

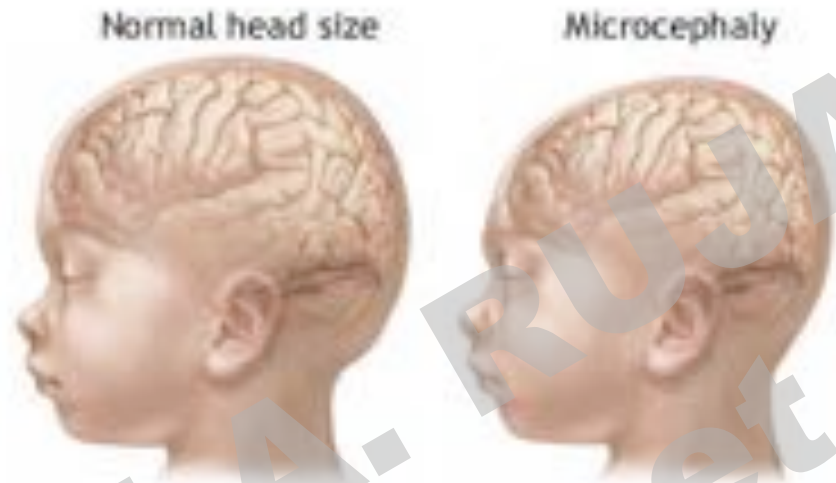
Drosophila as a model to study neurodevelopmental disorders

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Institut Imagine*

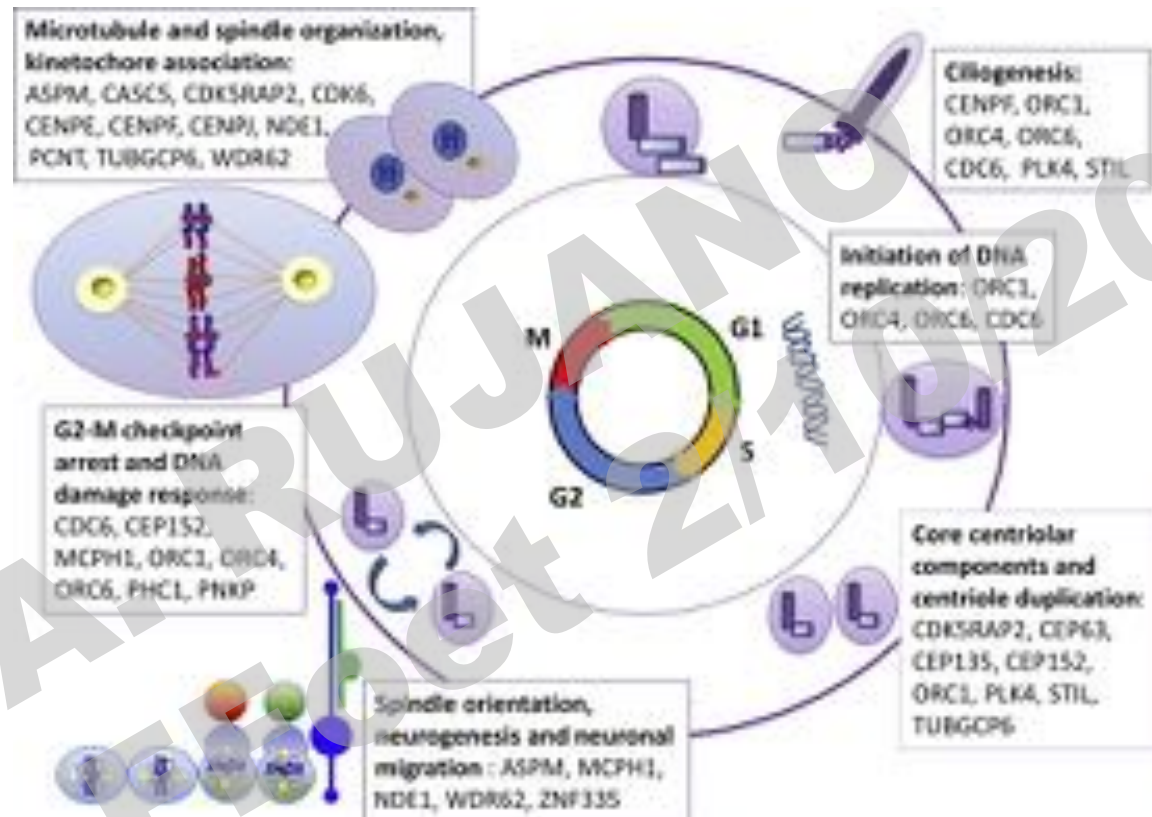
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Microcephaly



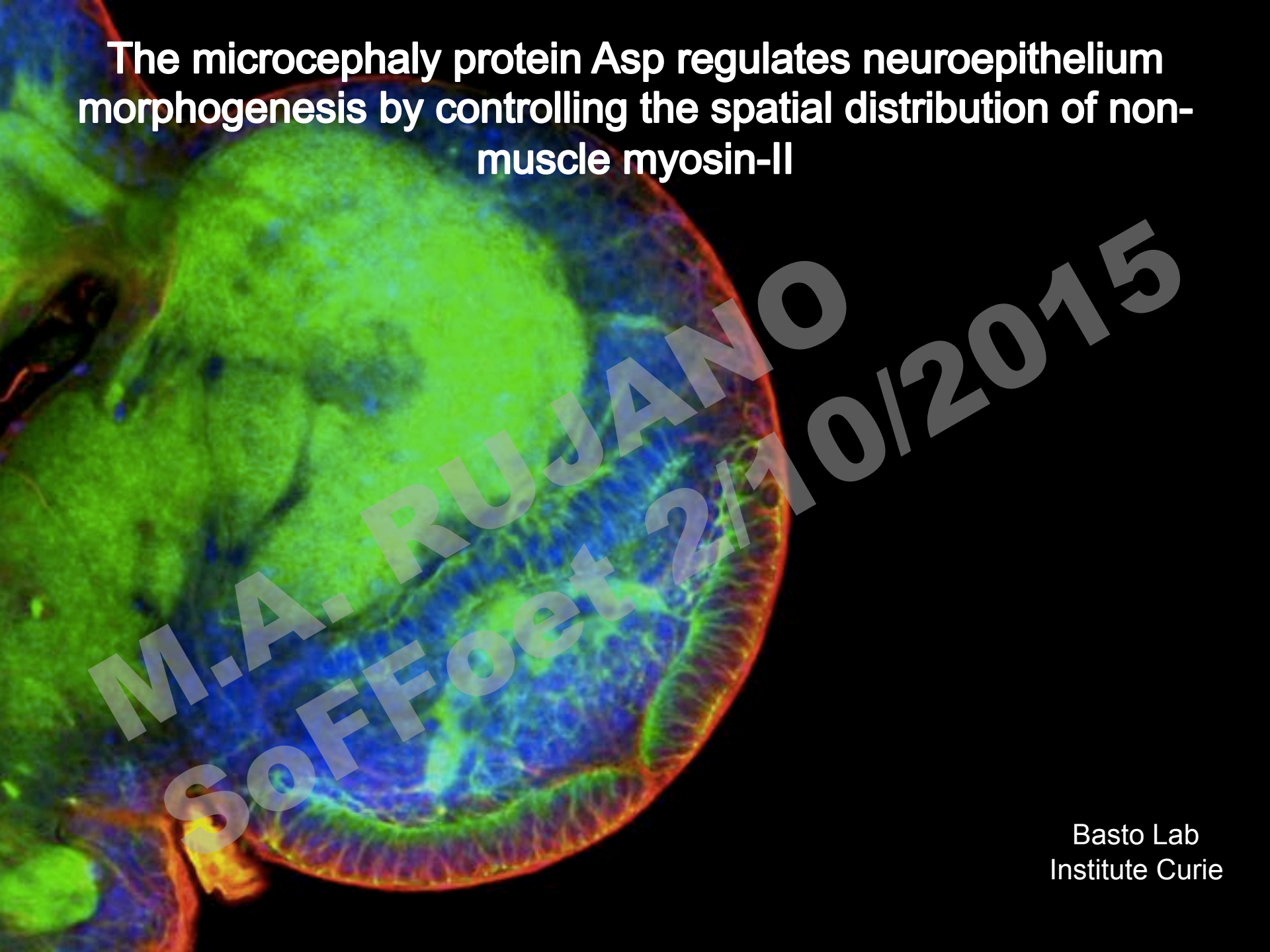
Human genes		Drosophila Orthologues
MCPH1	Microcephalin	Mcph1
MCPH2	WDR62	CG7337
MCPH3	CDK5RAP2	Centrosomin
MCPH4	CASC5	-
MCPH5	ASPM	Asp
MCPH6	CENPJ	DSas-4
MCPH7	STIL	Ana2
MCPH8	CEP135	Cep135
MCPH9	CEP152	Asl
MCPH10	ZNF335	CG2889, CG18011
MCPH11	PHC1	ph-p, ph-d
MCPH12	CDK6	Cdk4
MCPH13	CENPE	CENP-ana

MCPH proteins are involved in cell cycle dynamics, the centrosome, ciliogenesis and neuronal migration.



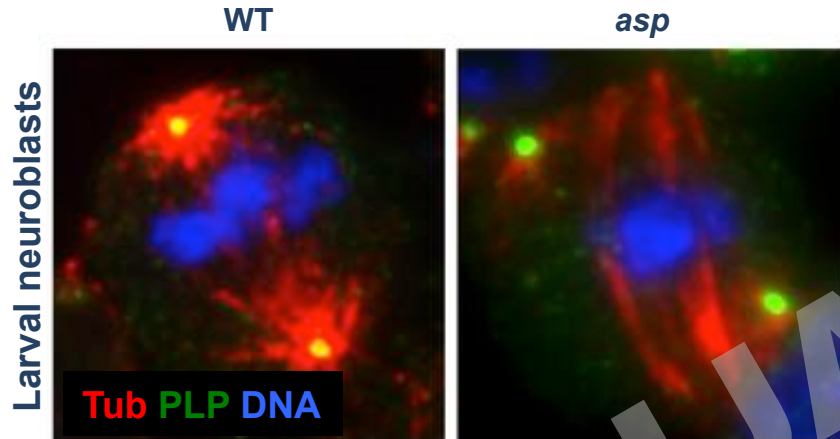
From: Deborah J. Morris-Rosendahl, Angela M. Kaindl, 2015

The microcephaly protein Asp regulates neuroepithelium morphogenesis by controlling the spatial distribution of non-muscle myosin-II



Drosophila Asp and mouse ASPM

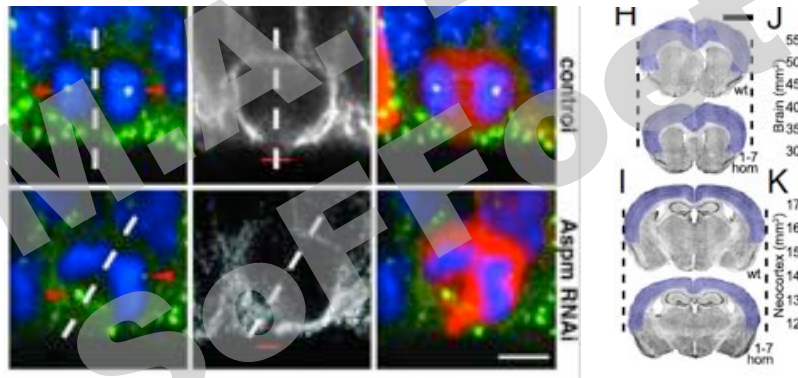
In *Drosophila*



Lethality at larval-pupal transition
Mitotic defects
Meiotic defects
Cytokinesis defects
Prometaphase arrest

Ripoll et al. 1985, Gonzalez et al. 1988, 1990, Casal, et al. 1990, Saunders et al. 1997, do Carmo-Avides and Glover, 1999, Wakefield et al. 2001, do Carmo-Avides et al. 2002, Riparbelli et al. 2002, Morales-Mulia & Scholey 2005

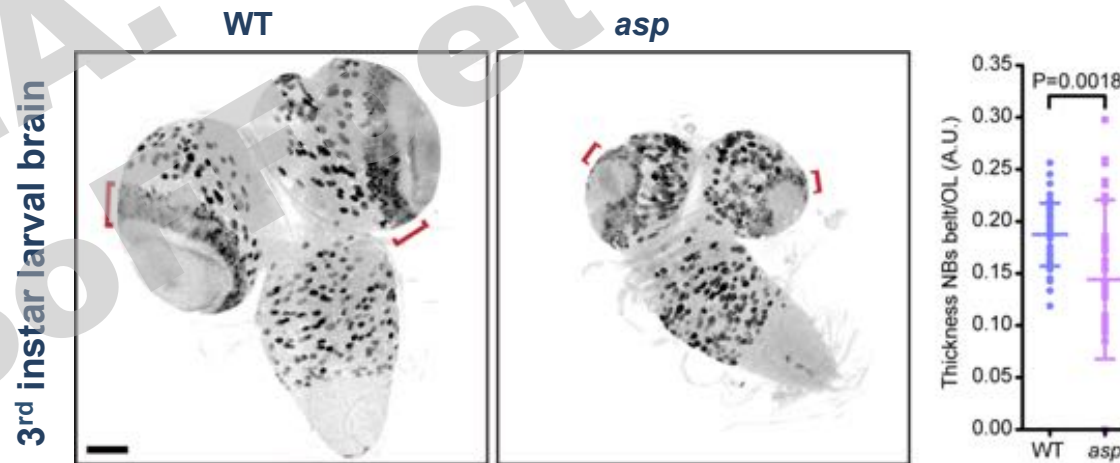
In vertebrates (mouse model)



Mitotic spindle positioning defects
Mild defect in brain size

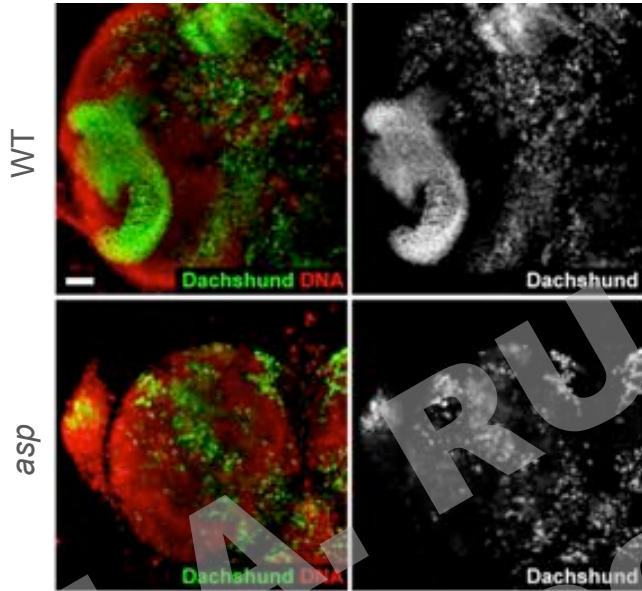
Fish, et al 2006 and Pulvers, et al, 2010.

Head and brain size are reduced in *asp* mutants

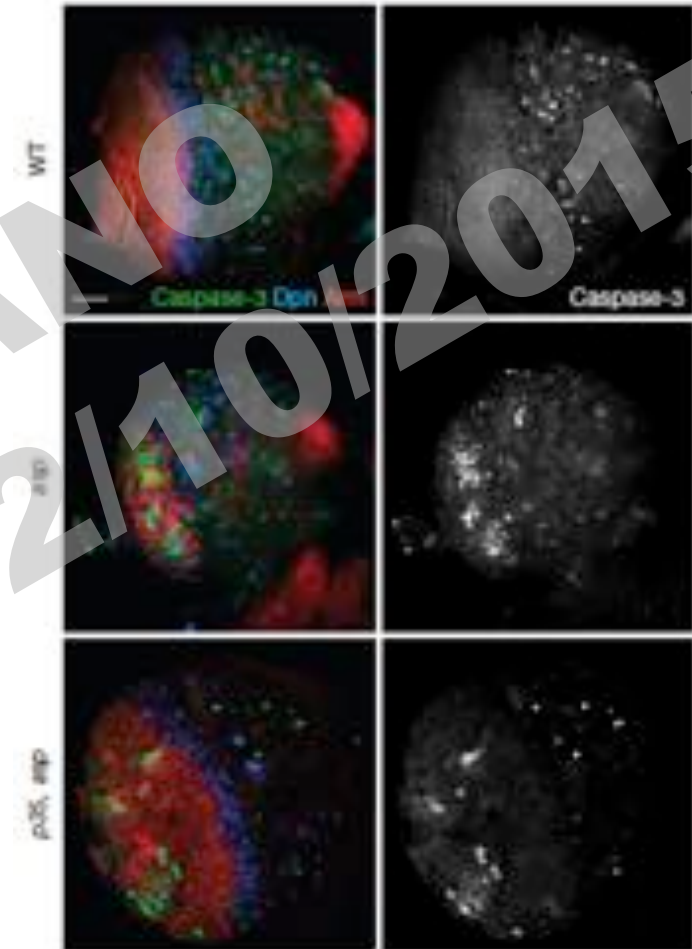


Optic lobe neurons are missing in *asp*

Optic lobe neurons are missing in *asp*

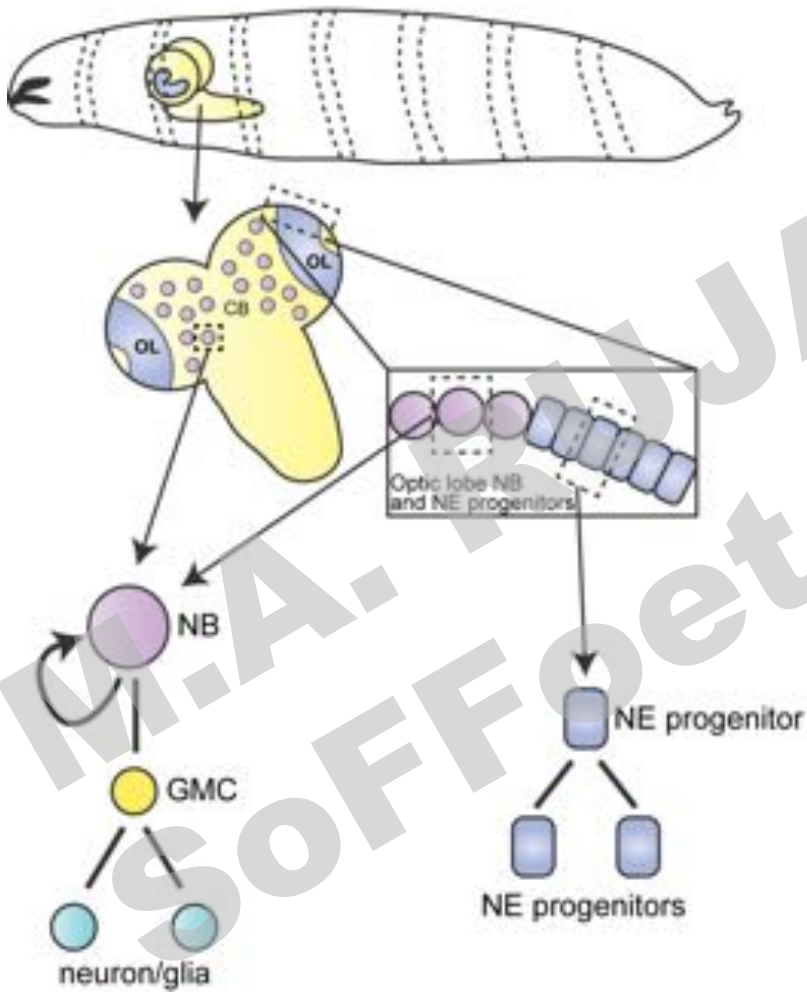


Apoptosis is increased in *asp*

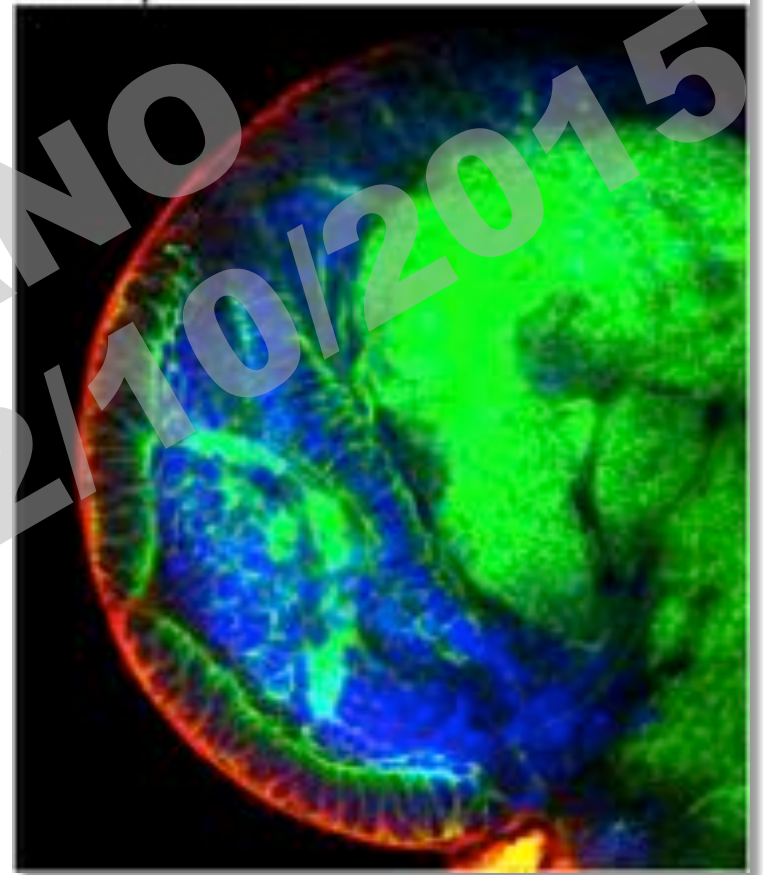


Drosophila larval brain

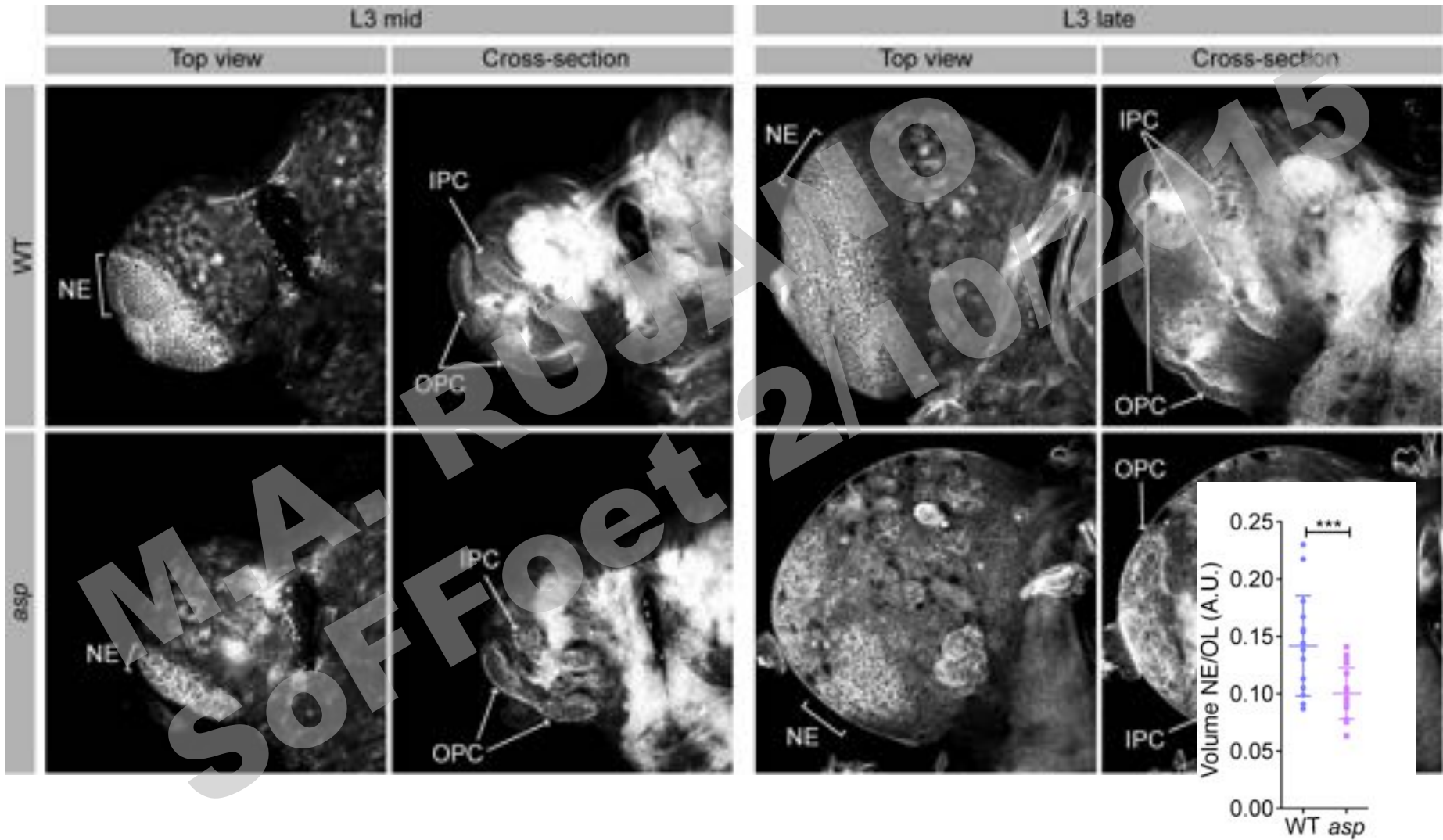
Drosophila 3rd instar larvae



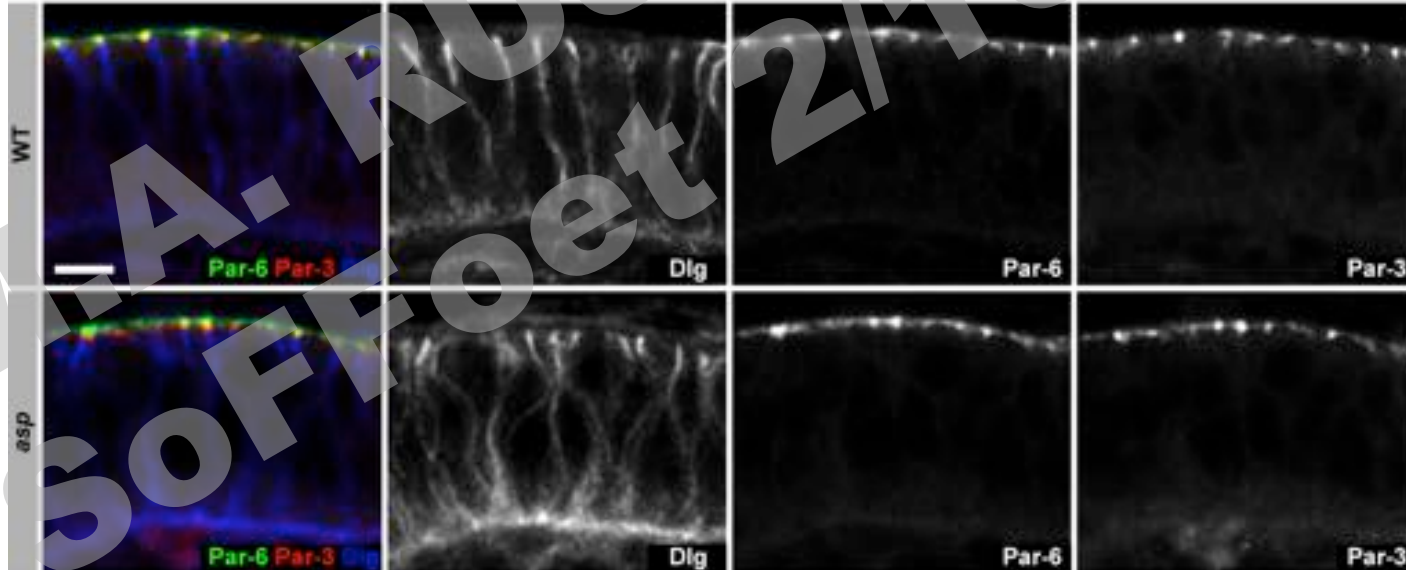
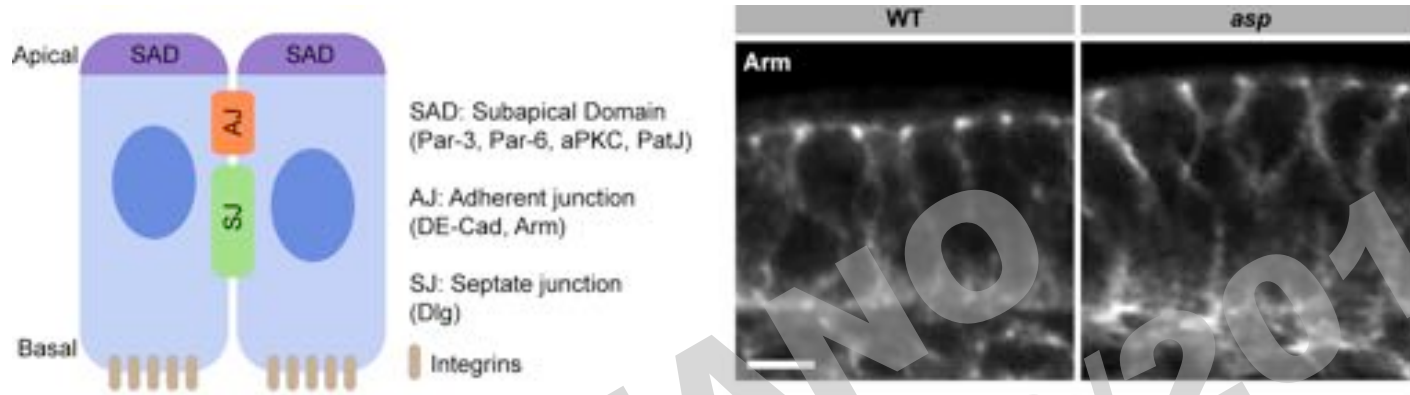
Neuroepithelium



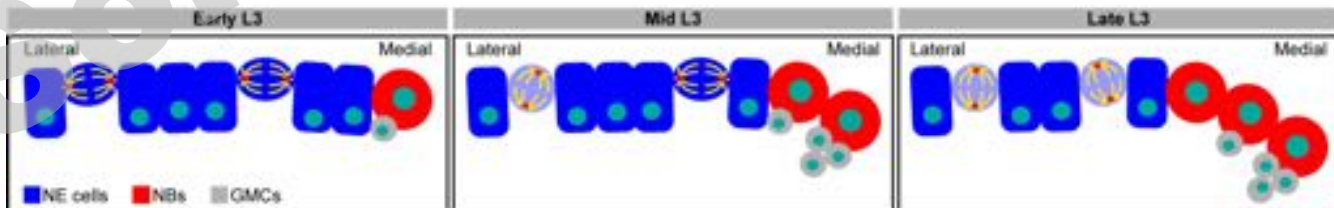
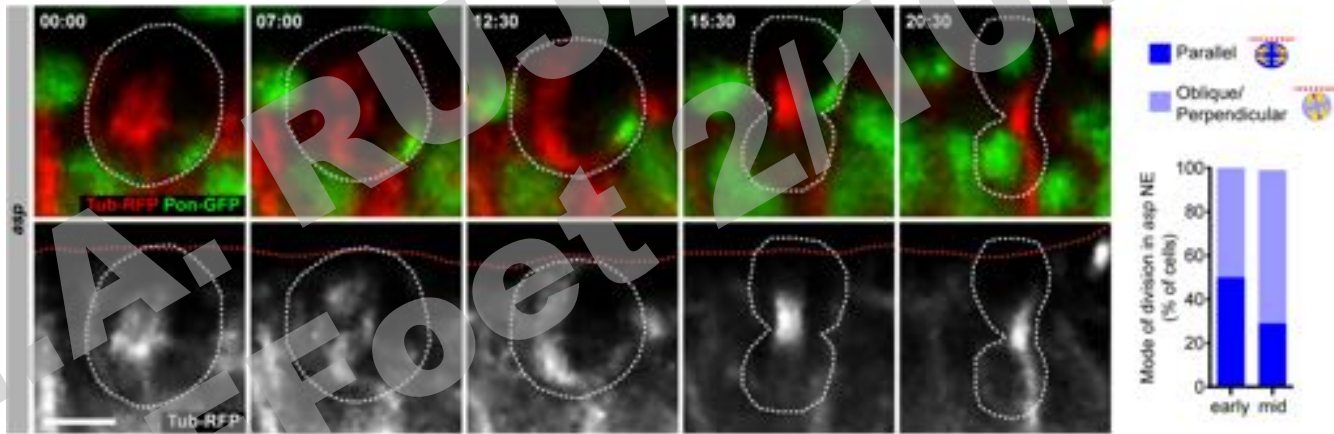
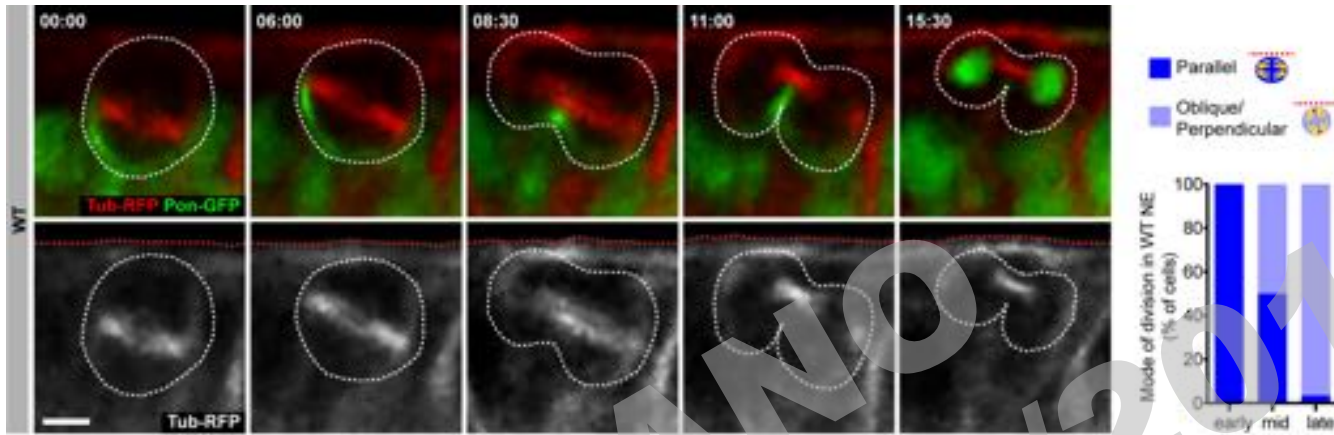
asp mutation affects neuroepithelium (NE) morphogenesis



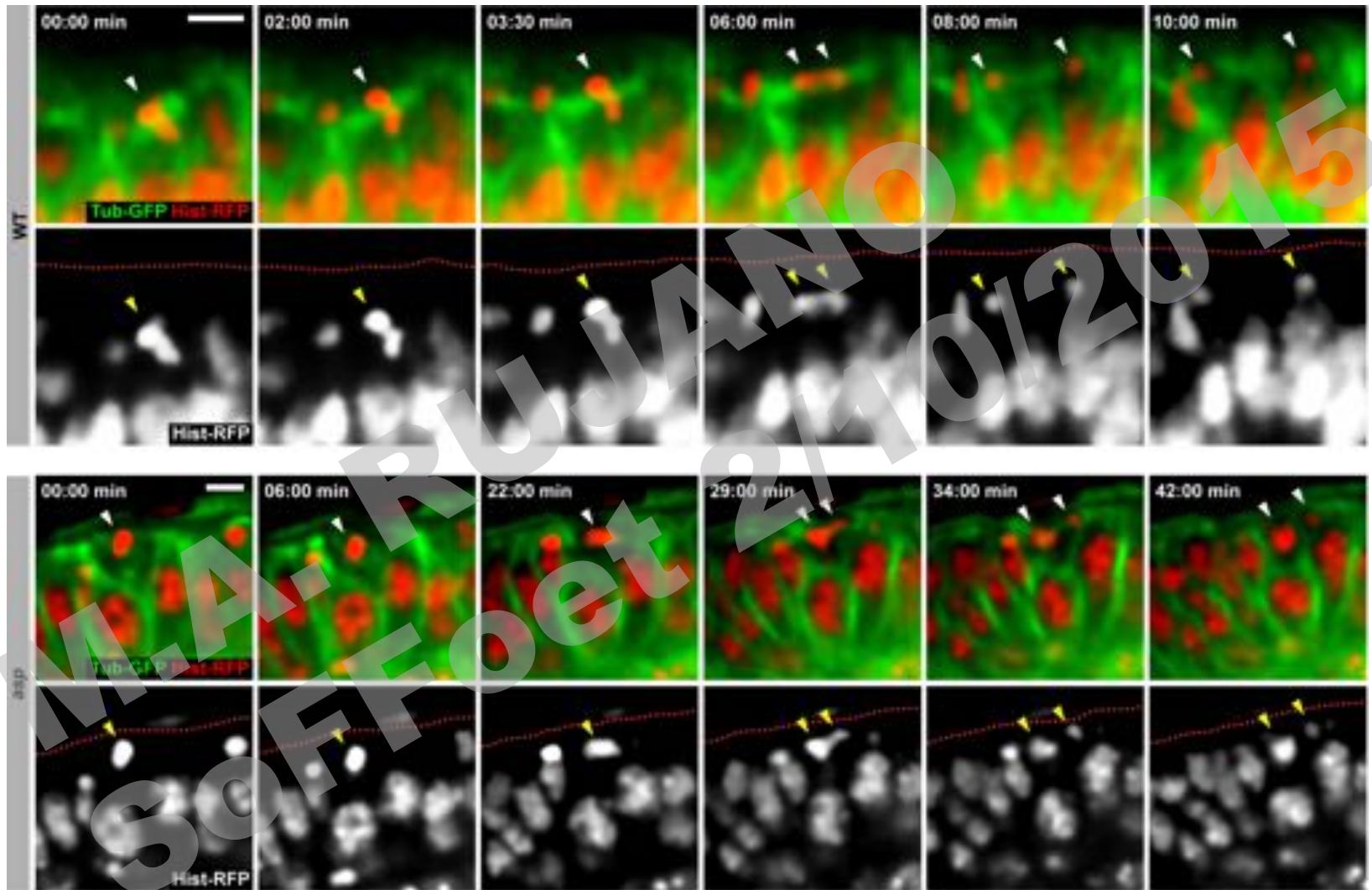
Epithelial polarity is not affected in *asp* tissue



Mitotic spindle orientation changes prematurely in *asp* NE cells



Chromosome segregation defects in mitotic *asp* NE cells



Summary of defects in *asp* NE that lead to “small brain phenotype”

Defects in chromosome segregation

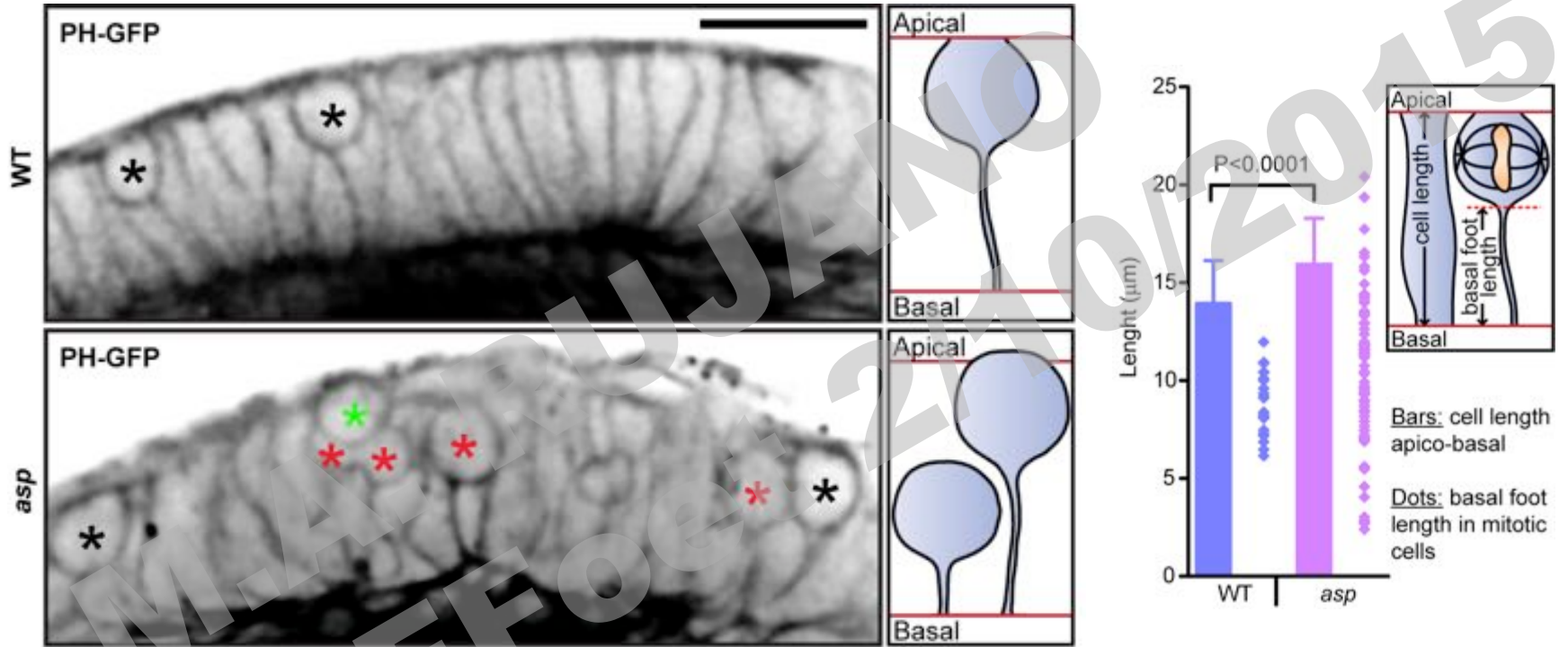
- Aneuploidy
- Cell death

Defects in mitotic spindle

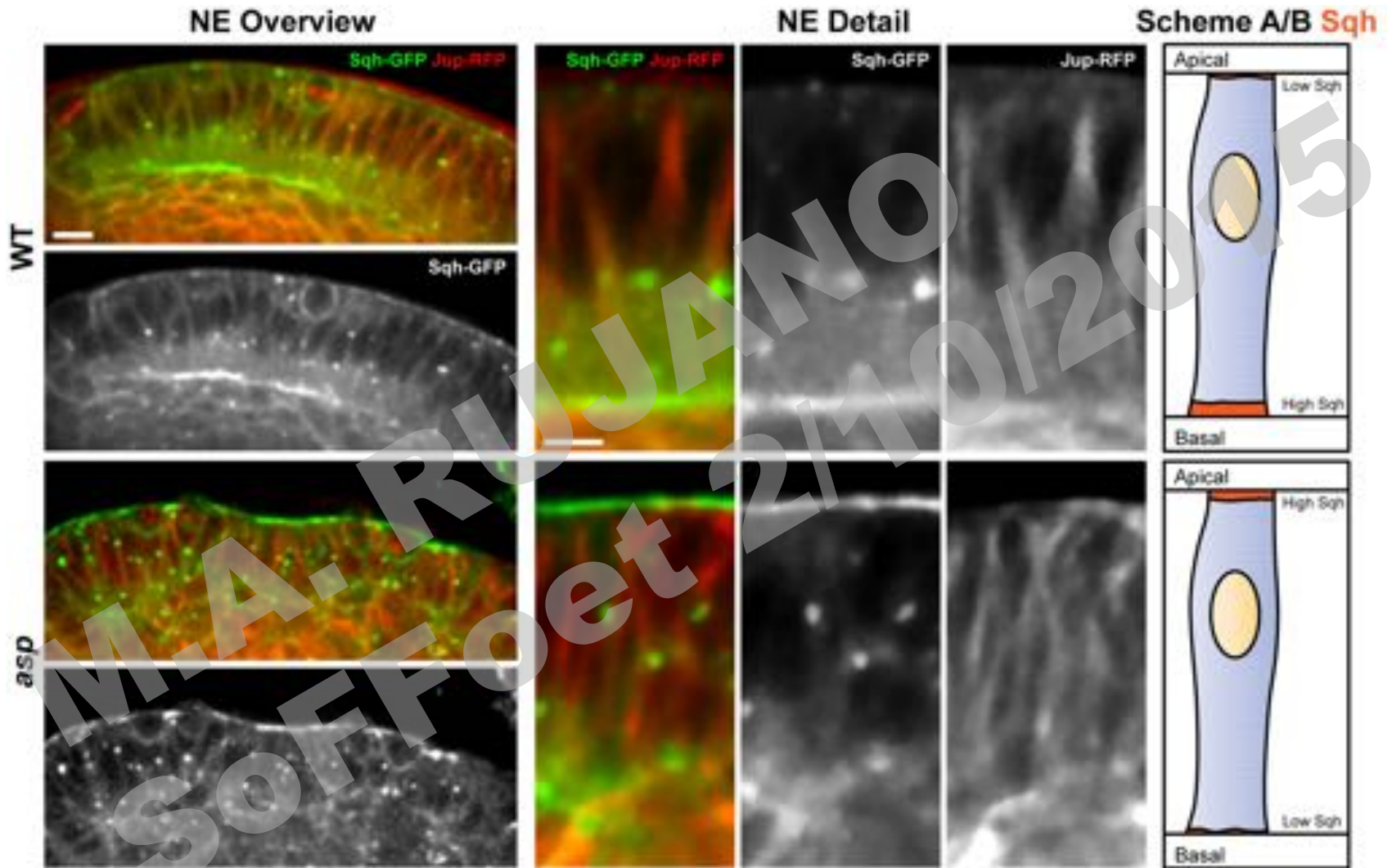
- Focusing
- Spindle orientation

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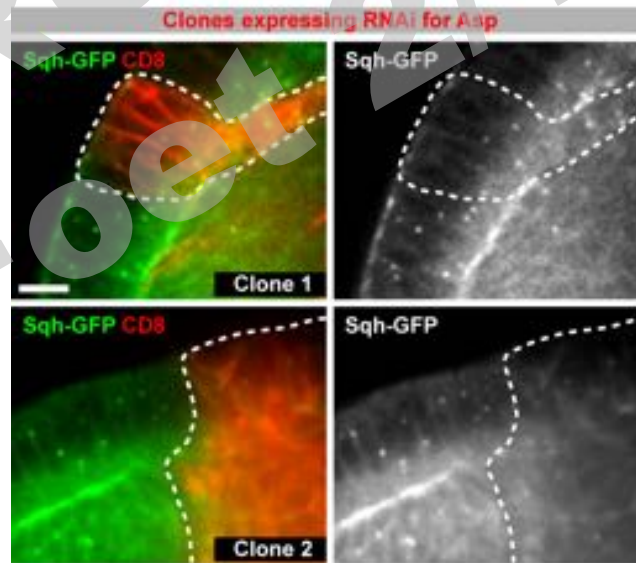
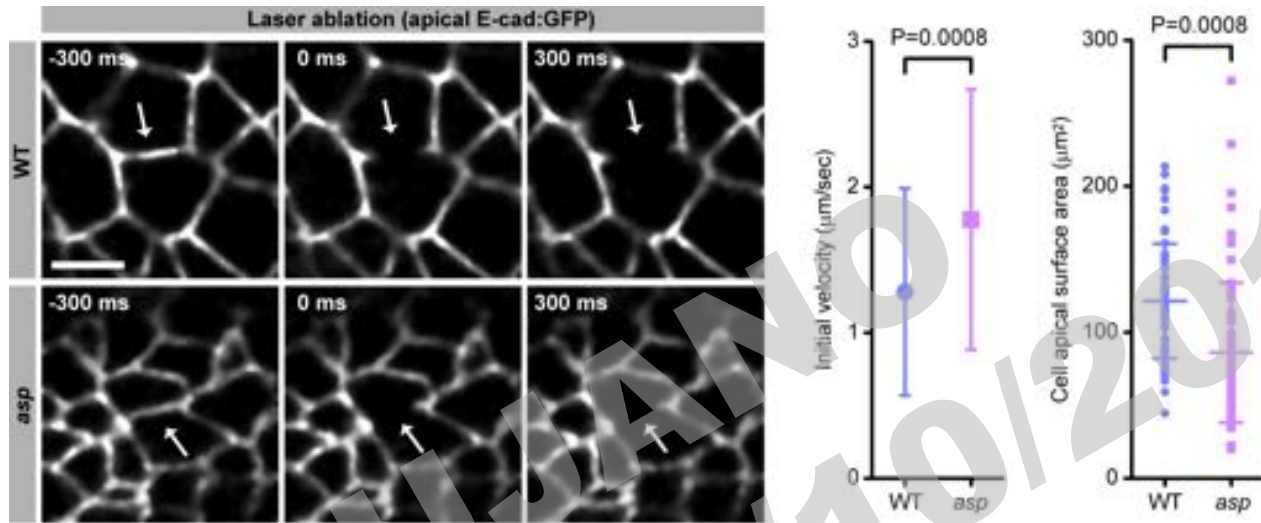
Interkinetic nuclear migration is impaired in *asp* NE



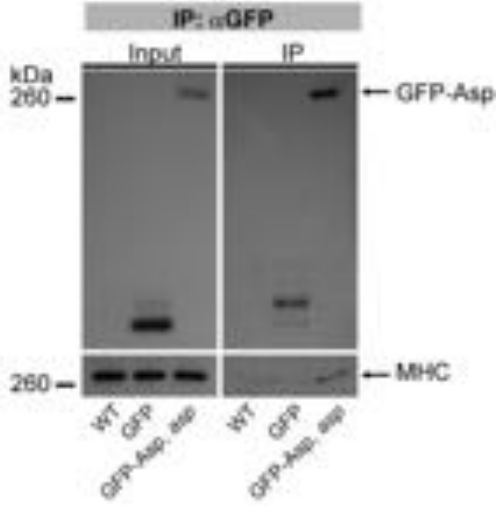
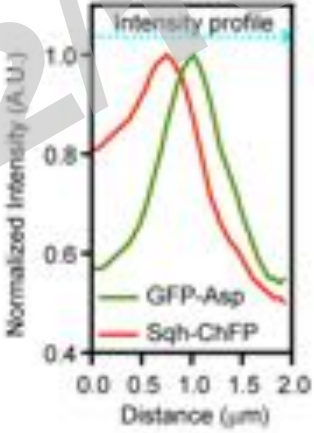
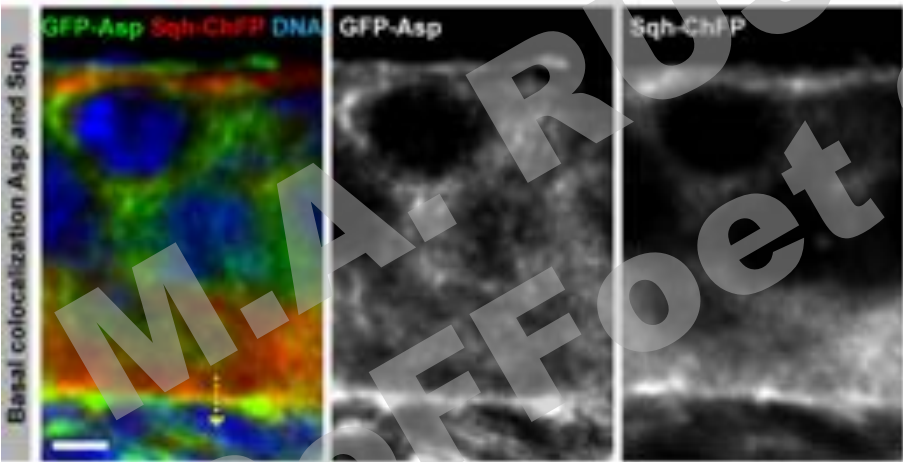
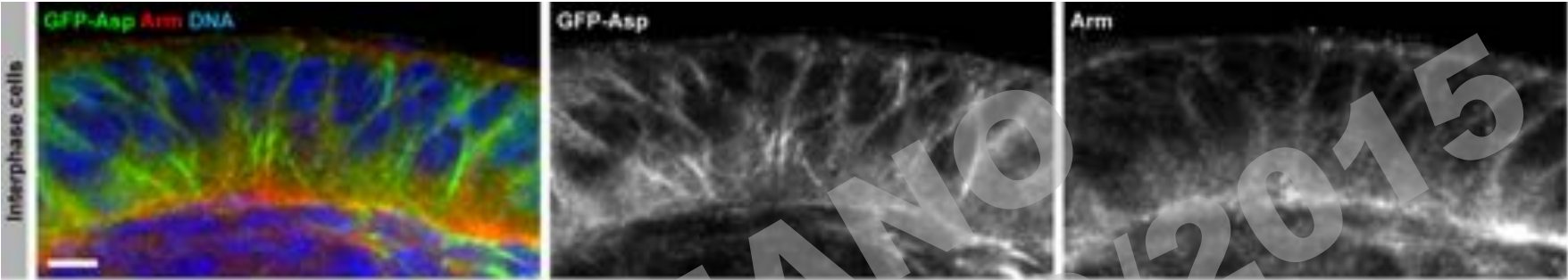
Myosin II distribution is impaired in *asp* neuroepithelium



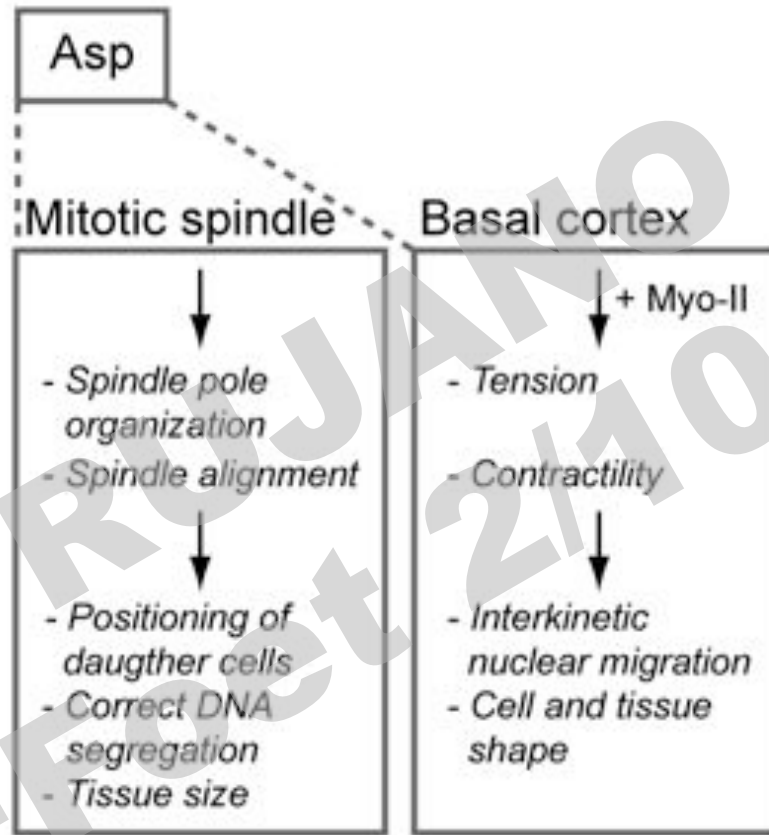
Apical tension and tissue cohesiveness are affected in *asp* mutants



Asp associated with the basal cortex and interacts with Myosin II



Asp regulates neuroepithelium morphogenesis



Neuroepithelium organization and integrity

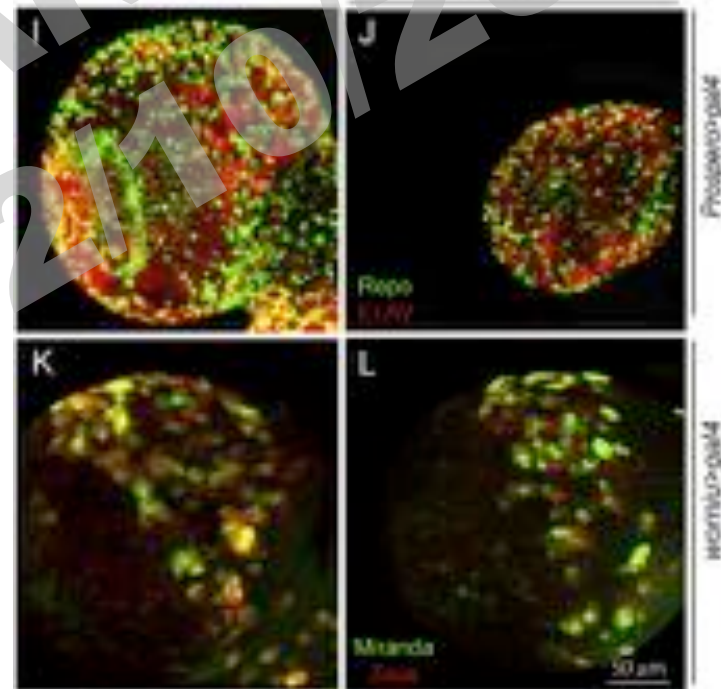
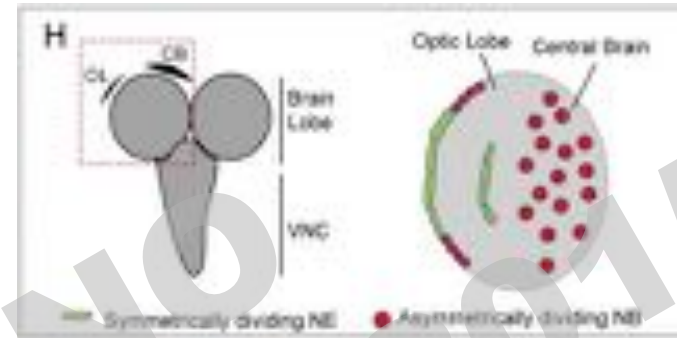
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Drosophila as a model to study other neurodevelopmental disorders

Mutations in KATNB1 cause complex cerebral malformations by disrupting asymmetrically dividing neural progenitors
Mishra-Gorur K., et al. Neuron. 2014.

Using a fly model model:

- Supernumerary centrosomes
- Spindle abnormalities during mitosis
- Delay in cell cycle progression
- Reduced cell numbers



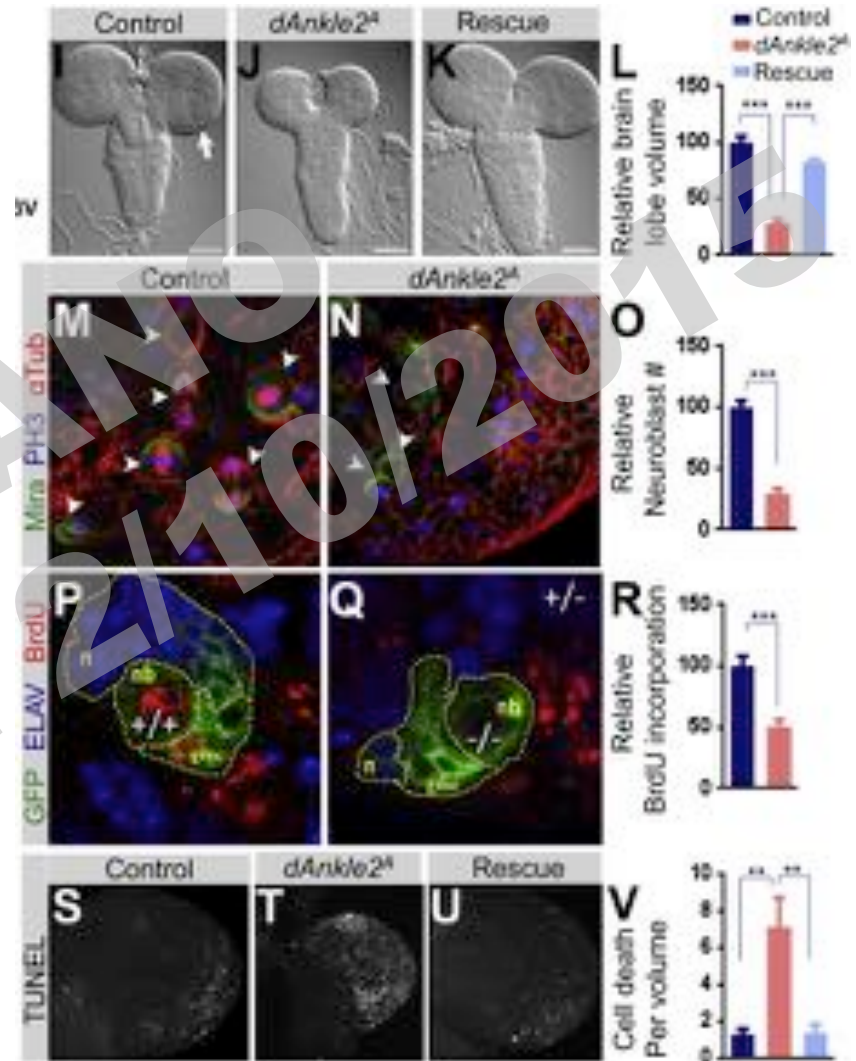
Drosophila as a model to study other neurodevelopmental disorders

A Drosophila Genetic Resource of Mutants to Study Mechanisms Underlying Human Genetic Diseases

Yamamoto S., et al. Cell. 2014.

Using a fly model model (ANKLE2):

- Reduction in neural stem cell number
- Reduced proliferation
- Less progeny produced
- Increased apoptosis



Acknowledgements

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