

Génétique et mécanismes physiopathologiques des MCPH



Réunion SOFOET 5 Juin 2015

Sandrine Passemard

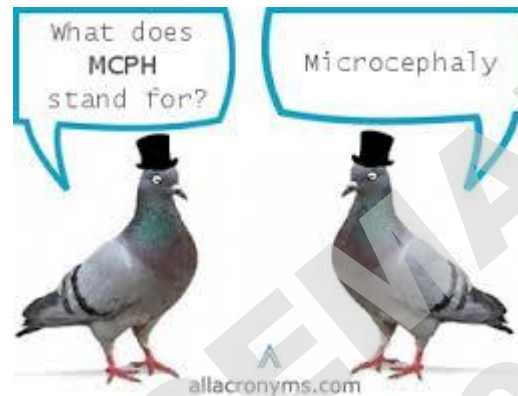
Département de Génétique

Inserm U1141

Hôpital Robert Debré

Paris

MCPH: De quoi parle-t-on ?



Autosomal recessive primary microcephaly

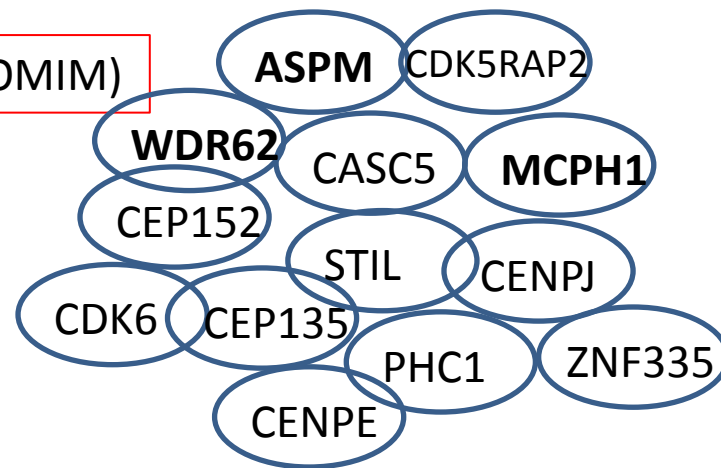
Microcephaly primary hereditary

13 Loci, 13 gènes aujourd'hui (OMIM)

Microcephalia vera

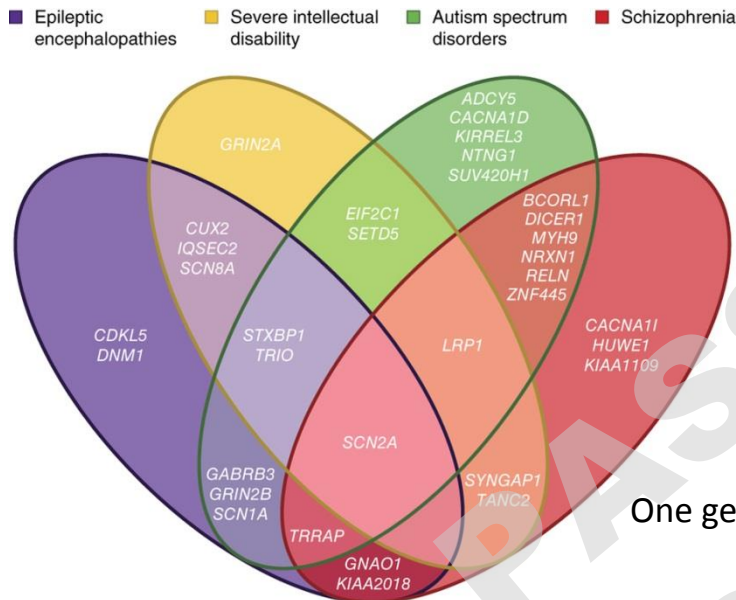
Microcephalie & troubles de migration

Microcephalie & petite taille



la génétique repousse les limites phénotypiques ...

Un gène, plusieurs phénotypes ...



One gene, many neuropsychiatric disorders: lessons from Mendelian diseases.
Xiaolin Zhu & David B Goldstein, Nature Neurosciences 2014

Un phénotype, plusieurs gènes ...

Quid des MCPH ????

Quelles sont les limites cliniques/moléculaires de l'entité MCPH ?

Microcephaly & dwarfism ?

Seckel, MOPD2, Meyer Gorlin ?

MCPH6 = SCKS4

MCPH9 = SCKS5



CDC6 (Obs. P Sarda)

Quelles sont les limites cliniques/moléculaires de l'entité MCPH ?

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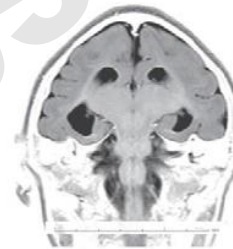
Seckel, MOPD2, Meyer Gorlin ?

MCPH6 = SCKS4

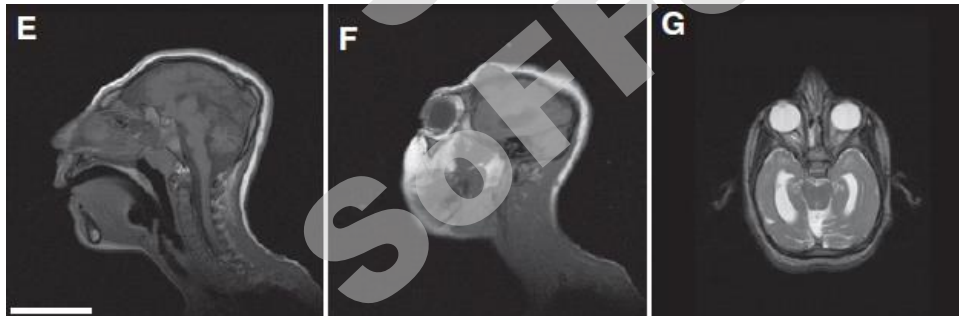
MCPH9 = SCKS5

Microcephaly & lissencephaly ?

Microlissencephaly ? **NDE1**



Barkircioglu & Woods, AJHG 2011



Alkuraya & Walsch, AJHG 2011

Quelles sont les limites cliniques/moléculaires de l'entité MCPH ?

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TUBGCP6

PLK4

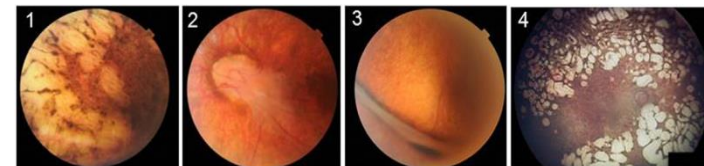
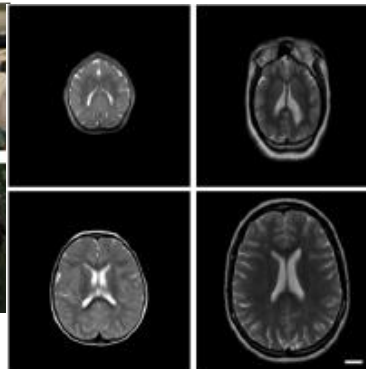
TUBGCP4

Microcephaly & Eye ?

Chorioretinopathy & Microcephaly (Type 1, 2, 3) ?

Chrorioretinal dysplasia & microcephaly ?

KIF11



Martin, Nat genet 2014

Scheidecker, AJHG 2014

Quelles sont les limites cliniques/moléculaires de l'entité MCPH ?

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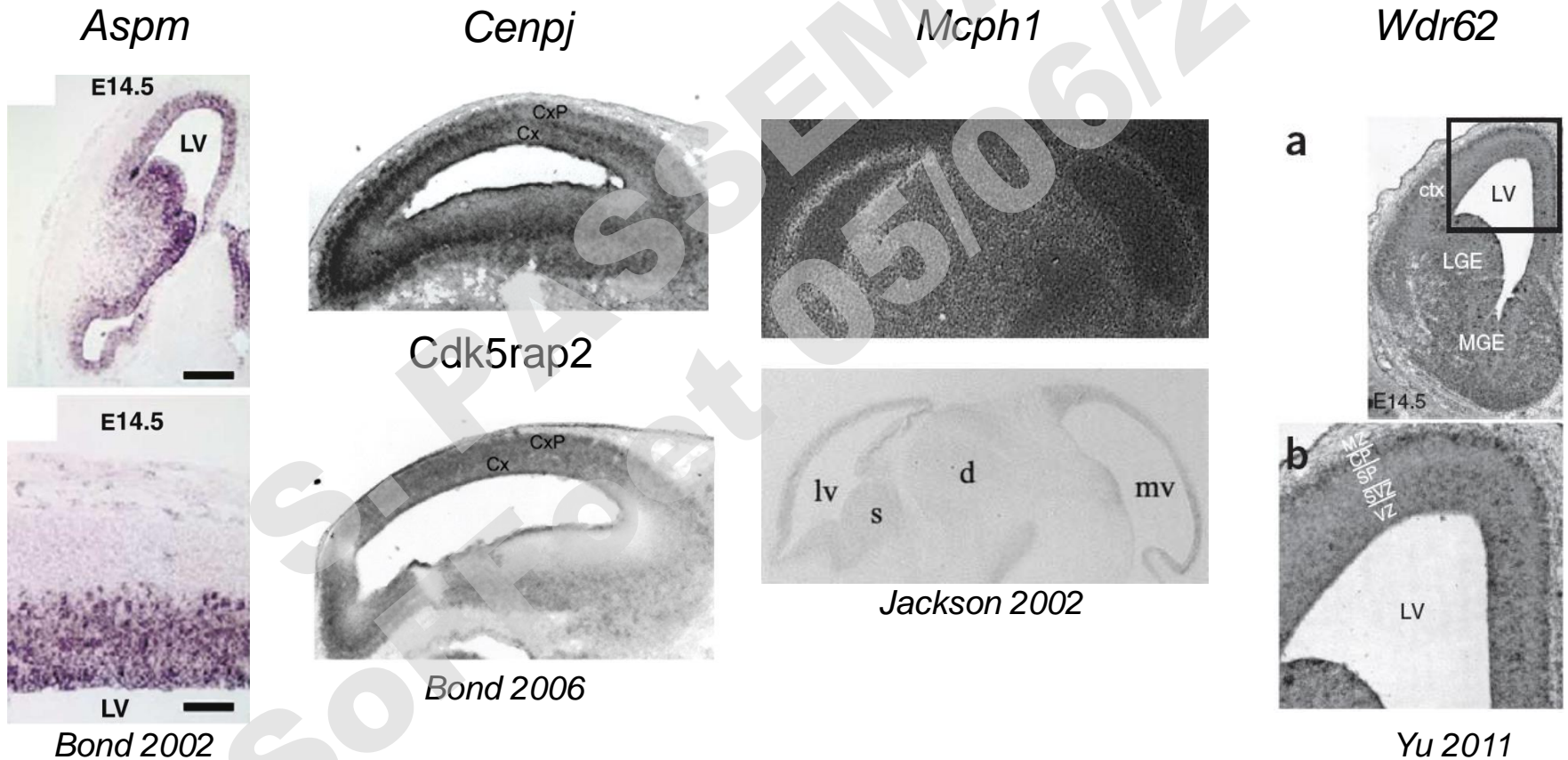
Mécanismes physiopathologiques proches des MCPH

Microcephaly & DNA repair deficiency?

Fanconi Anemia, Nijmegen syndrome ...

Gènes MCPH: mécanismes communs ???

Expression dans la zone ventriculaire pendant la neurogénèse chez la souris

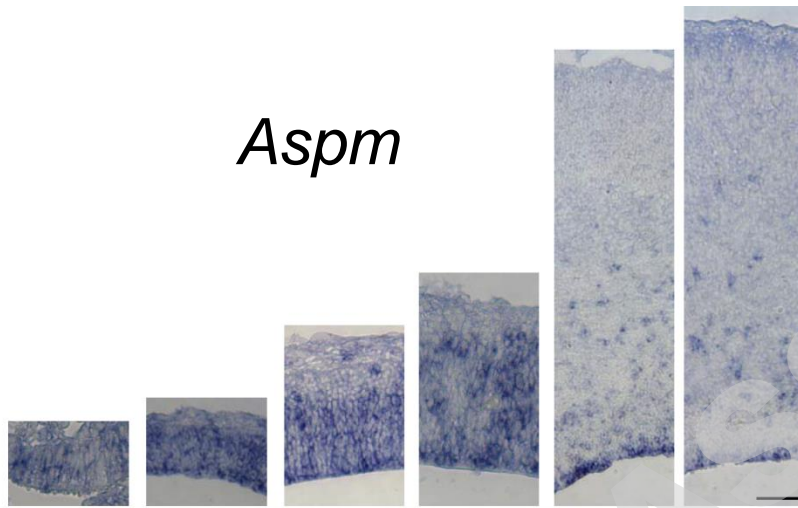


E13,5-E15,5

Gènes MCPH: mécanismes communs ???

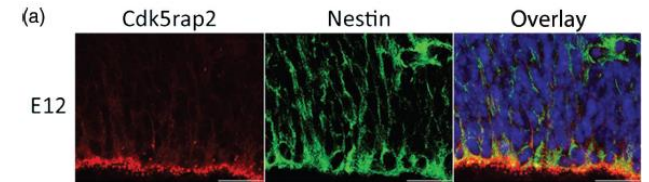
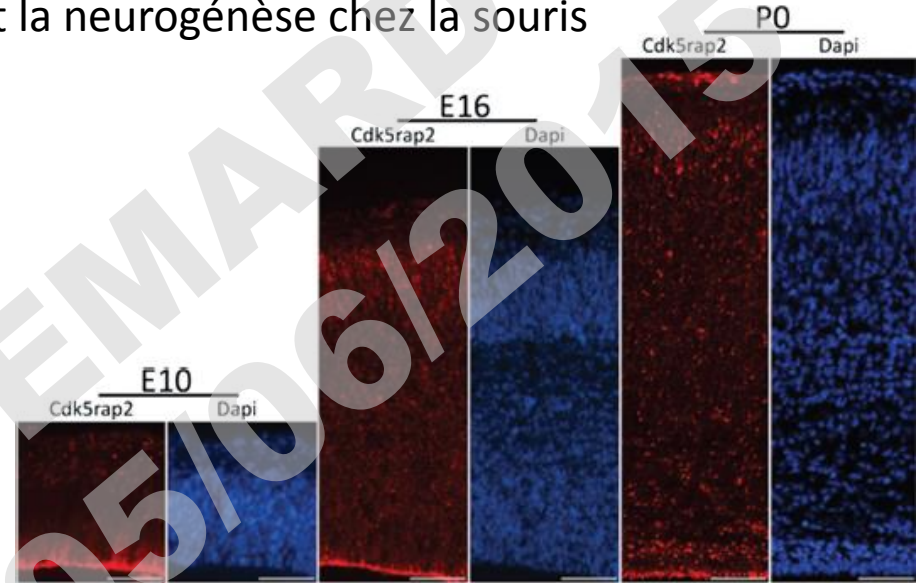
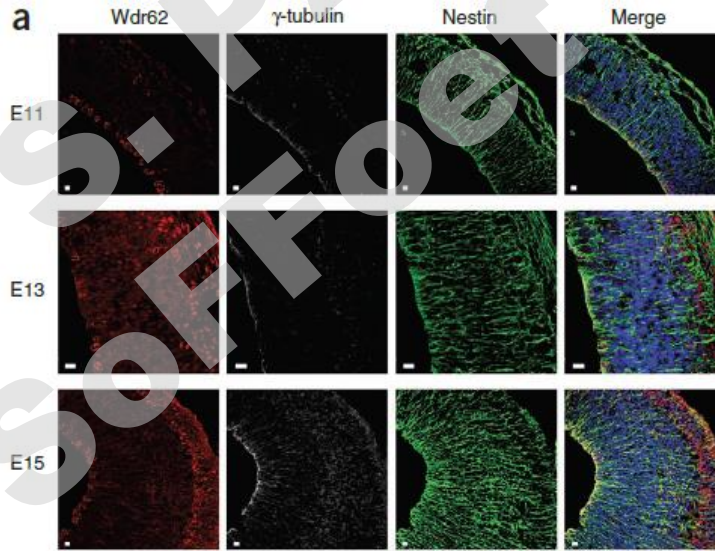
Expression dans la zone ventriculaire pendant la neurogénèse chez la souris

Aspm

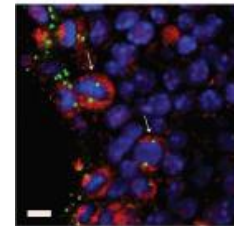


E8.5 E9.5 E11.5 E13.5 E15.5 E17.5

Fish, PNAS 2006

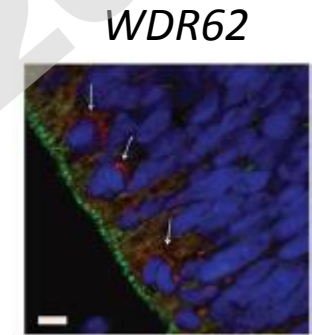


Issa, cerebral cortex 2013



Nicholas, Nat Genet 2010

Et chez l'homme ???



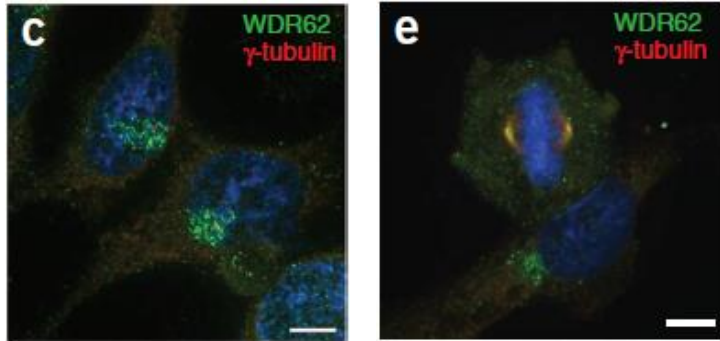
Nicholas, Nat Genet 2010

MCPH1

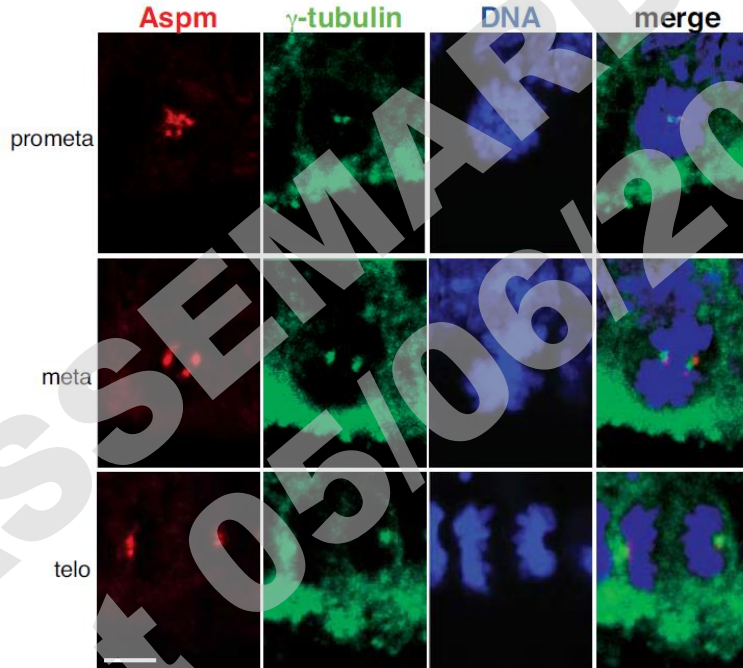
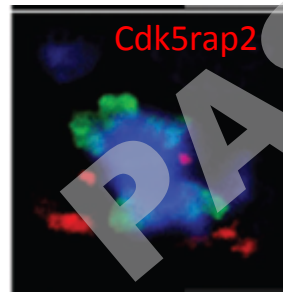
Issa, cerebral cortex 2013

Gènes MCPH: mécanismes communs ???

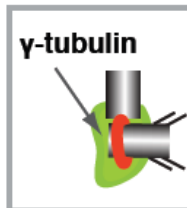
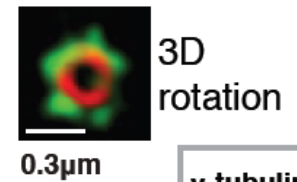
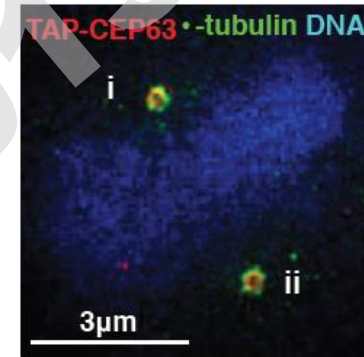
Localisation sub-cellulaire nucléaire en interphase, au centrosome pendant la mitose



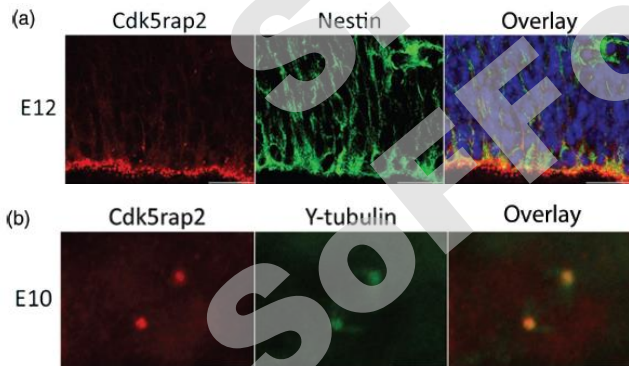
Nicholas, Nat Genet 2010



Fish, PNAS 2006



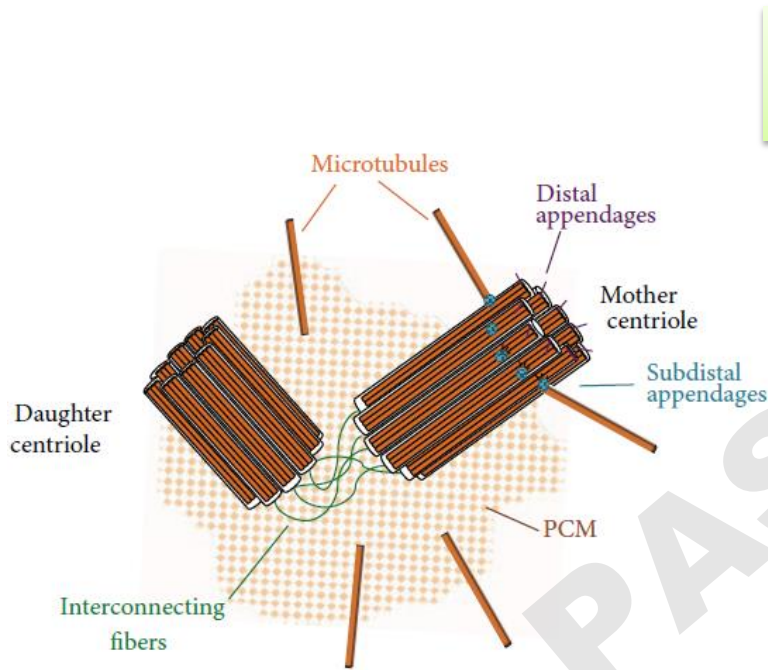
Sir, 2011 Nat Genet



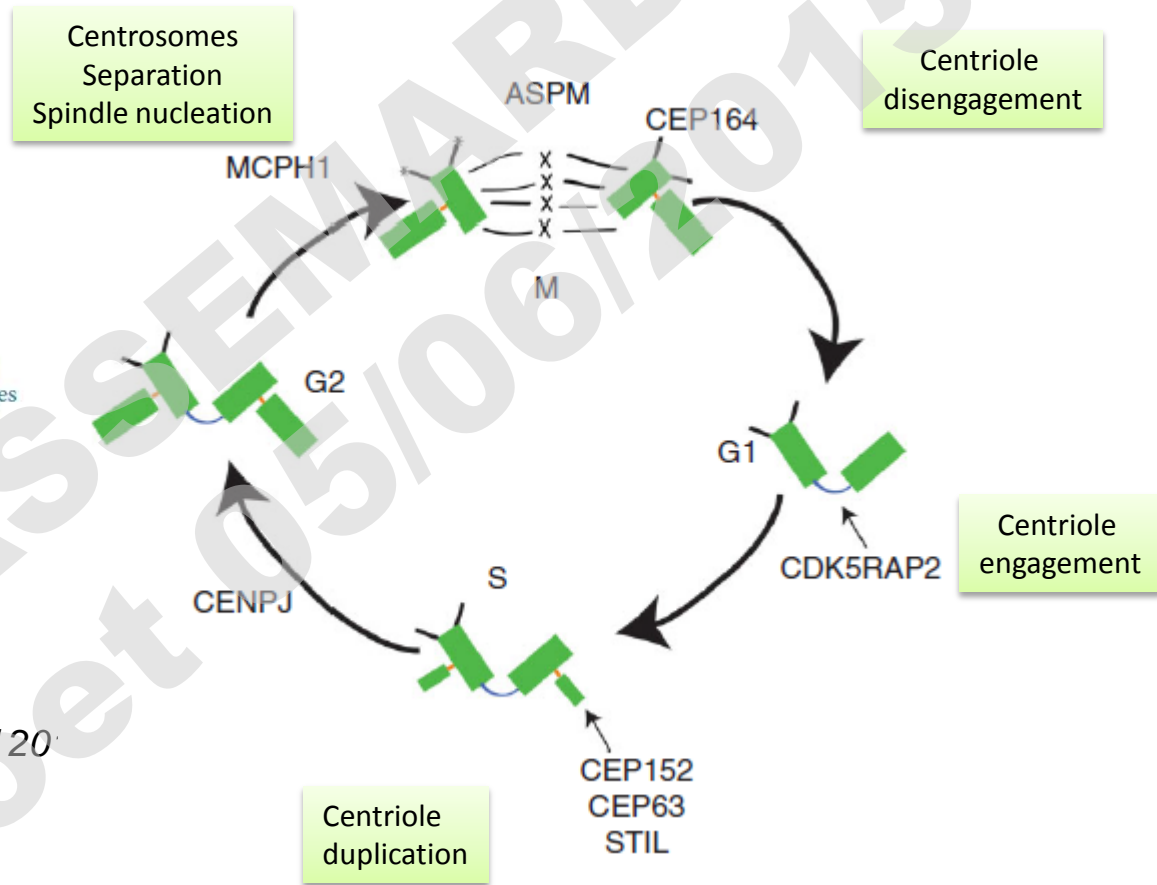
Issa, cerebral cortex 2013

Gènes MCPH: mécanismes communs ???

Localisation sub-cellulaire

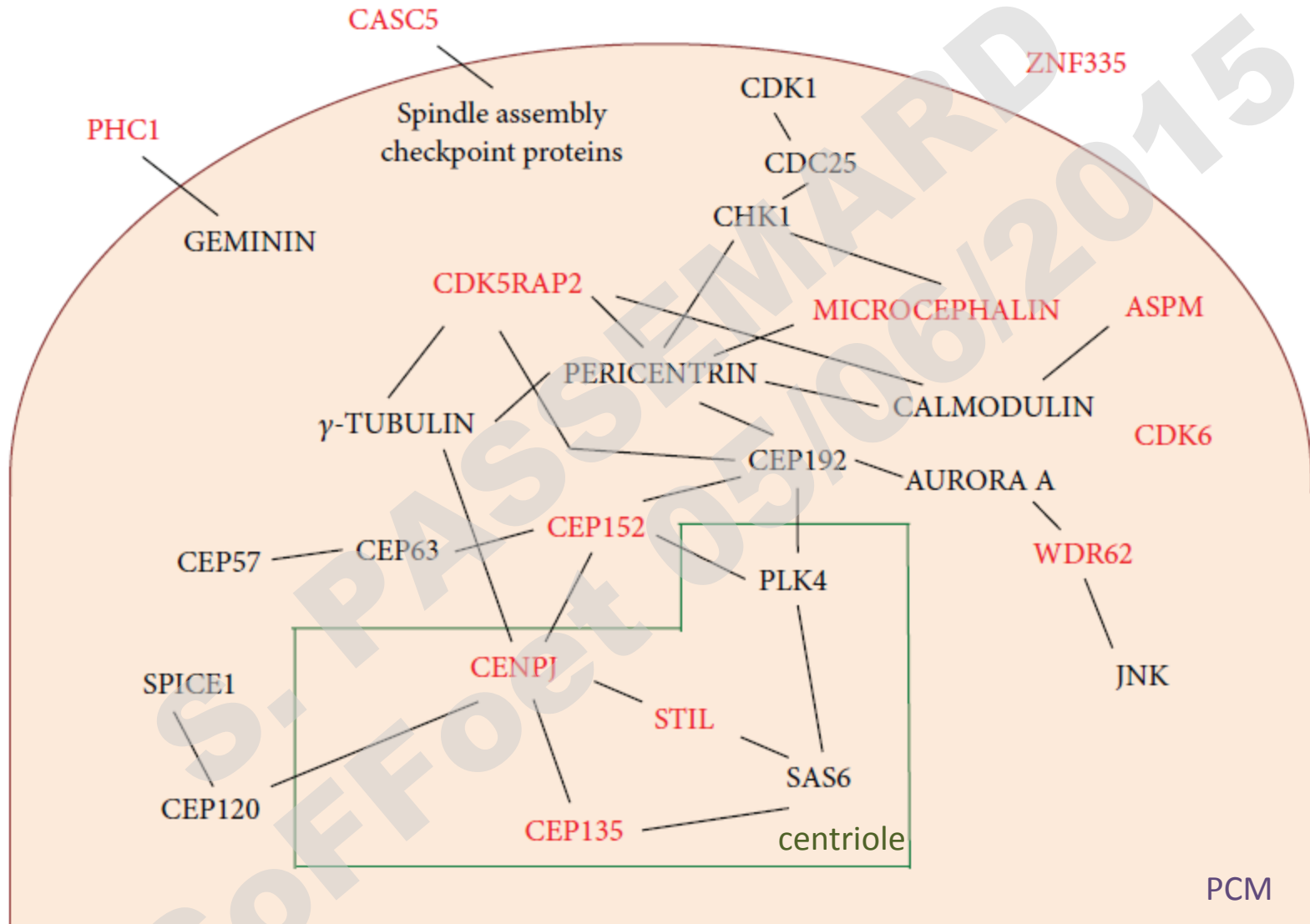


Barbelanne, *Biomed research international* 2010

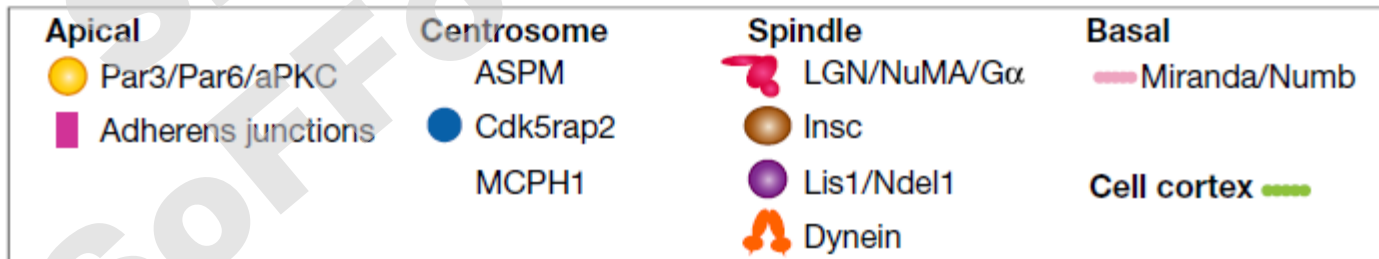
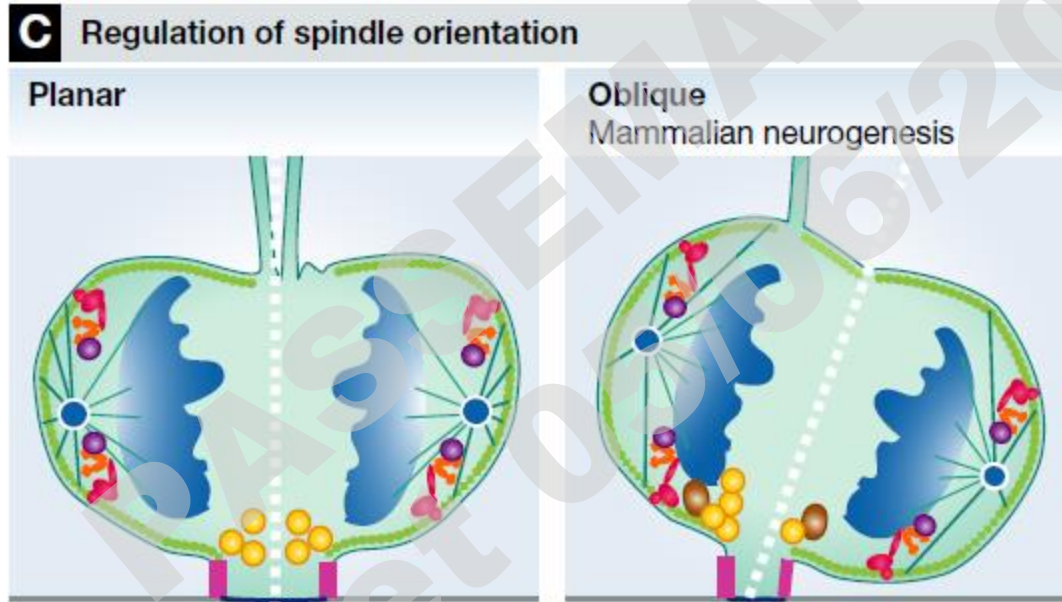


Gilmore, *WIREs Dev Biol* 2013

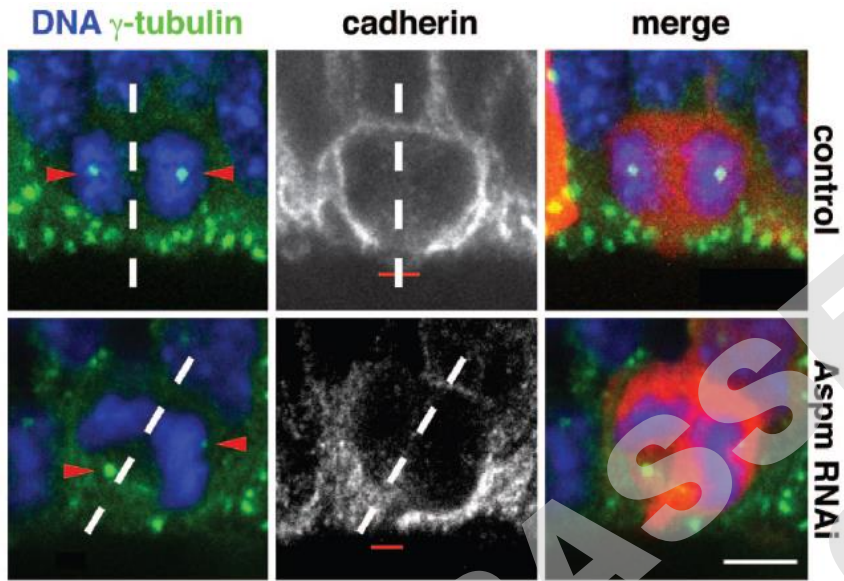
MCPH: un réseau ...



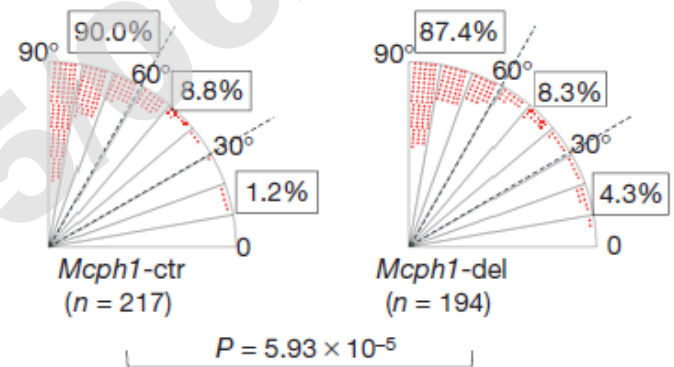
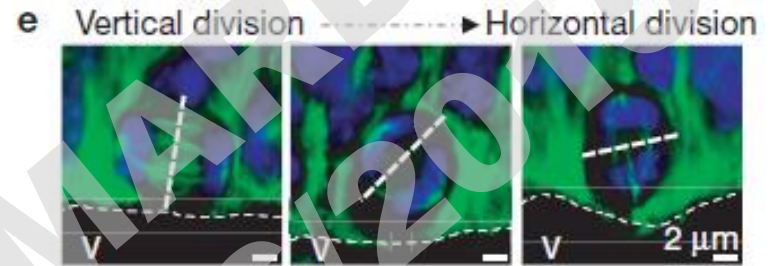
Gènes MCPH: mécanismes communs ???



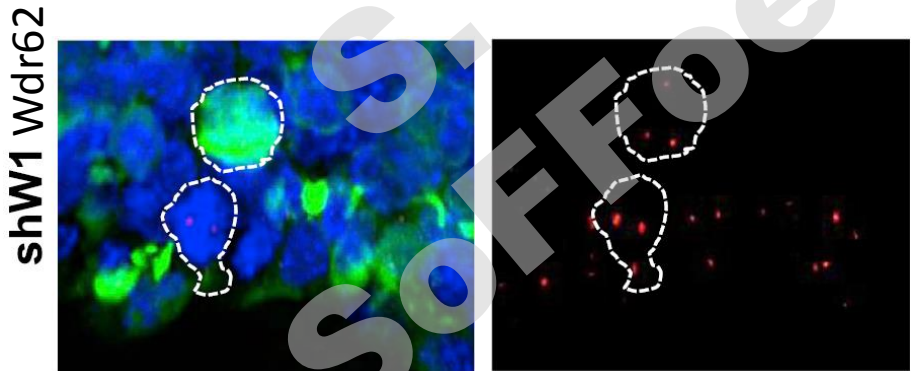
Rôle des gènes MCPH ???



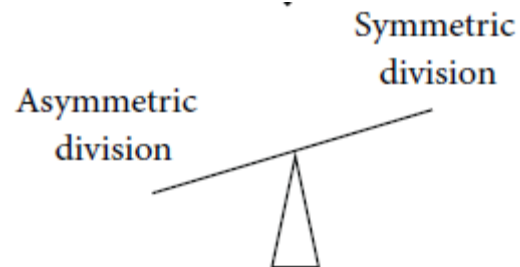
Fish, PNAS 2006

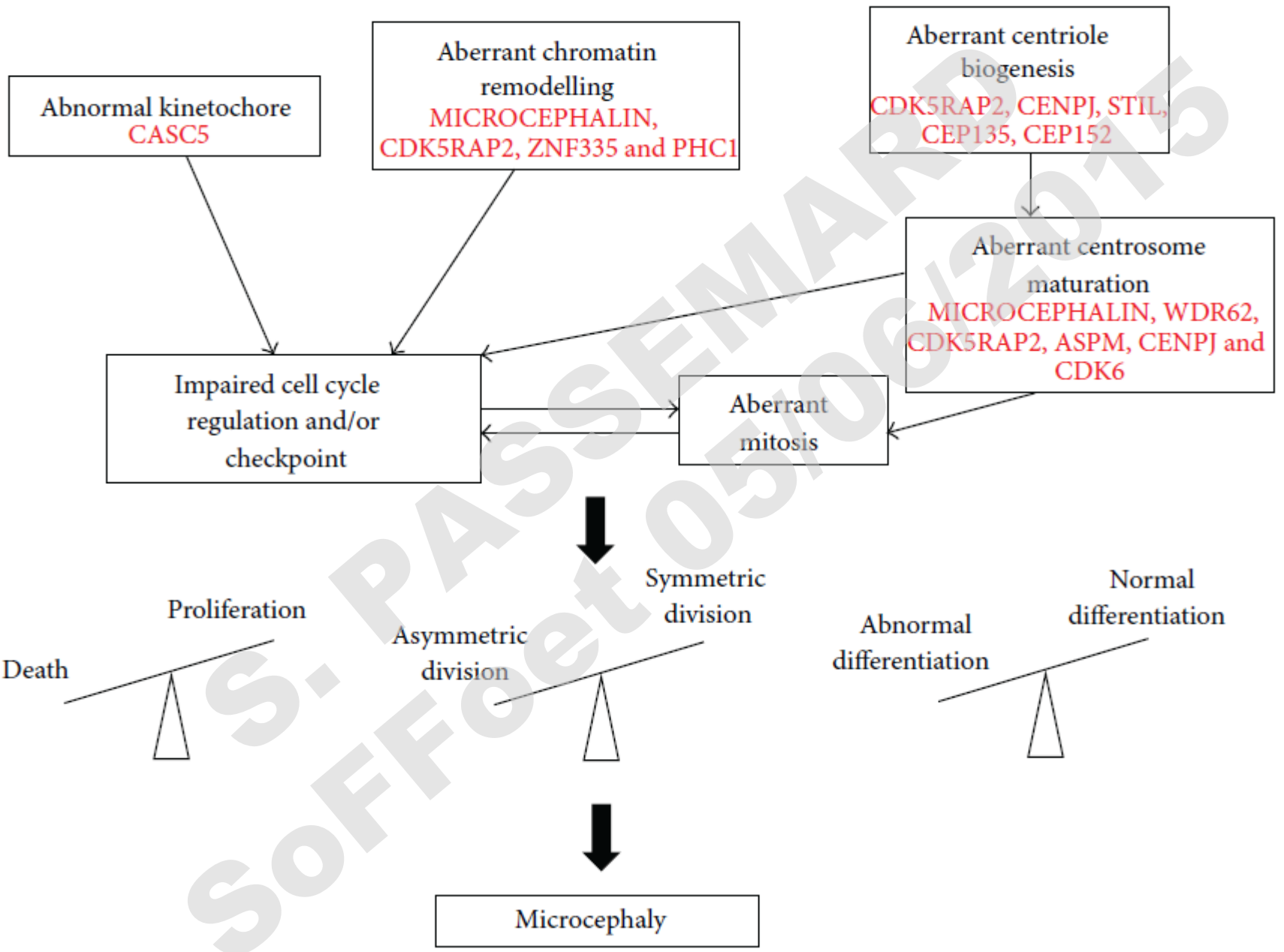


Gruber, Nat cell biol 2011



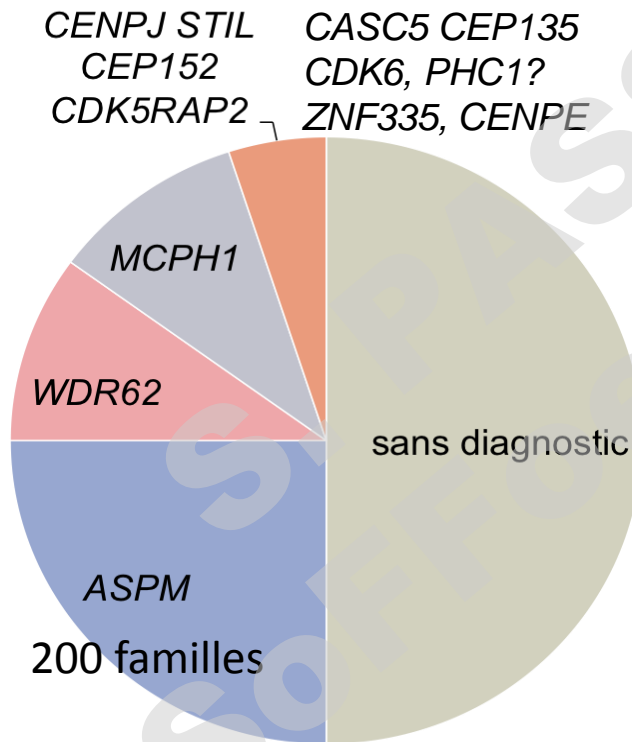
Xu, cell report 2014





Quels sont les points communs entre ces gènes ???

La majorité des mutations : nonsense ou frame shift
(Faux sens pour WDR62)



Phénotype Microcéphalie bien sûr
Mais quelle « microcéphalie »?

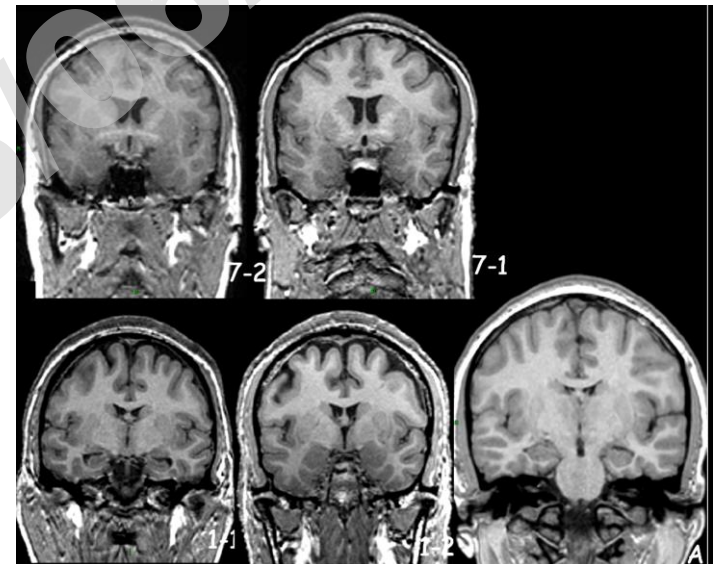
Quel est le phénotype MCPH chez l'enfant ?

Microcephalia vera



ASPM

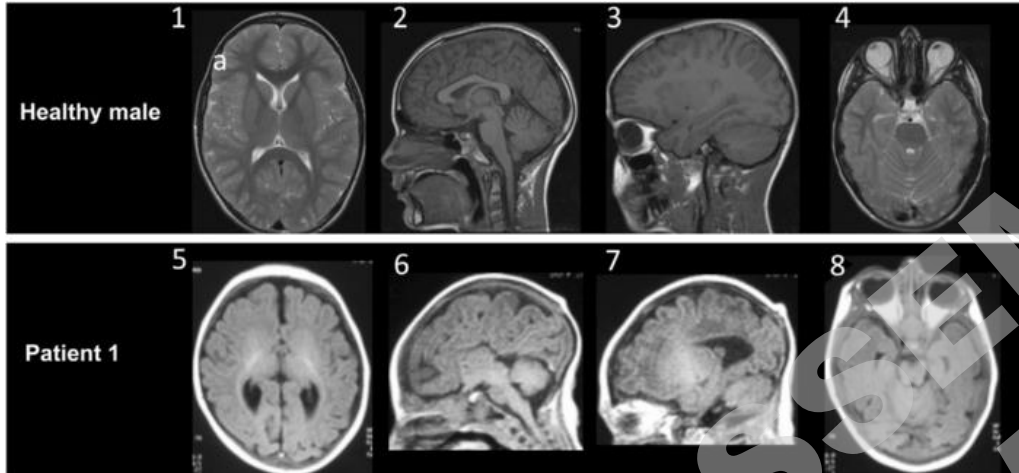
IRM



Déficiência intellectuelle légère à modérée
Epilepsie facilement traitable

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Microcephalia vera

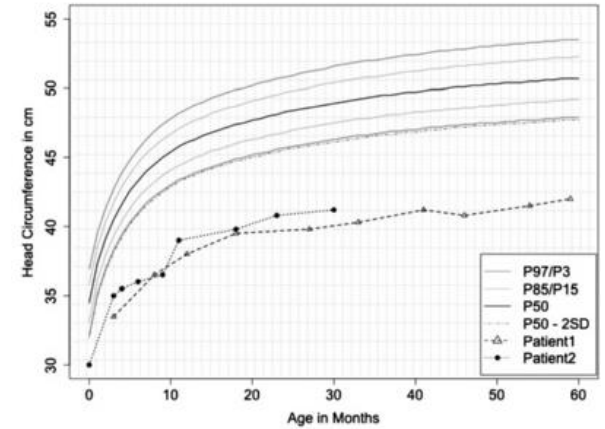


Issa, ojrd 2013

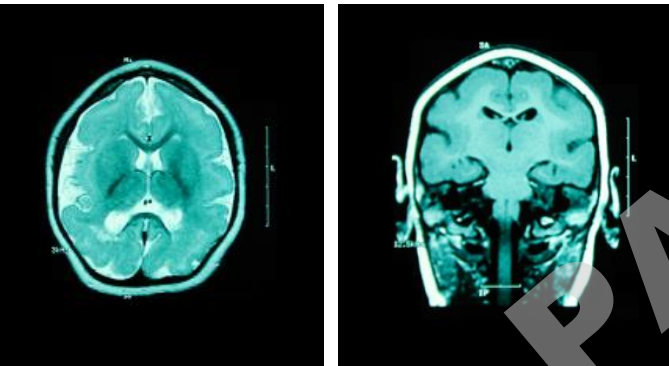


Tan, Brain dev 2013

CDK5RAP2



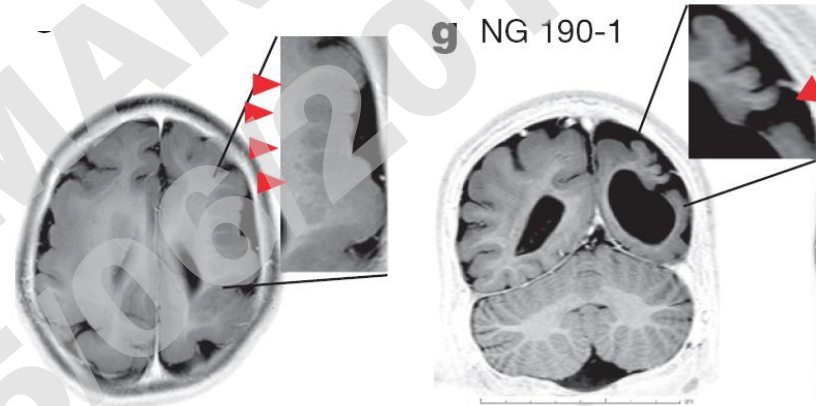
Quel est le phénotype MCPH chez l'enfant?



Nicholas, Nat Genet 2010



Troubles de migration
Microlissencéphalie



WDR62

Bilguvar, Nature, 2011

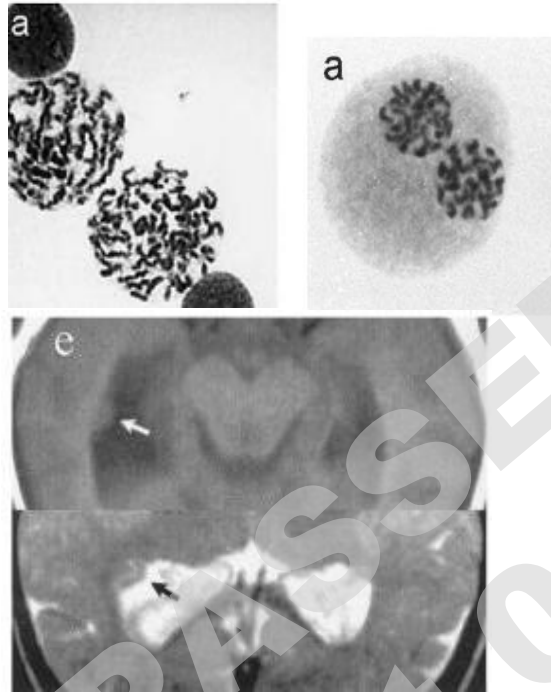
SOFFOET 05062015

Quel est le phénotype MCPH chez l'enfant?

Troubles de migration



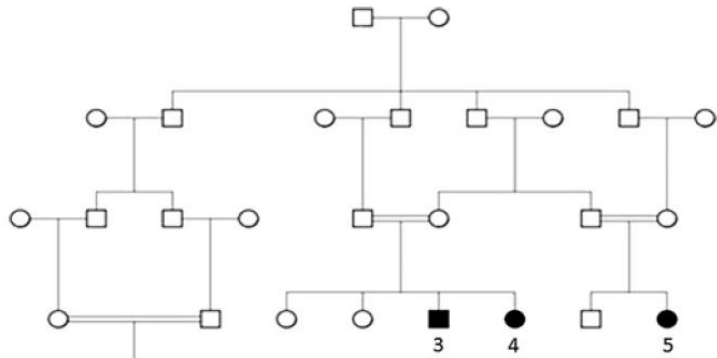
Neizel et al, AJHG 2002



Trimborn et al, AJHG 2004

MCPH1

Quel est le phénotype MCPH chez l'enfant?



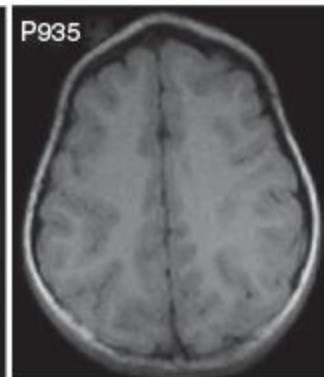
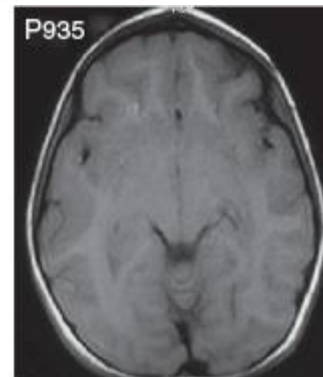
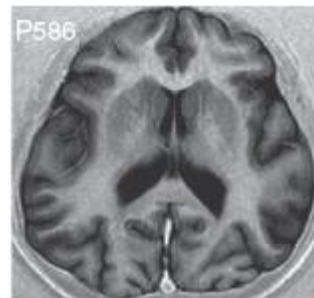
Seckel

1,4kg, 38,7cm, 30,25 cm
 1,5kg, 39cm, 30cm

CEP152



CENPJ

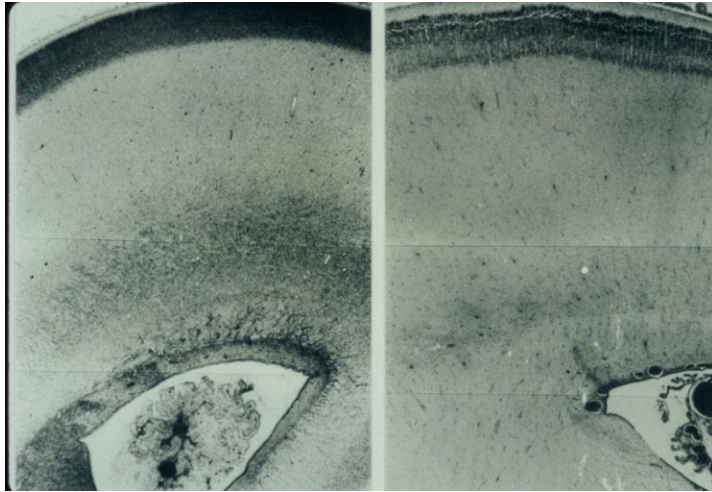


Arabie Sahoudite

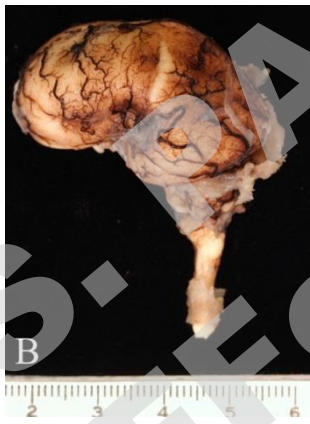
Al Dosari, jmg 2010

kalay, nat genet 2011

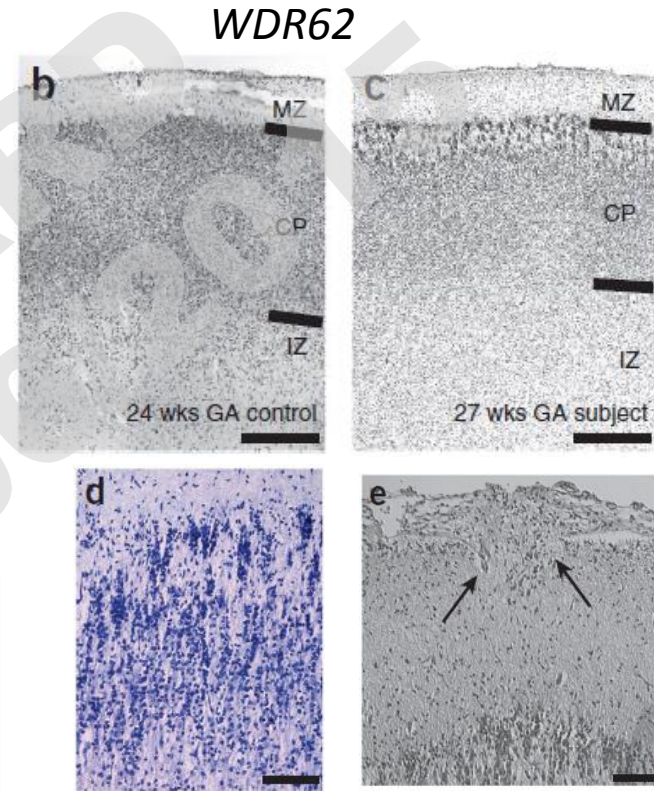
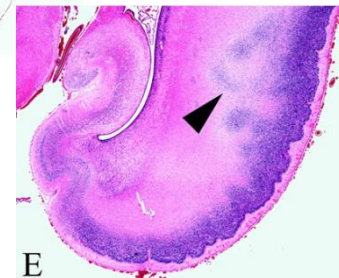
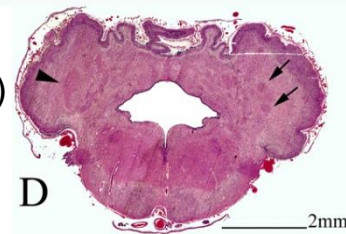
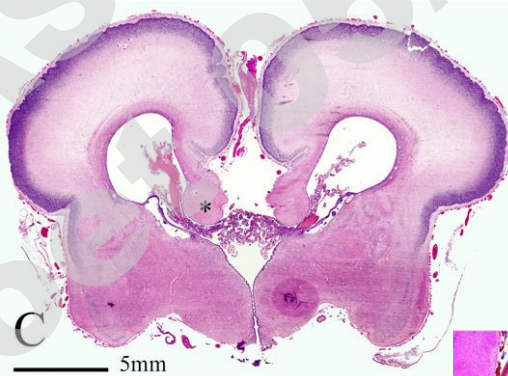
Quel est le phénotype MCPH chez le fœtus?



Evrard, Gadisseux 1989



Brain: 21g (vs 160g)



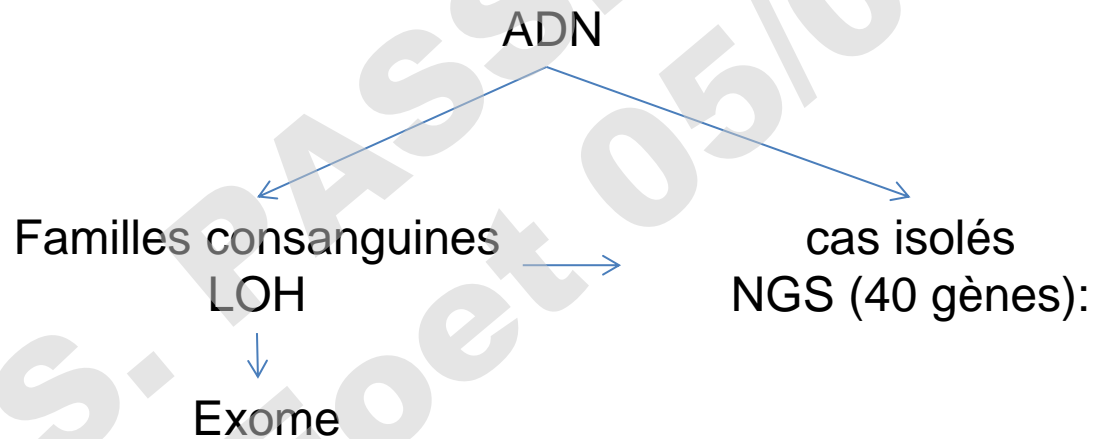
Yu, Nat Genet 2010

ETUDES NECESSAIRES ...

Collaboration A. Laquerrière et membres de la SOFOET

- équipe de Génétique de Robert Debré
- INSERM U1141 P. Gressens

1. IDENTIFICATION MOLECULAIRE



Séverine Drunat

2. DESCRIPTION du PHENOTYPE



Annie Laquerrière
Homa Adle
Pierre Gressens
Alain Verloes
Séverine Drunat
Fabien Guimiot



Et tous les membres de la SOFOET!