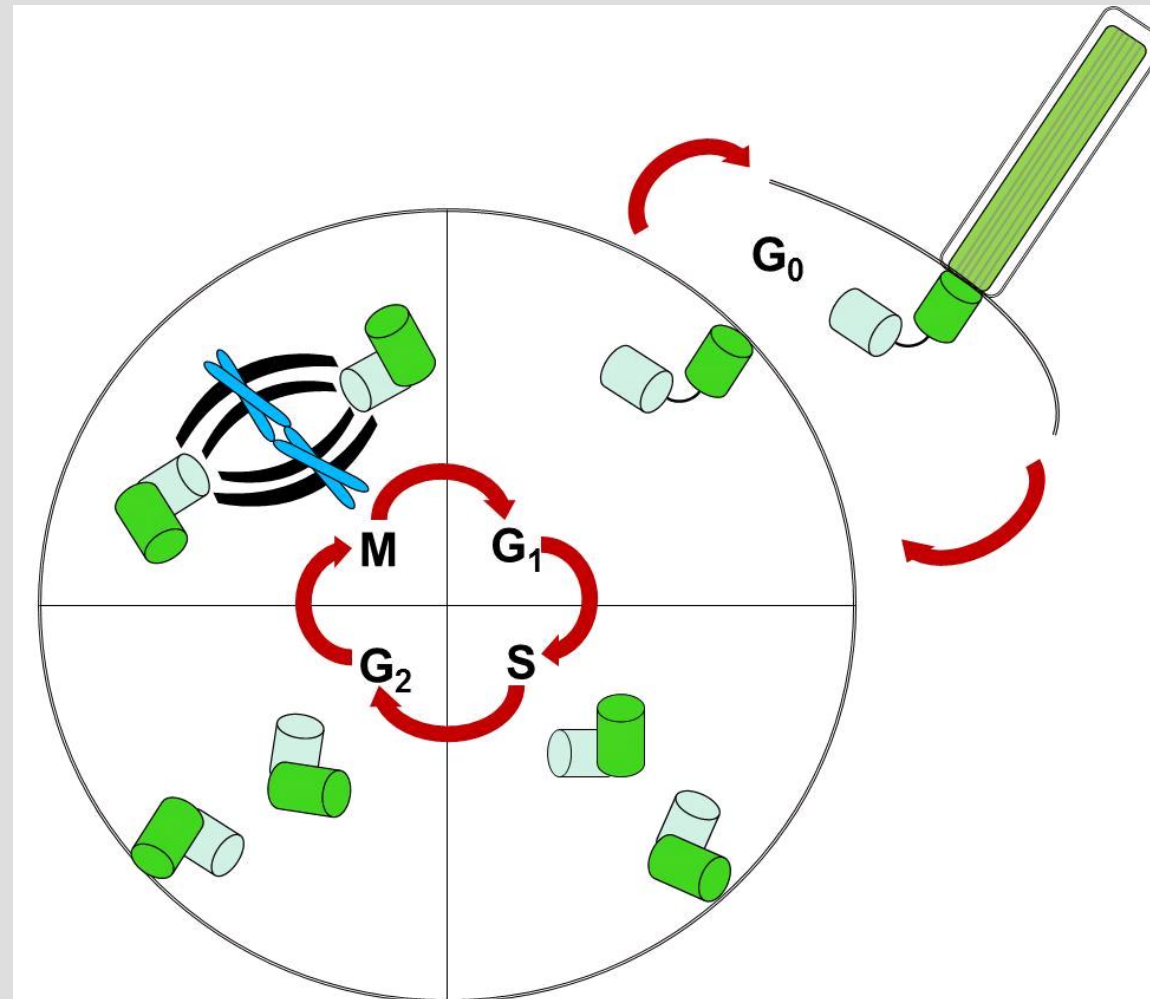
**CIFASD** | Collaborative Initiative on  
Fetal Alcohol Spectrum Disorders

# SHH AND FACIAL WIDTH



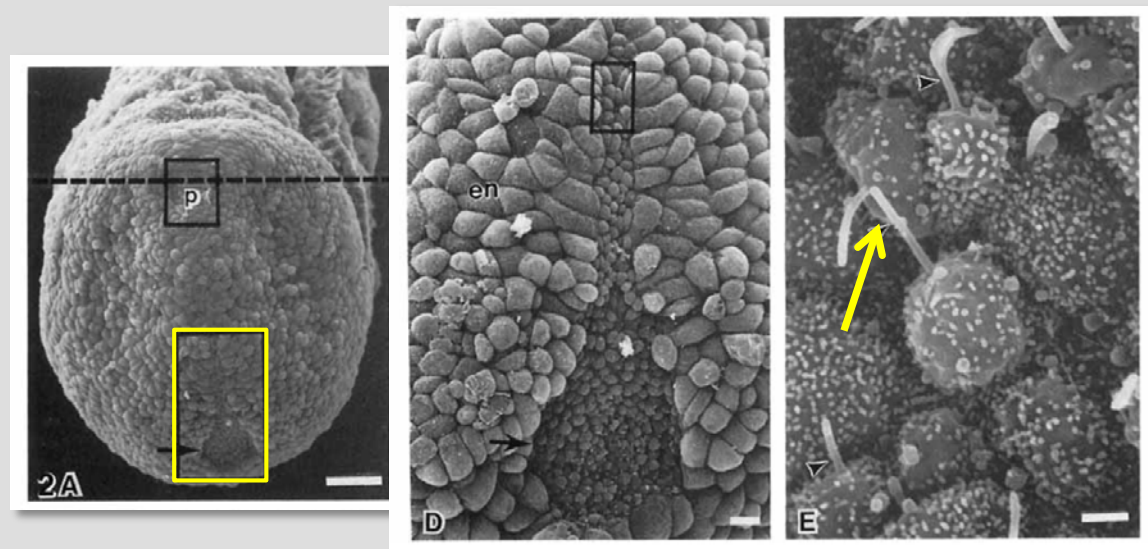
# CILIA RETRACT DURING ACTIVE MITOSIS

MOTHER CENTRIOLE BECOMES CILIA'S BASAL BODY





# MOTILE CILIA IN THE PRIMITIVE NODE



*Sulik et al., 1994*