New mechanism driving cortical gyrification and hydrocephalus found in mice suggests scope for novel therapy

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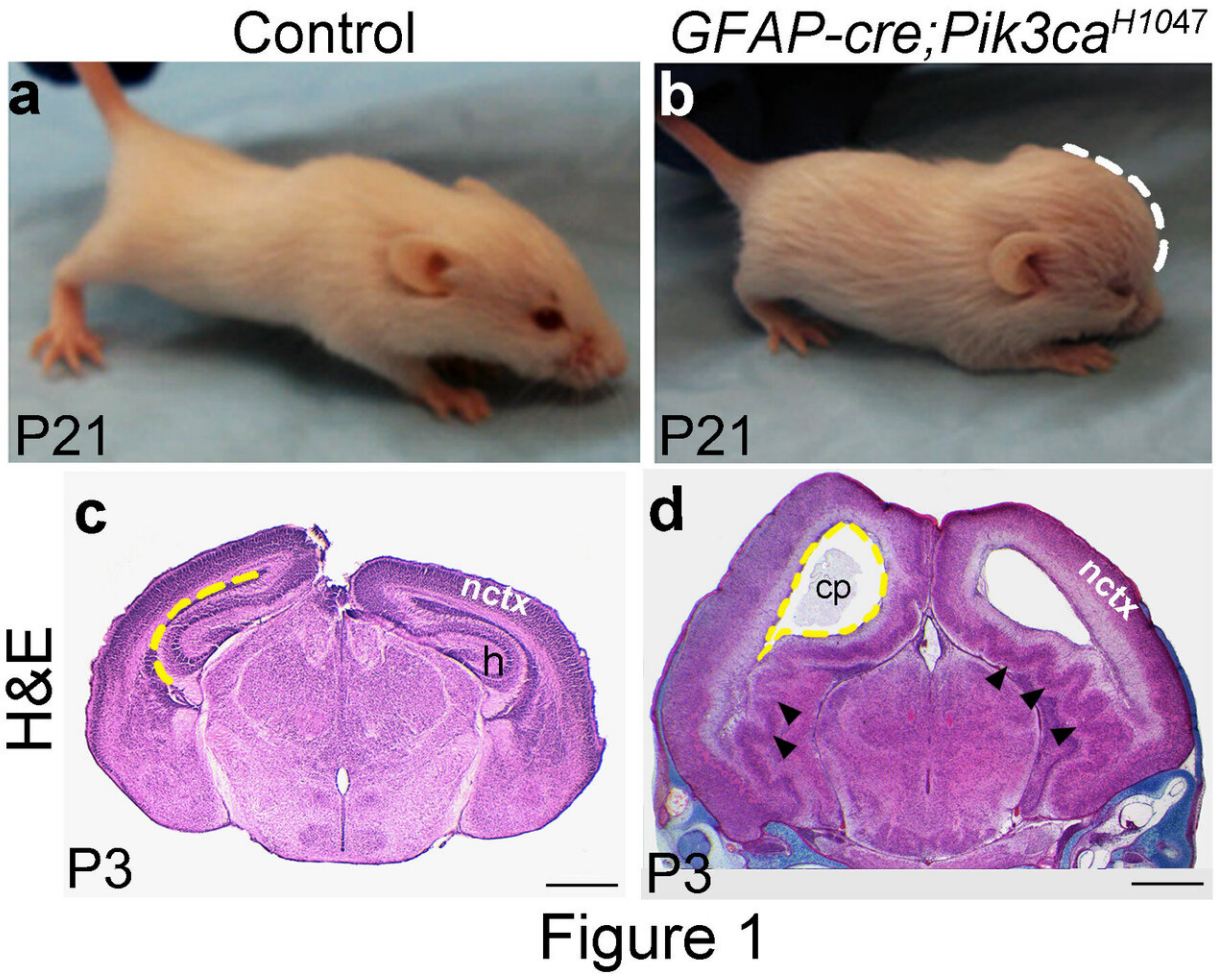

Figure 1

Mouse models of activating PI3K mutations recapitualte human phenotypes like brain overgrowth, cortical dysplasia and hydrocephalus. Nctx – neocortex, h-hippocampus, cp – choriod plexus. Credit: (Roy et al., 2015)

Cortical gyrification, or the stereotypic folding pattern in the forebrain, is implicated in the development of human cognition. During evolution, the mammalian brain went through several transitions between smooth and folded brains. What mechanism underlies the extent and pattern of folds is yet to be deciphered. Moreover, defects with brain folding are very commonly found in neurodevelopmental disorders and are often associated with other severe comorbidities like intellectual disability, epilepsy and hydrocephalus. Thus, understanding the biology behind these disorders is of both evolutionary and clinical significance, more so since most of these neurodevelopmental disorders lack non-invasive small-molecule therapies. Our study provides molecular mechanistic insights toward novel therapeutic approaches for brain disorders such as cortical dysplasia and hydrocephalus.

Previous studies, including ours, demonstrated that gain-of-function mutations in phosphoinositide 3-kinase (PI3K) pathway genes cause cancers and a spectrum of developmental disorders in humans and model systems. Using a brain-specific activating PI3K mutant mouse model of human megalencephaly (brain overgrowth), we (Roy et al., 2019) identified embryonic regulation of PI3K signaling and Yap signaling pathways required to maintain the unfolded, smooth nature of the mouse forebrain and prevent developmental hydrocephalus. This work was recently published in *eLife*; it was led by Dr. Achira Roy under the supervision of Dr. Kathleen Millen at Seattle Children's Research Institute and collaboration with labs in University of Washington.

In this study, we discovered that transient embryonic activation of PI3K mutation results in focal disruption of developing ependyma, cell-cell adhesion, proliferation and apical tissue integrity, leading to cortical gyrification (in both neocortex and hippocampus) and developmental hydrocephalus in mice.

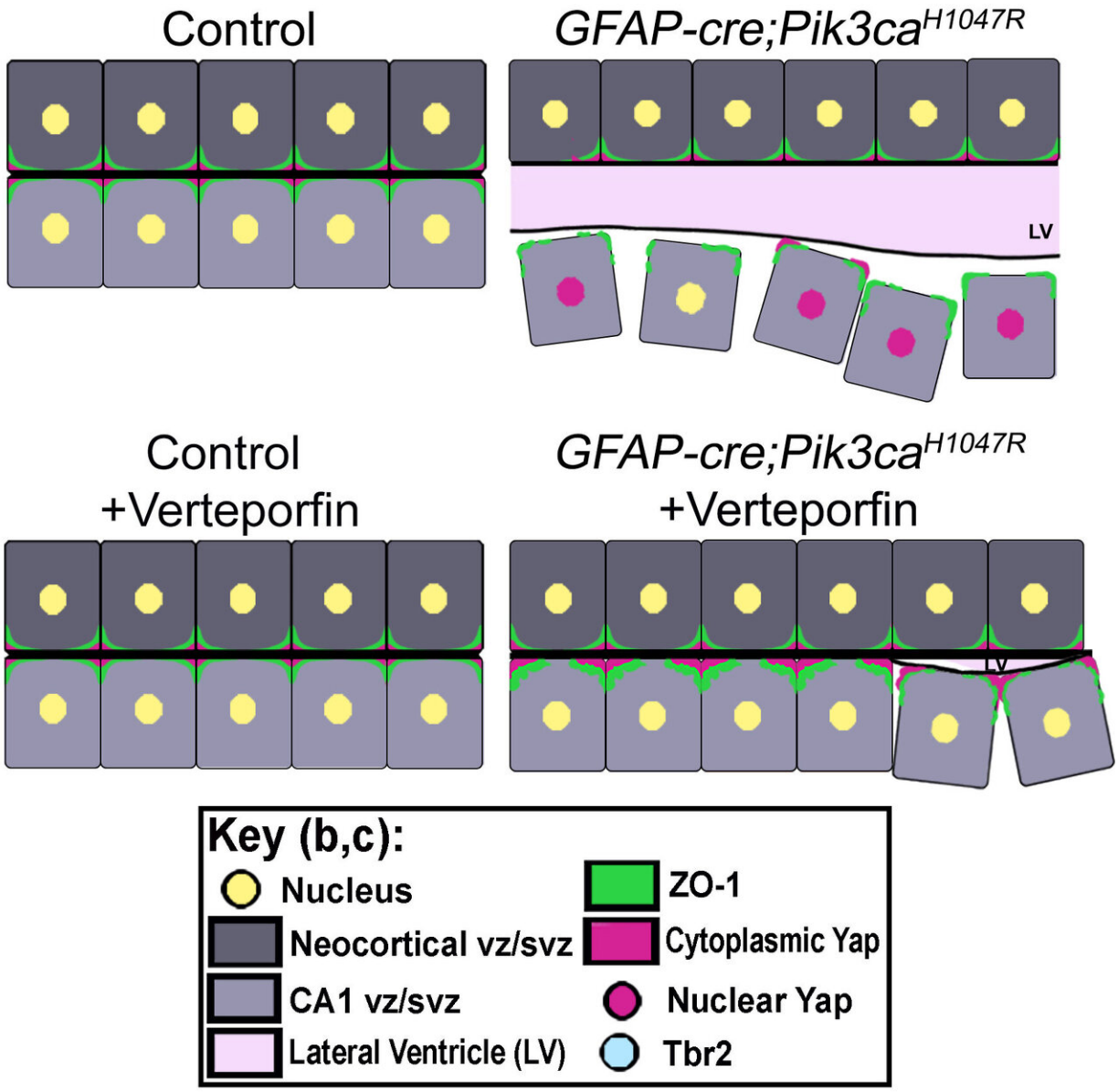

Figure 2

Summary of (Roy et al., 2019): PI3K over-activation resulted in disruption of cell adhesion at the neural-ependymal transition zone causing ventriculomegaly, and also in differential proliferation of progenitors, thus triggering the gyrification sequence cascade (effect of genotype). In mutant mice, verteporfin attenuated these anomalies (effect of drug), leading to reduction in gyrification severity as well as ventriculomegaly.

We identified differential focal expression of an ependymal marker, Yap, along the mutant ventricular lining. Normally, Yap is expressed in the cytoplasm of cells lining the ventricles (fluid cavities in the brain) and is required for maintaining cell adhesion and ependymal integrity. In the PI3K mutants, Yap localization significantly relocated from the cytoplasm to the nuclei of these cells. These focal changes also strongly correlated with focal sites of disrupted cell adhesion and extra neurons being born, causing cortical folding. RNA sequencing following laser microdissection of this ventricular zone confirmed a distinctly different transcriptomic profile of controls and mutants. Interestingly, the mutant transcriptomic profiles showed significant overlap with the brains of developing ferrets, a mammal with a naturally folded cerebral cortex. This suggests preserved evolutionary mechanisms drive bona-fide gyrification across species.

We next asked if suppressing nuclear Yap embryonically could rescue the tissue integrity and in turn prevent the abnormal phenotypes of cortical gyrification and hydrocephalus in mouse. Indeed, embryonic treatment with verteporfin, a nuclear Yap inhibitor, restored apical surface integrity, normalized proliferation, attenuated gyrification and rescued the associated hydrocephalus both morphologically and transcriptionally. This work clearly demonstrates the highly interrelated role of regulated PI3K-Yap signaling in normal neural-ependymal development and cell integrity. It also explains why cortical dysplasia is associated with hydrocephalus, since both cortical neurogenesis and ependymal development are controlled by the normal integrity of the apical surface.

Notably, our data converges with other recent data demonstrating that aberrant Yap signaling is implicated in hydrocephalus caused by brain bleeds in premature infants (Park et al., 2016). Together, these animal

models suggest that Yap-related small-molecule therapeutics may represent a novel therapy for multiple types of hydrocephalus in infants.

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More information: Park R, Moon UY, Park JY, Hughes LJ, Johnson RL, Cho SH, Kim S (2016) Yap is required for ependymal integrity and is suppressed in LPA-induced hydrocephalus. Nat Commun 7:10329. DOI: 10.1038/ncomms10329

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