constriction of neuroepithelial cells which drives dynamic closure of the neural tube.

Our results establish NUAK2 as an indispensable kinase for brain development and may also provide valuable insights into the processes that govern cell shape and migration in NUAK2-associated cancers.

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PS1.19
Linking cilia motility and cerebrospinal fluid flow to the etiopathogenesis of idiopathic scoliosis

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Adolescent idiopathic scoliosis (IS), a disease characterized by 3D spinal curvatures, afflicts 3% of children worldwide. However, the underlying developmental basis for this disease has remained unknown. Recently, the teleost fish have emerged as robust models of IS. Using zebrafish, we have discovered that spinal curves are caused by loss of motile cilia function, which in turn results in defective CSF flow. Human IS can be caused by mutations in *PTK7*, and we find that cilia/CSF flow defects are also the basis of spinal curves in *ptk7* zebrafish mutants. Thus, we propose that IS can be caused by disruptions to CSF flow during the growth phase, providing a novel mechanism for this prevalent disease. We also give evidence that spinal curves can be partially rescued by restoring cilia motility after curve onset, opening potential therapeutic avenues. Overall, our study provides new insight into spine formation and the maintenance of spine linearity.

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PS1.20
Elk1 in congenital and late onset heart disease: at the heart of the matter

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Elk1 is an ETS Class I, TCF subfamily transcription factor known as a well established downstream effector of the MAPK pathway and implicated in the causation of a variety of cancers. Recent *in-vitro* evidence places Elk1 and the other TCFs in the context of the cardiogenic transcription factor network but the *in-vivo* role of the TCFs in cardiogenesis remains unexplored.

Here, we provide the first *in-vivo* evidence of the role of the Elk1 in cardiogenesis using a zebrafish mutant with disrupted DNA binding domain (*elk1* $^{-543/-543}$) and cardiac defects, including valve displacement/elongation and hypertrophic/hyperplastic changes. *elk1* $^{-543/-543}$ are predisposed to early embryonic death, with high incidence of heart looping defects and accelerated growth among survivors.

RNA-sequencing (RNA-seq) at 6dpf provides insights into the basis of anatomical defects, with upregulation of MAPK components and downregulation of *trim63a*, encoding a homeostatic protein involved in reducing muscle mass, downregulation of which is associated with Hypertrophic Cardiomyopathy (HCM) in humans.

The inverse relationship between MAPK components and Trim63a is well-described although its fundamental basis is unknown. Here we provide the first mechanistic insight into this relationship, indicating that MAPK perturbations likely converge via the TCFs at the *trim63a* promoter, downregulating *trim63a* to mediate HCM.

RNA-seq at the tail bud stage has allowed us to identify putative, genomically hard-wired compensation mechanisms whereby loss of TCF function causes downregulation of tumor suppressor genes. We hypothesize this promotes proliferation and embryonic survival via non-optimal (compensatory) pathways, and is the fundamental mechanism underlying observed phenotypic defects.

The sum of anatomical and molecular changes observed in *elk1* $^{-543/-543}$ mimic a group of congenital syndromes known as "RASopathies" in humans. Overall, our data provides high resolution insights into the time line of molecular events underlying RASopathies/MAPK pathway defects and their relationship to molecules imperative in heart patterning and homeostasis.

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PS1.21
Rab23 deficient mice exhibit lambdoid suture craniosynostosis through aberrant Fgf signaling

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Background: Rab23 is a GTPase protein and is proposed to regulate intracellular vesicle trafficking. Mutations in *Rab23* causes Carpenter Syndrome; heart defect, polysyndactyly, obesity and most prominently craniosynostosis. Craniosynostosis is a premature fusion of calvarial sutures that largely affecting brain, facial, skull growth & development. Craniosynostosis is the second largest human birth defects.

Results: We show that in *Rab23*$^{-/-}$ mice *Fgf10* is overexpressed in the lambdoid suture. Upregulation of Fgf10 enhances the expression of its receptor *Fgfr1b* and *Fgfr2b* in the mutant lambdoid sutural sites that subsequently activate MAPK signaling and enhance pErk levels. *Pitx2,* a homeodomain transcription factor is known as an upstream regulator of Fgf10 expression. Our study shows that Rab23 deficiency causes lambdoid suture craniosynostosis through a positive regulatory axis of Pitx2-Fgf10-MAPK signaling. Moreover, overall upregulation of *Gli* transcription factors and *Hh* giving further evidence of MAPK pathway over activation, which results in higher cell proliferation in the mutant lambdoid suture and leading to premature suture fusion due to an imbalance between osteoblast proliferation and differentiation. We further validated our hypothesis by in vitro lambdoid sutural tissue culture in presence or absence of Mapk signaling antagonist U0126. Our result suggests that inhibiting Mapk signaling by U0126 can rescue mutant lambdoid suture from premature fusion in *Rab23*$^{-/-}$mice.

Conclusion: These findings suggest a novel role of Rab23 during lambdoid suture development through Pitx2-Fgf10-MAPK signaling.

Significance: Targeting Fgf10 or inhibiting MAPK signaling might be a potential tool to treating patients with lambdoid suture craniosynostosis.

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