

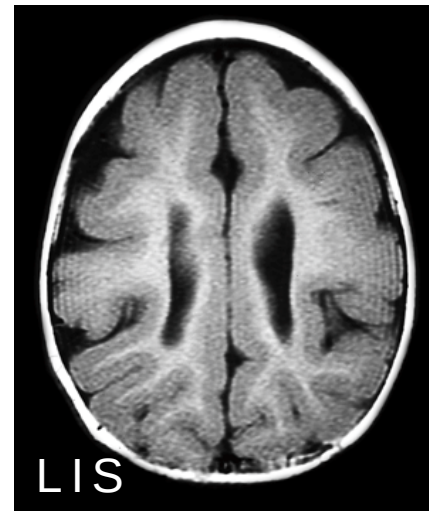
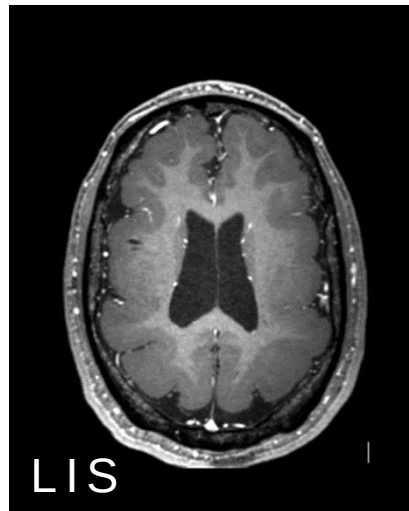
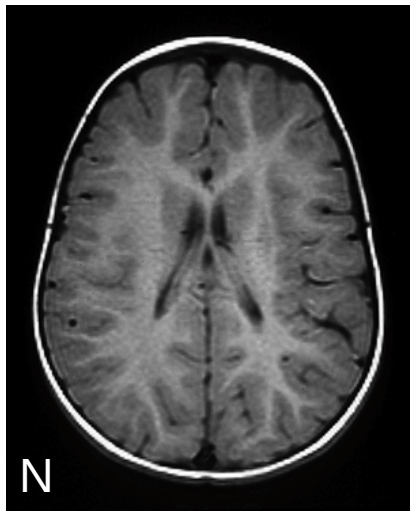
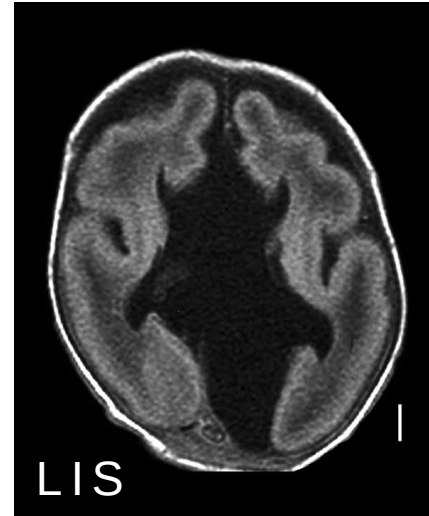
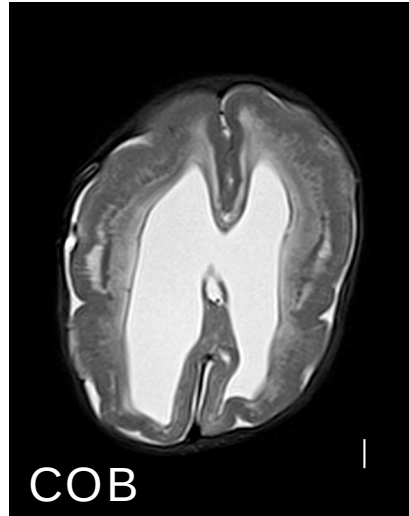
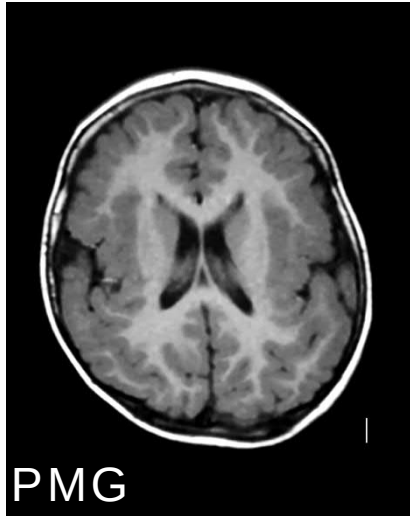
Lissencephaly

Nataliya Di Donato, MD

nataliya.didonato@uniklinikum-dresden.de

1. Clinical forms
2. Mutational landscape
3. Genotype-phenotype correlation
4. Genetic counseling
5. Clinical management

How many images with lissencephaly?



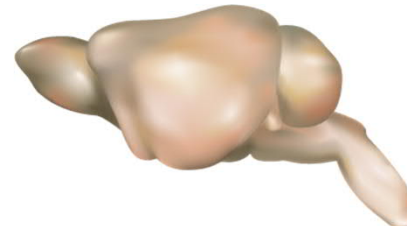
“lissos” – smooth “enkephalos” – in the head



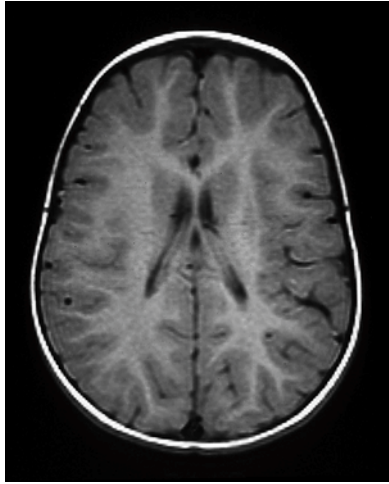
“walnut” versus “hazelnut”



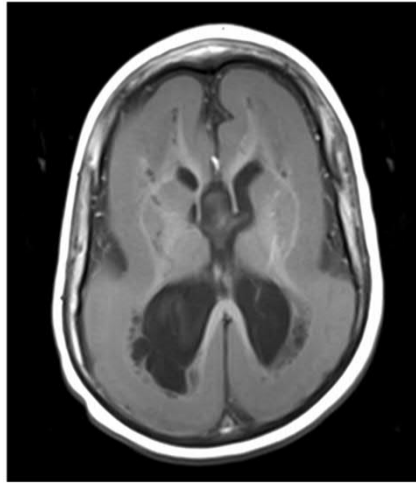
“human



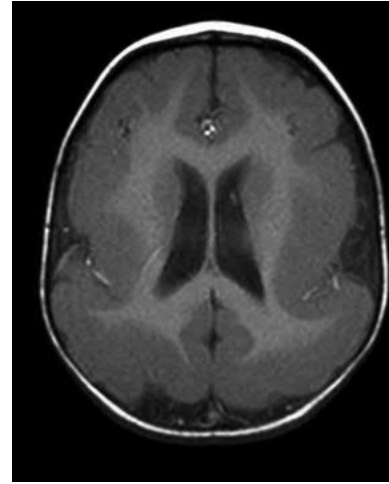
“mouse



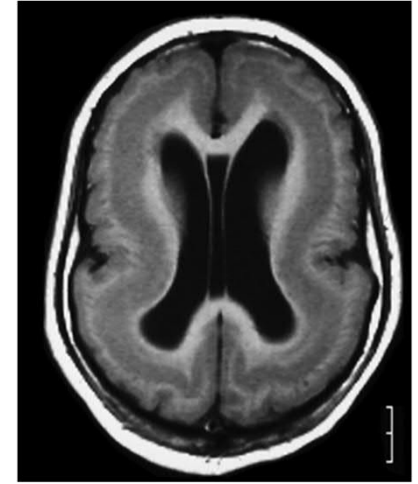
Normal



Agyria (AGY)



Pachygyria (PGY)

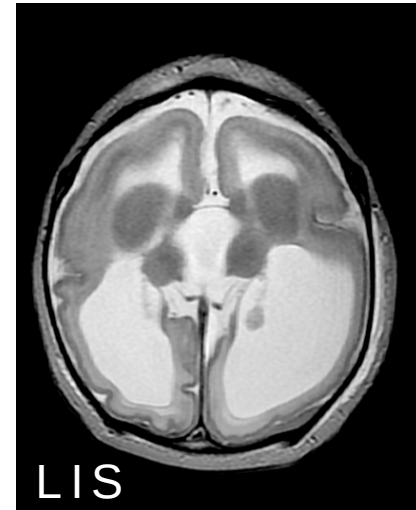
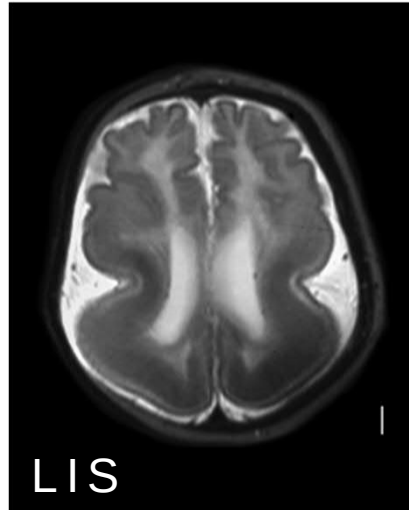
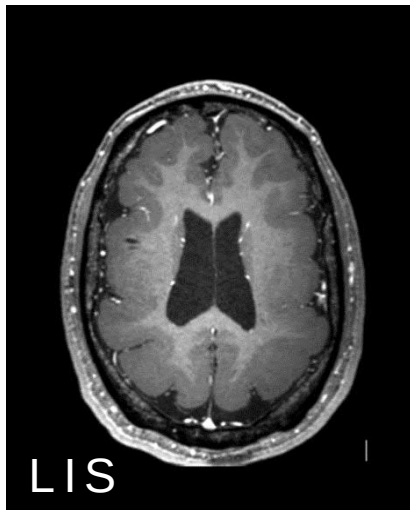
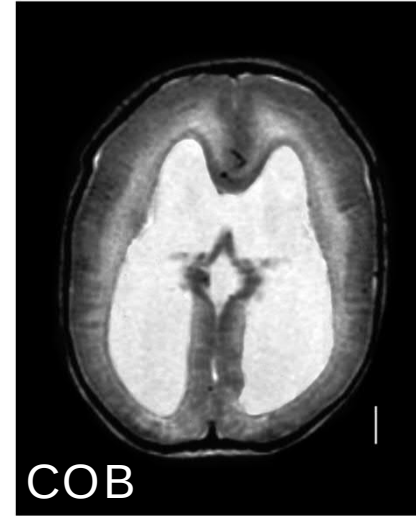
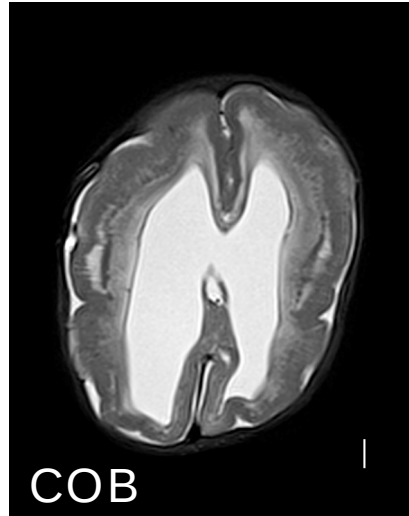
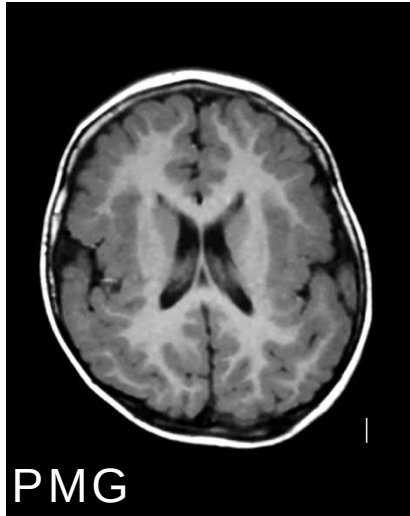


Band
Heterotopia

AGY-PGY defined as abnormally thick cortex with reduced or absent cerebral convolutions and smooth brain surface and gray-white border

SBH – abnormal bands of gray matter beneath a normally appearing cortex (although sulci may be very shallow)

LIS – reduced gyration with smooth surface and gray-white border.



21 LIS types based on MRI imaging

Lissencephaly types based on imaging	Häufigkeit	Vererbung
LIS with cerebellar hypoplasia, Agyria diffuse (thick or thin cortex)	4%	AD/AR
Classic thick lissencephaly		
Agyria diffuse	6%	AD/Xchr
Agyria-pachygyria p>a (mixed)	30%	AD
Agyria-pachygyria a>p (mixed)	<< 1%	Xchr
Pachygyria p>a (complete or partial)	13%	AD
Pachygyria a>p (complete or partial)	5%	Xchr/AD
Pachygyria p>a with non-cortical malformations ¹	5%	AD
Pachygyria a>p with non-cortical malformations	<< 1%	AD
Pachygyria-band a>p (complete or partial)	1%	AD/Xchr
Tubulinopathy-related dysgyria		
Dysgyria p>a (complete or partial)	11%	AD
Dysgyria a>p (complete or partial)	-	AD
Subcortical band heterotopia		
SBH diffuse thick (band >5 mm)	10%	Xchr
SBH diffuse thin (band <5 mm)	3%	Xchr
SBH partial p>a (band thick or thin)	3%	AD
SBH partial a>p (band thick or thin)	1%	Xchr
Thin undulating lissencephaly		
Pachygyria a>p thin with cerebellar hypoplasia ²	1%	AR
Pachygyria a>p thin with normal cerebellum	4%	AR
Pachygyria p>a thin with ACC, abnormal WM	1%	Xchr
Microlissencephaly (MLIS)		
MLIS with cerebellar hypoplasia (TUB features)	2%	AD / AR
MLIS with MOPD1	<<1%	AR
MLIS Barth type	<<1%	AR?

Major groups based on cortical morphology

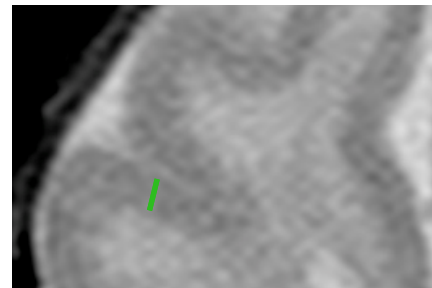
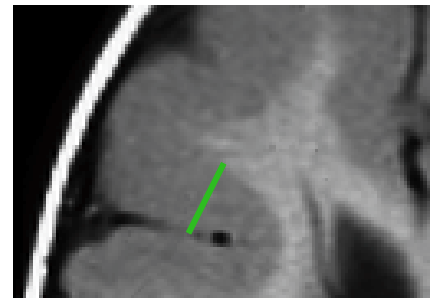
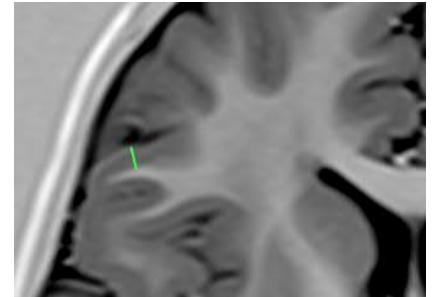
LIS major subtypes	Frequency	Inheritance
Diffuse agyria with cerebellar hypoplasia	4%	AD/AR
Classic pachygyria (cortex > 10 mm)	60%	AD
Tubulinopathy-related dysgyria	11%	AD
Subcortical band heterotopia	17%	Xchr/AD
Pachygyria with cortex 5-10 mm	6%	AR
Microlissencephaly (MLIS)	2%	AD/AR

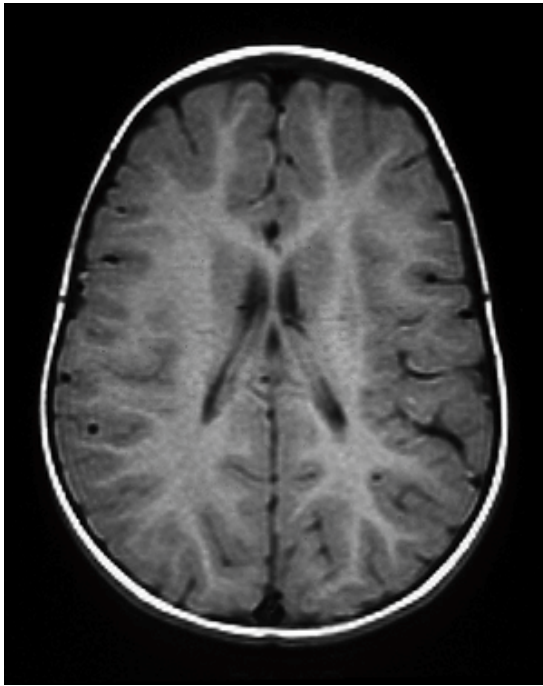
Normal cortex → 3-4 mm

- FL motor strip → 4.5 mm
- OL visual cortex → 2.5 mm

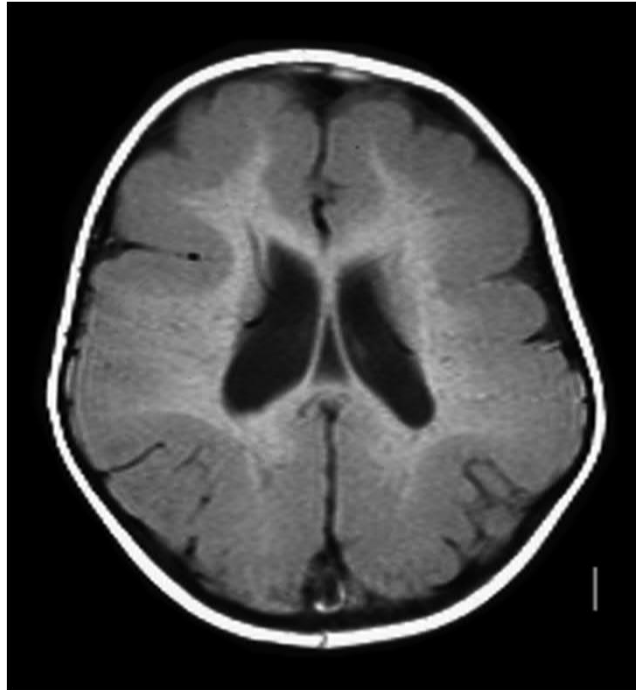
“Classic” LIS → 10-20 mm

“Thin” LIS → 5-10 mm

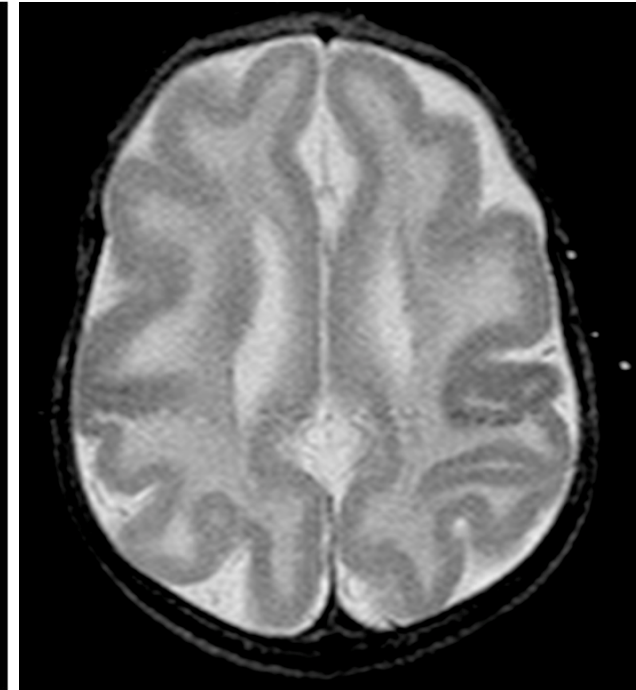




normal

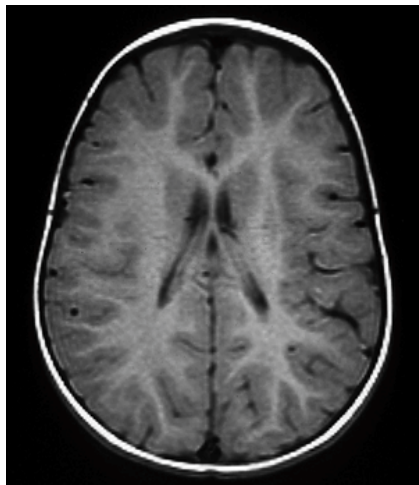


Pachygyria with
cortex > 10 mm

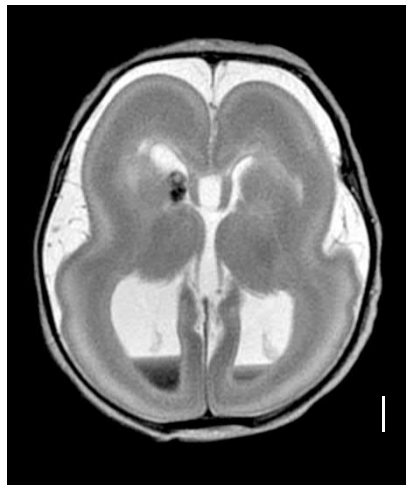


Pachygyria with
cortex < 10 mm

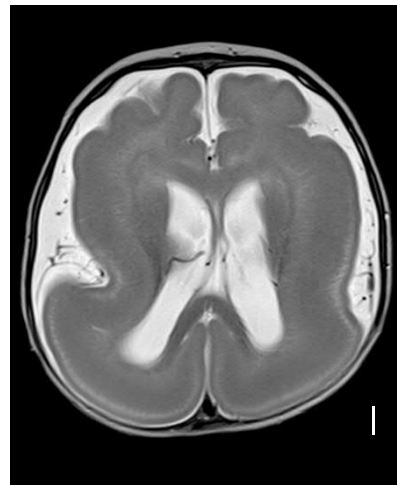
- o Agryria, mixed agryria-pachygyria, pachygyria-band
- o Anterior and posterior gradient
- o Isolated or with additional non-cortical malformations



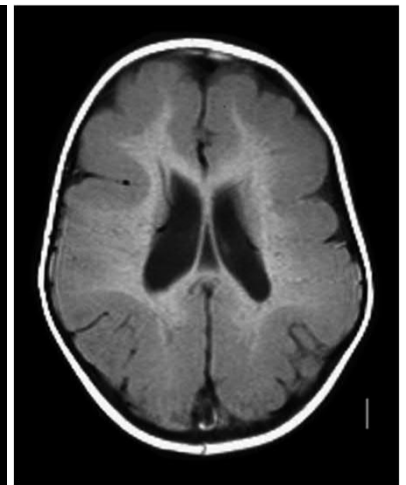
Normal



Diffuse
agryria

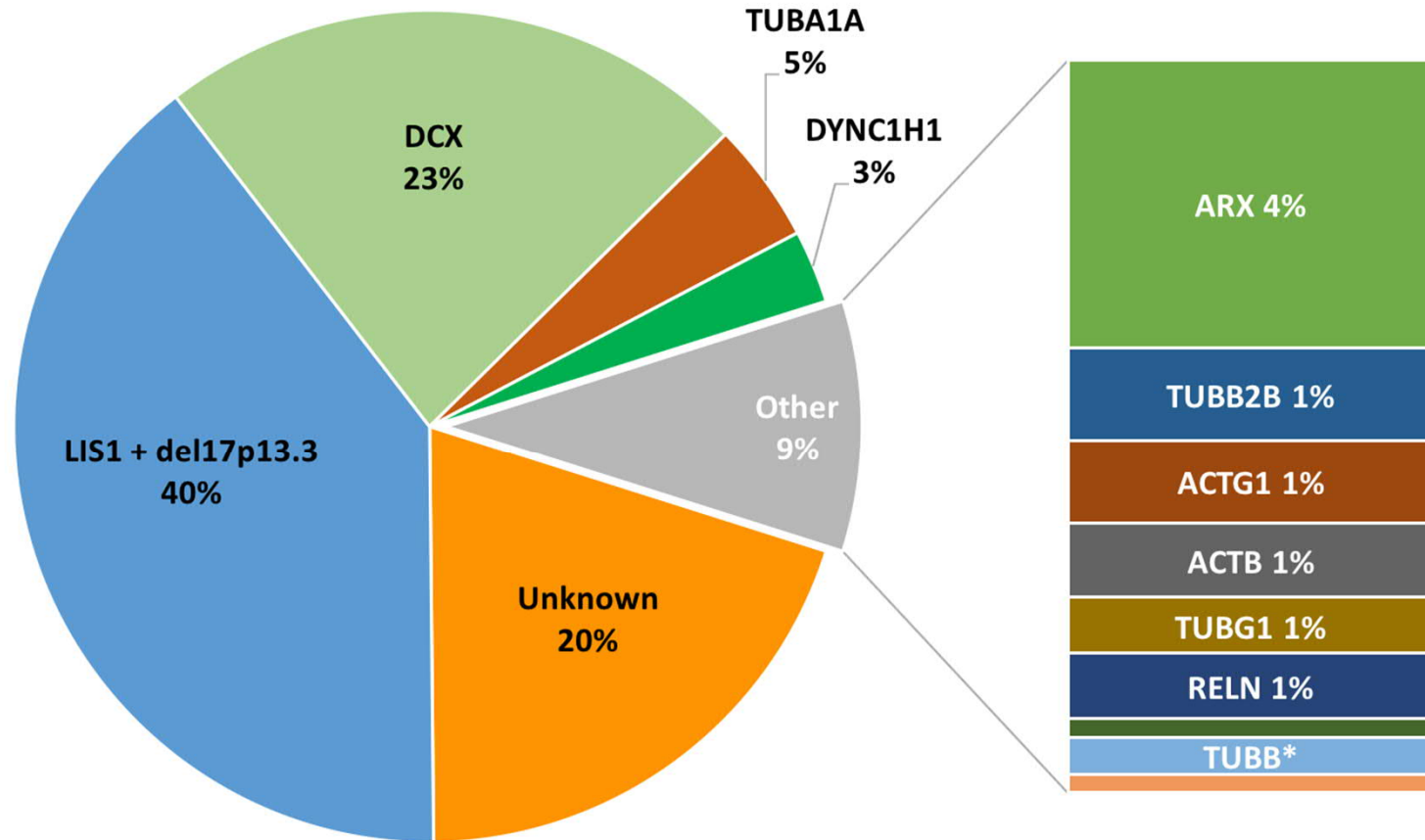


Posterior
gradient



Anterior
gradient

Lissencephaly – always genetic 20 genes and diagnostic yield over 80%



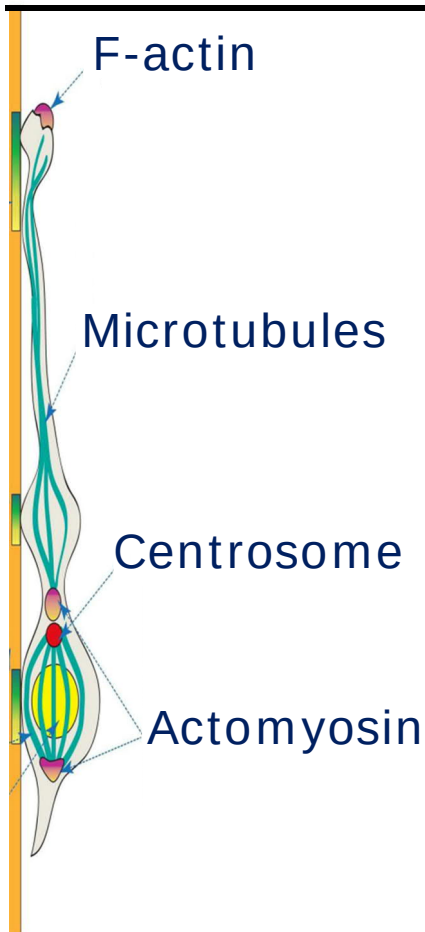
2018-2019 – 3 novel LIS genes:
APC2, MACF1, MAST1

■ VLDLR*	■ TUBB3*
CRADD	KIF2A
CDK5	KIF5C
NDE1	RNU4ATAC

15 of 20 LIS-associated genes are encoding for structural or regulatory cytoskeletal proteins

Pial membrane

Gajal-Rezius cells - Reelin



Protein networks

Genes

Reelin signaling

RELN, VLDLR

Actin / associated proteins

ACTB, ACTG1, DCX

Tubulins

TUBA1A, TUBB, TUBB2B, TUBB3, TUBA8

Microtubule motor proteins

DYNC1H1, KIF5C, KIF2A

Complex microtubuli associated proteins (MAPs)

CDK5

Centrosomal MAPs

LIS1 (aka PAFAH1B1), TUBG1, NDE1

Forebrain transcription

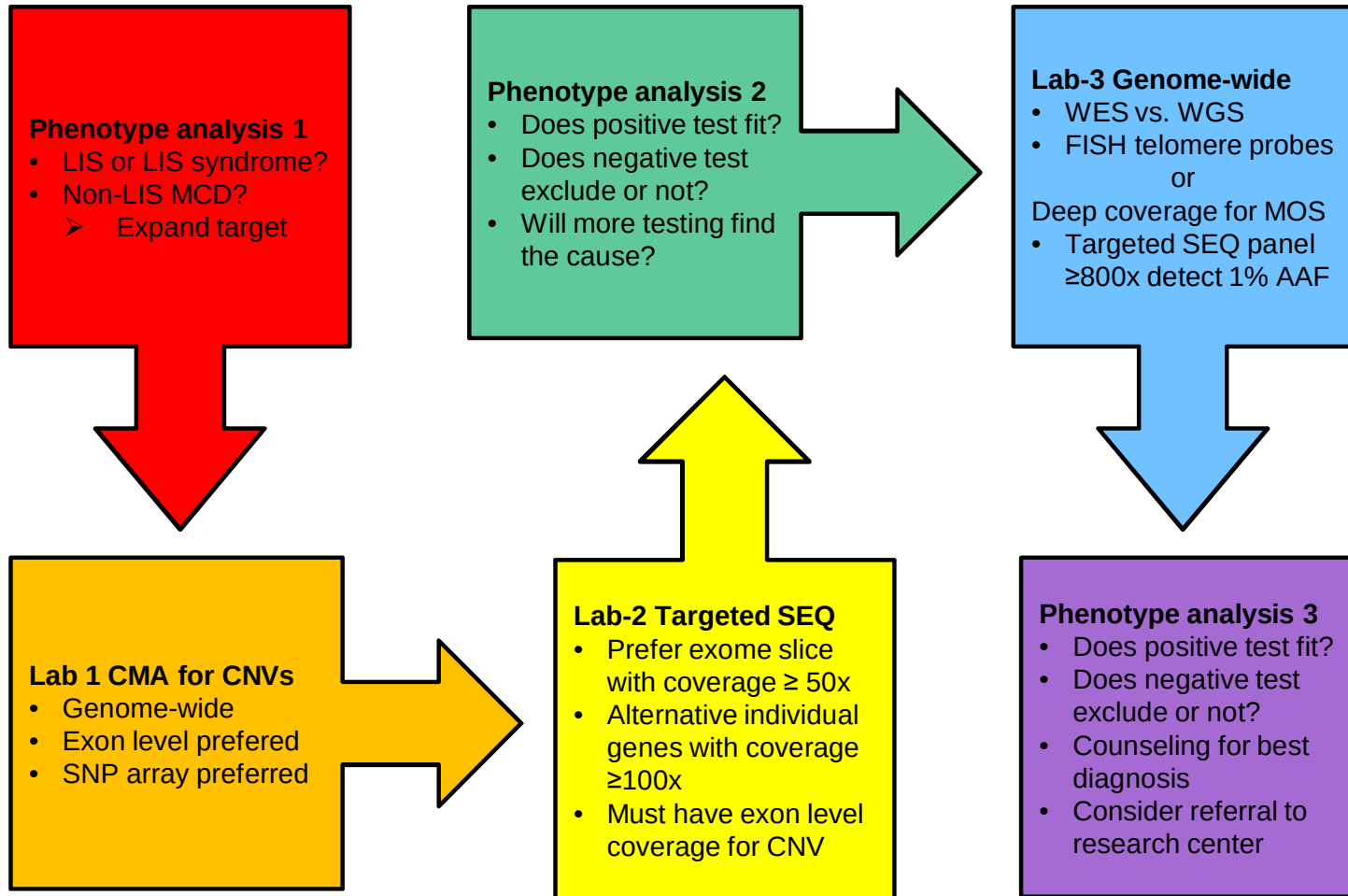
ARX

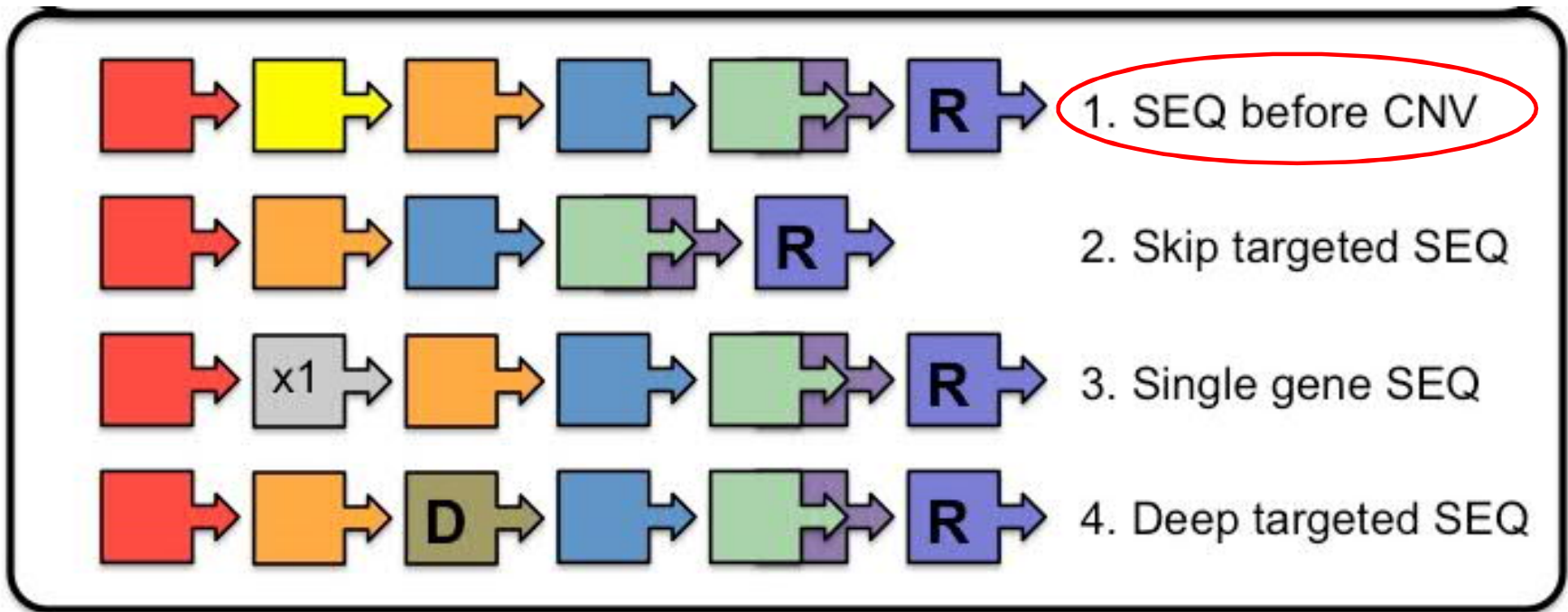
Apoptosis

CRADD

Moon&Wynshaw-Boris, 2013

LIS standard diagnostic strategy





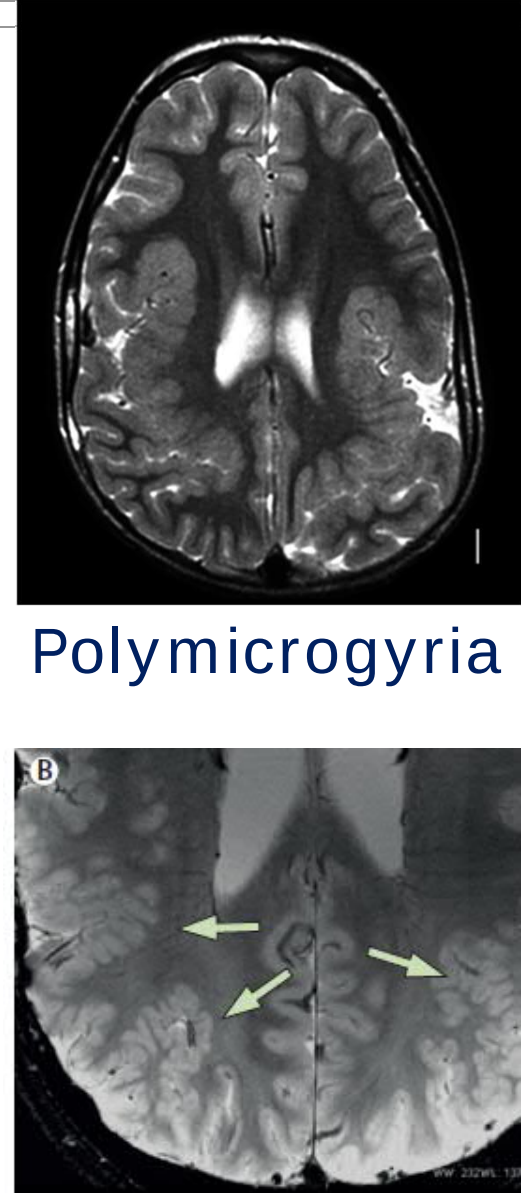
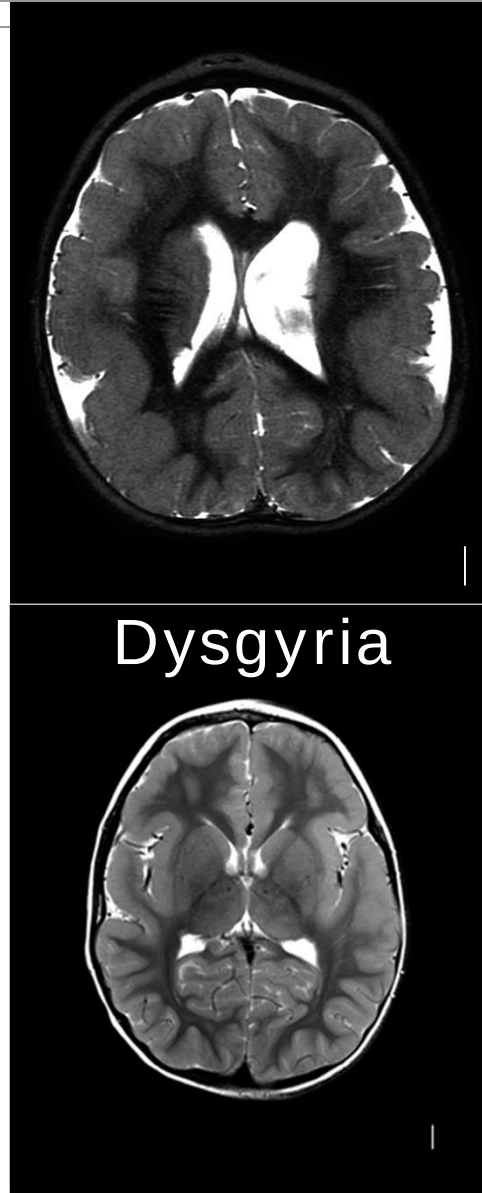
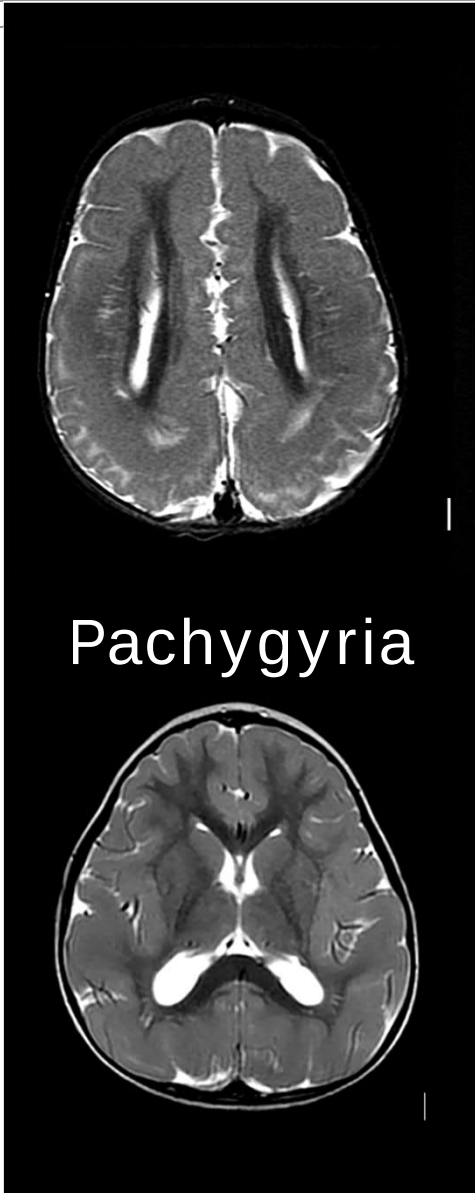
Initial phenotype analysis

CNV analysis

Targeted sequencing / exome slice

Whole exome sequencing

Tubulinopathy-associated dysgyria



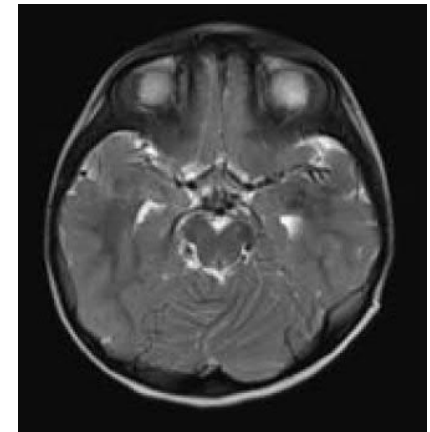
Agensis of
corpus callosum



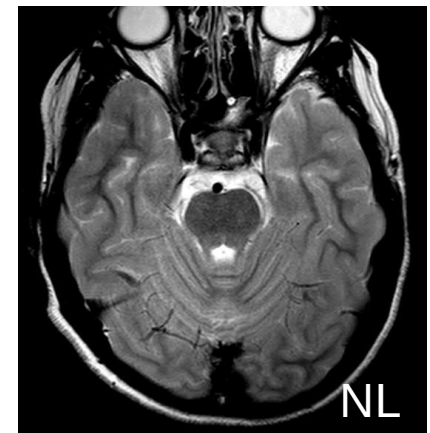
Large
tectum



Cerebellar
hypoplasia-
dysplasia



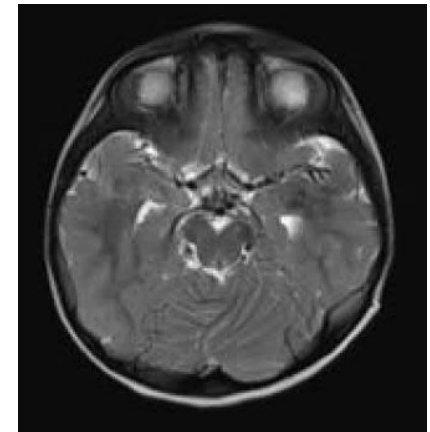
Oegema et al. 2015
doi: 10.1093/hmg/ddv250



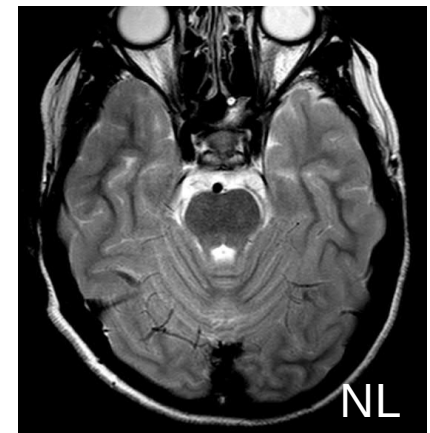
Agenesis of
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Large
tectum

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dysplasia



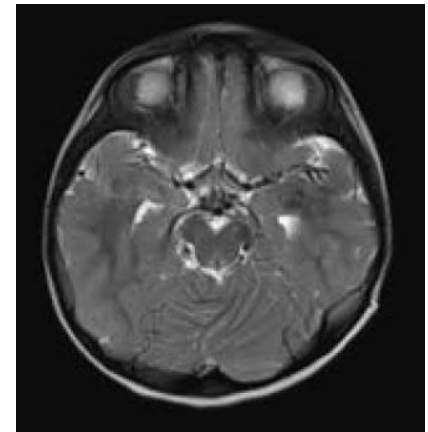
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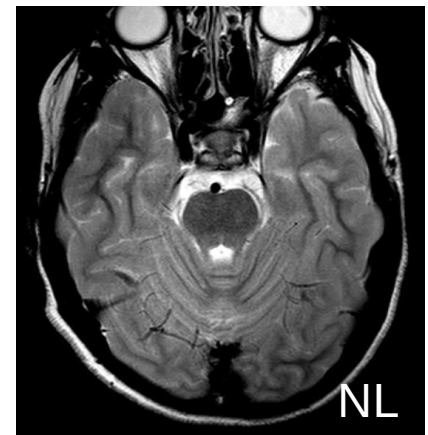
Agene-
sis of
corpus callosum

Large
tectum

Cerebellar
hypoplasia-
dysplasia



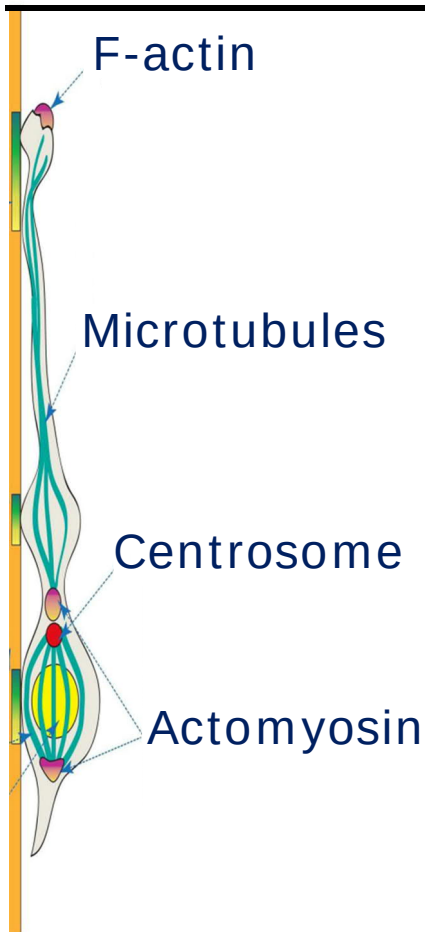
Oegema et al. 2015
doi: 10.1093/hmg/ddv250



Tubulinopathy is a recognizable phenotype without strict correlation with the responsible gene; expect missense mutation in TUB genes

Pial membrane

Gajal-Rezius cells - Reelin



Moon&Wynshaw-Boris, 2013

Protein networks

Genes

Reelin signaling

RELN, VLDLR

Actin / associated proteins

ACTB, ACTG1, DCX

Tubulins

TUBA1A (5 %), TUBB, TUBB2B, TUBB3, TUBA8

Microtubule motor proteins

DYNC1H1 (3 %), KIF5C, KIF2A

Complex microtubuli associated proteins (MAPs)

CDK5

Centrosomal MAPs

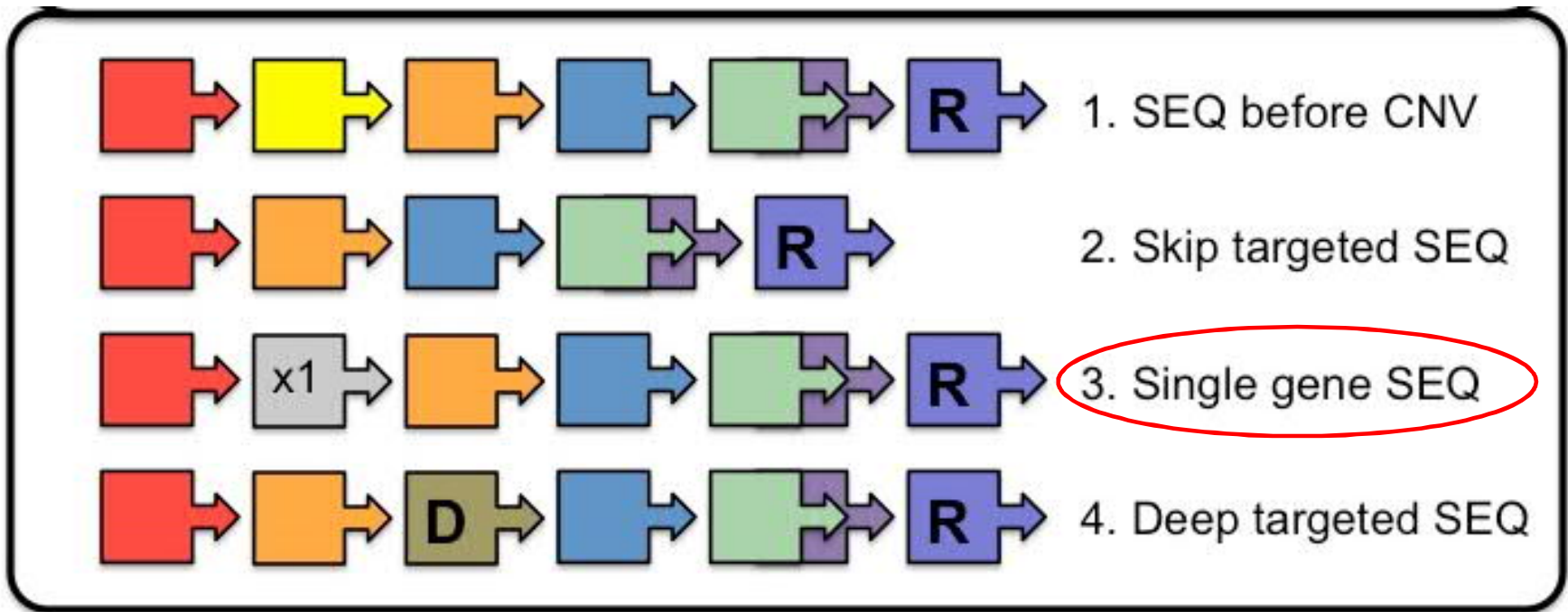
LIS1 (aka PAFAH1B1), TUBG1, NDE1

Forebrain transcription

ARX

Apoptosis

CRADD



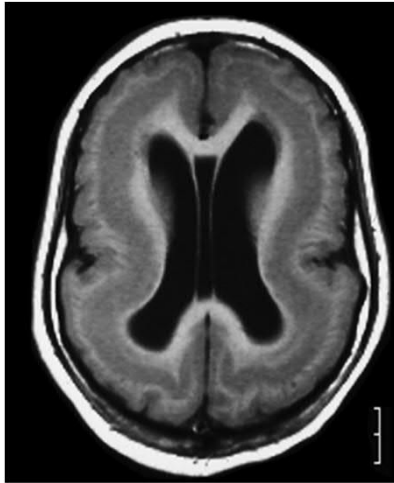
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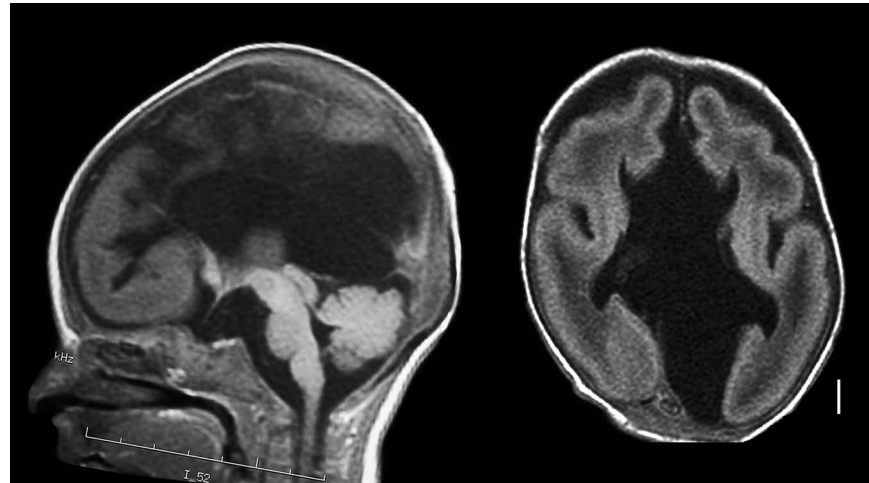
Targeted sequencing / exome slice

Whole exome sequencing

Single gene test for strong clinical diagnosis

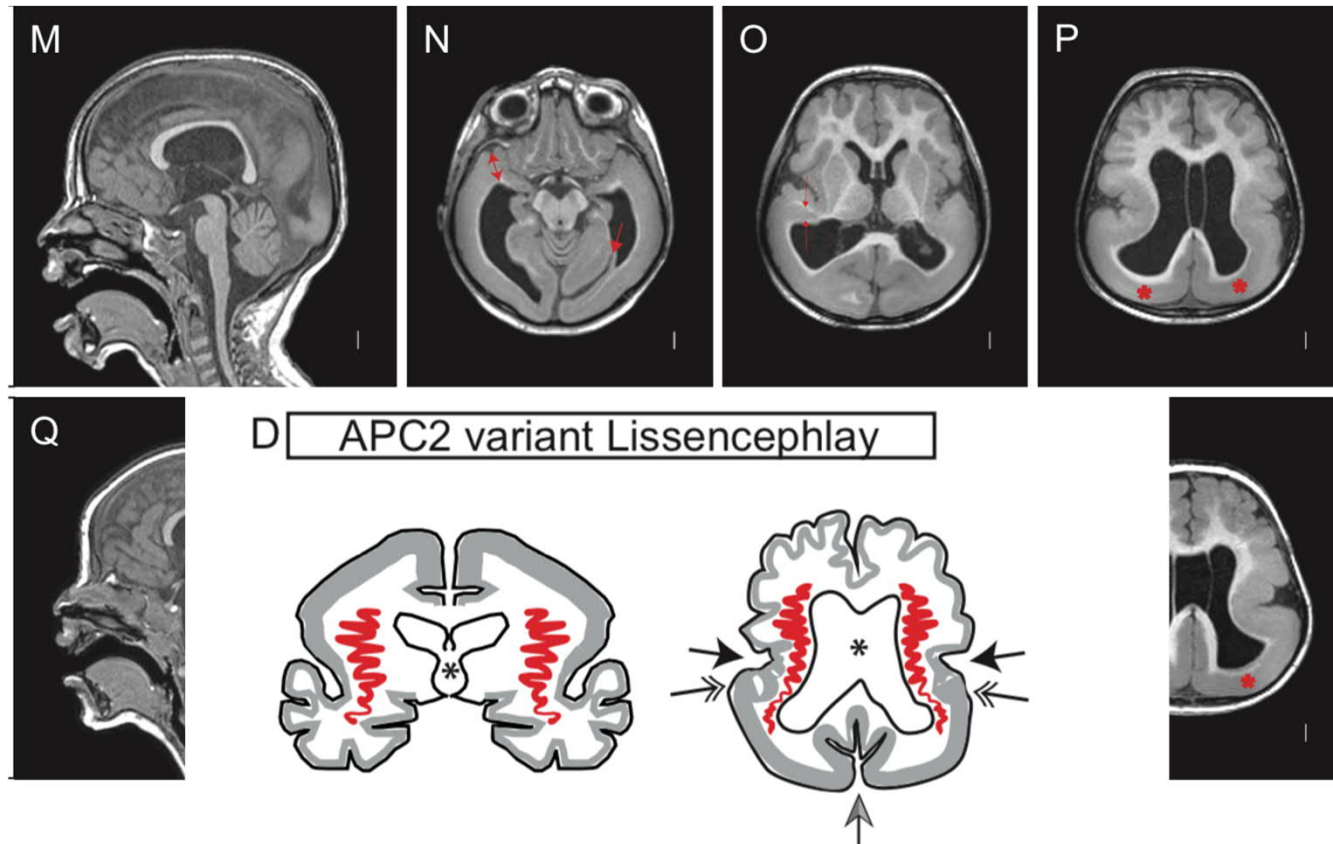


Diffuse SBH
DCX
Diagnostic yield
> 95 %



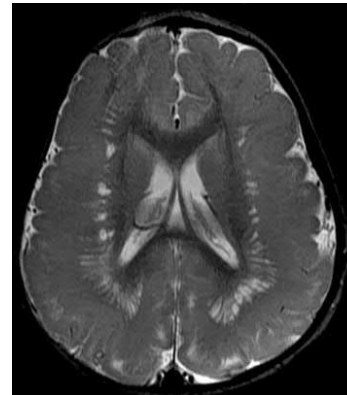
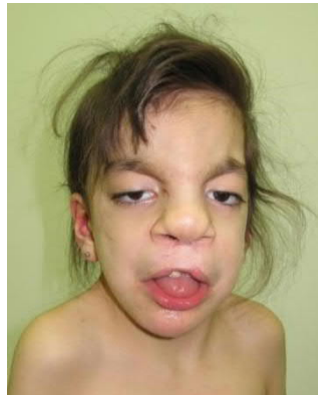
XLAG
ARX
Diagnostic yield ~ 100 %

Novel LIS gene with a distinct phenotype

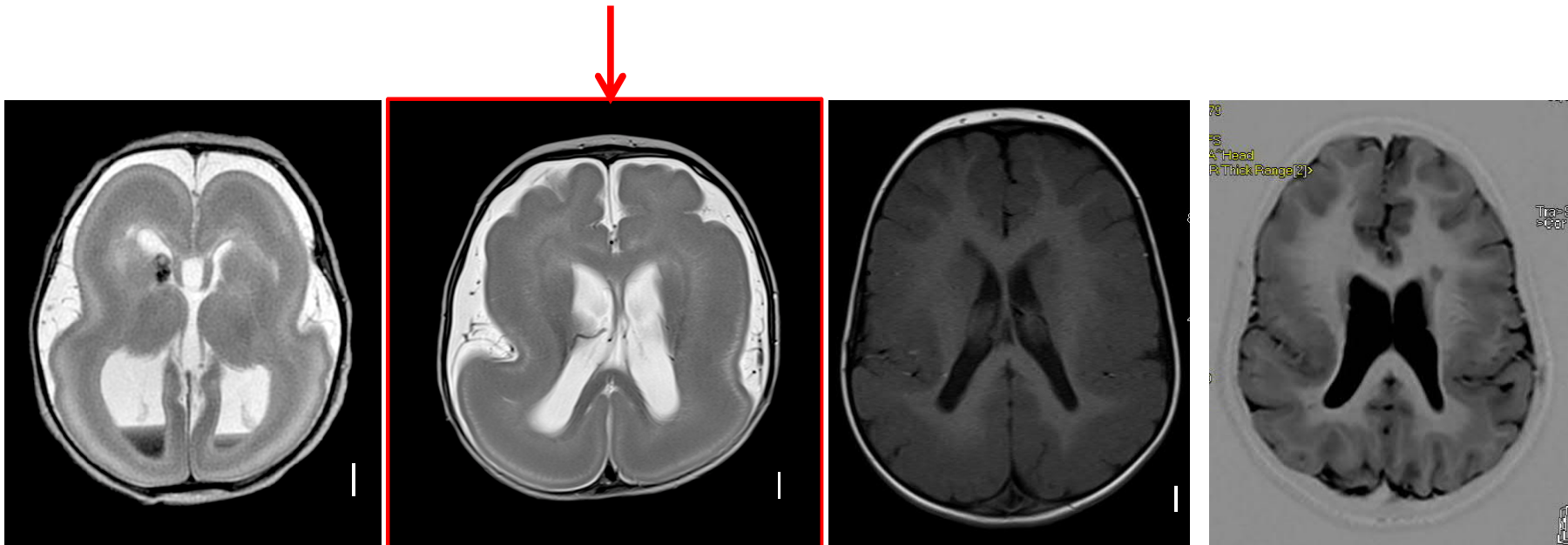


- * Ventriculomegaly
- ← Abrupt transition anterior to posterior
- ⇐ Reduced white matter
- ↩ Posterior infolding

- Baraitser-Winter-Cerebrofrontofacial syndrome (ACTB, ACTG1)



LIS1 (aka PAFAH1B1) – mutations in 40% of LIS patients



Diffuse AGY

del17p13.3

DCX

Posterior AGY

del17p13.3
intragenic LIS1 del
LoF mutations
TUBA1A: p.R402C

Posterior PGY

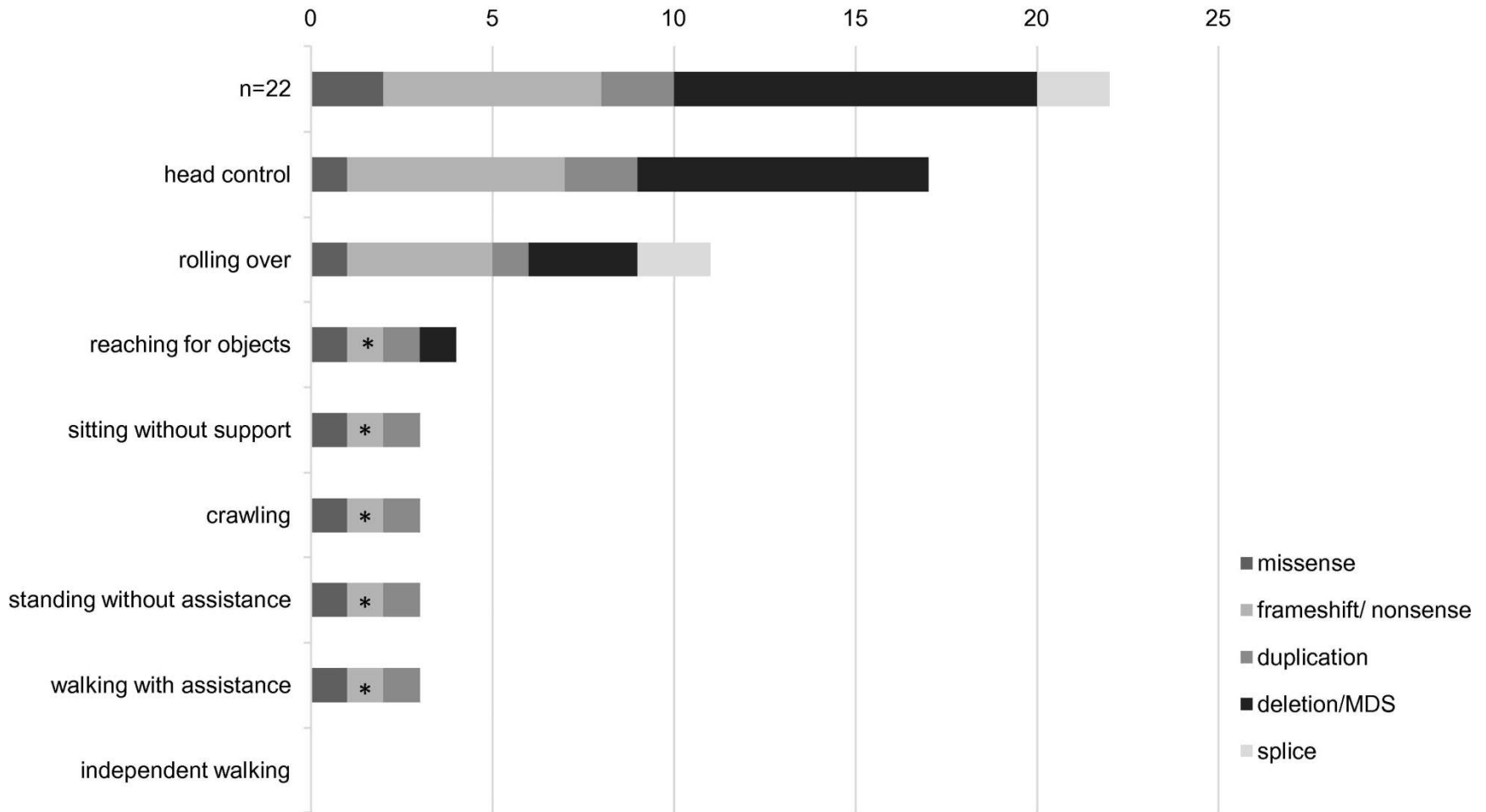
LIS1
DYNC1H1
TUBG1...

Posterior SBH

mosaic LIS1
...

LIS major subtypes	Frequency	Inheritance
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Classic pachygyria (cortex > 10 mm)	60%	AD
Tubulinopathy-related dysgyria	11%	AD
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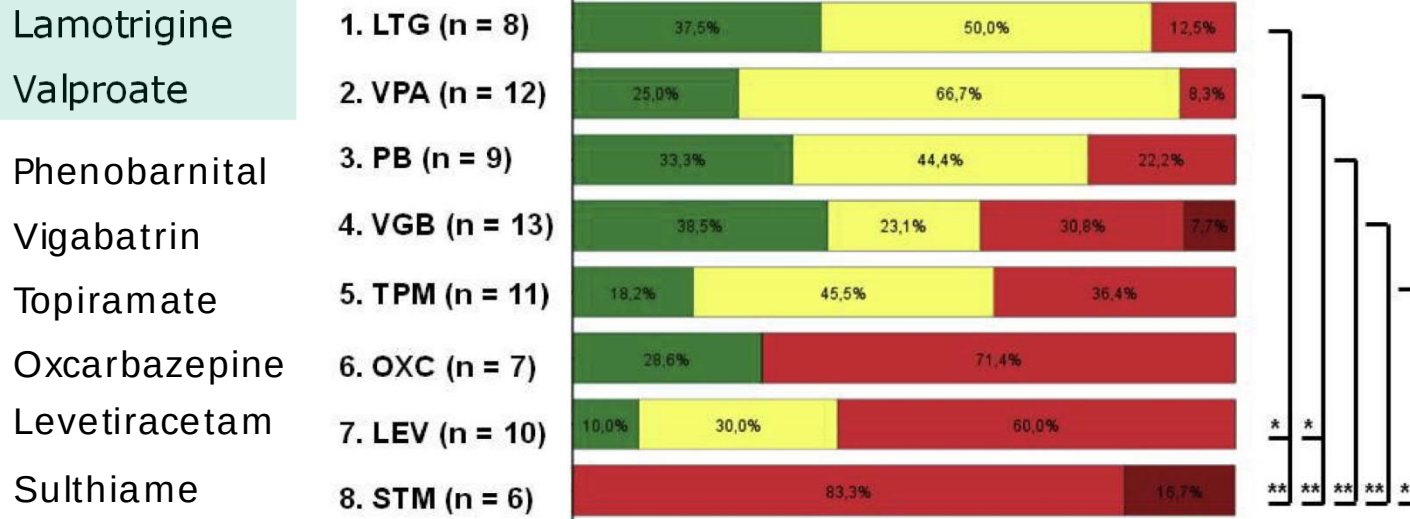
Patient prognosis and management changes depending on the causative mutation



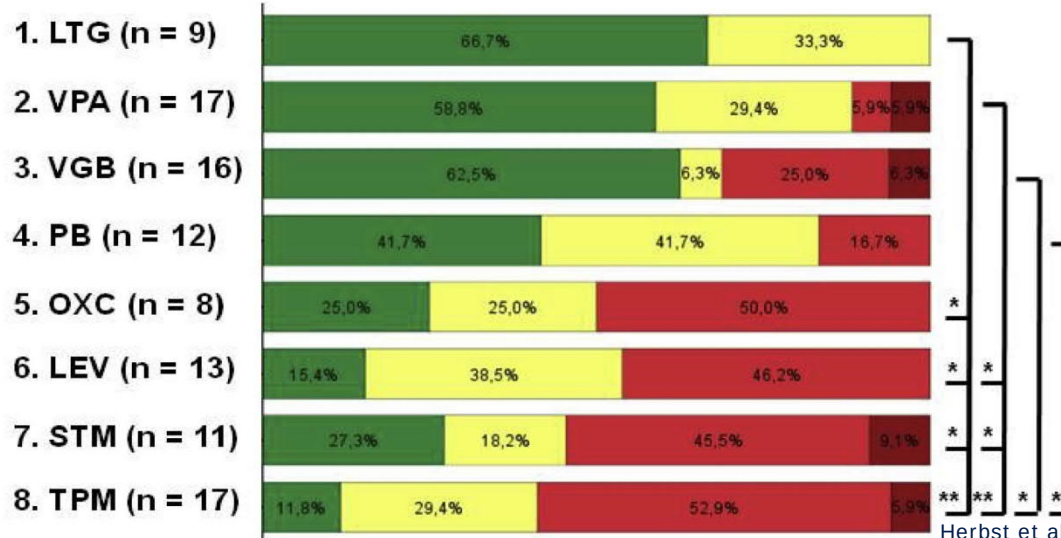
LIS1 - all 22 patients had early onset drug-resistant epilepsy

Distinct response to antiepileptic drugs

A Neuropediatric evaluation



B Family evaluation



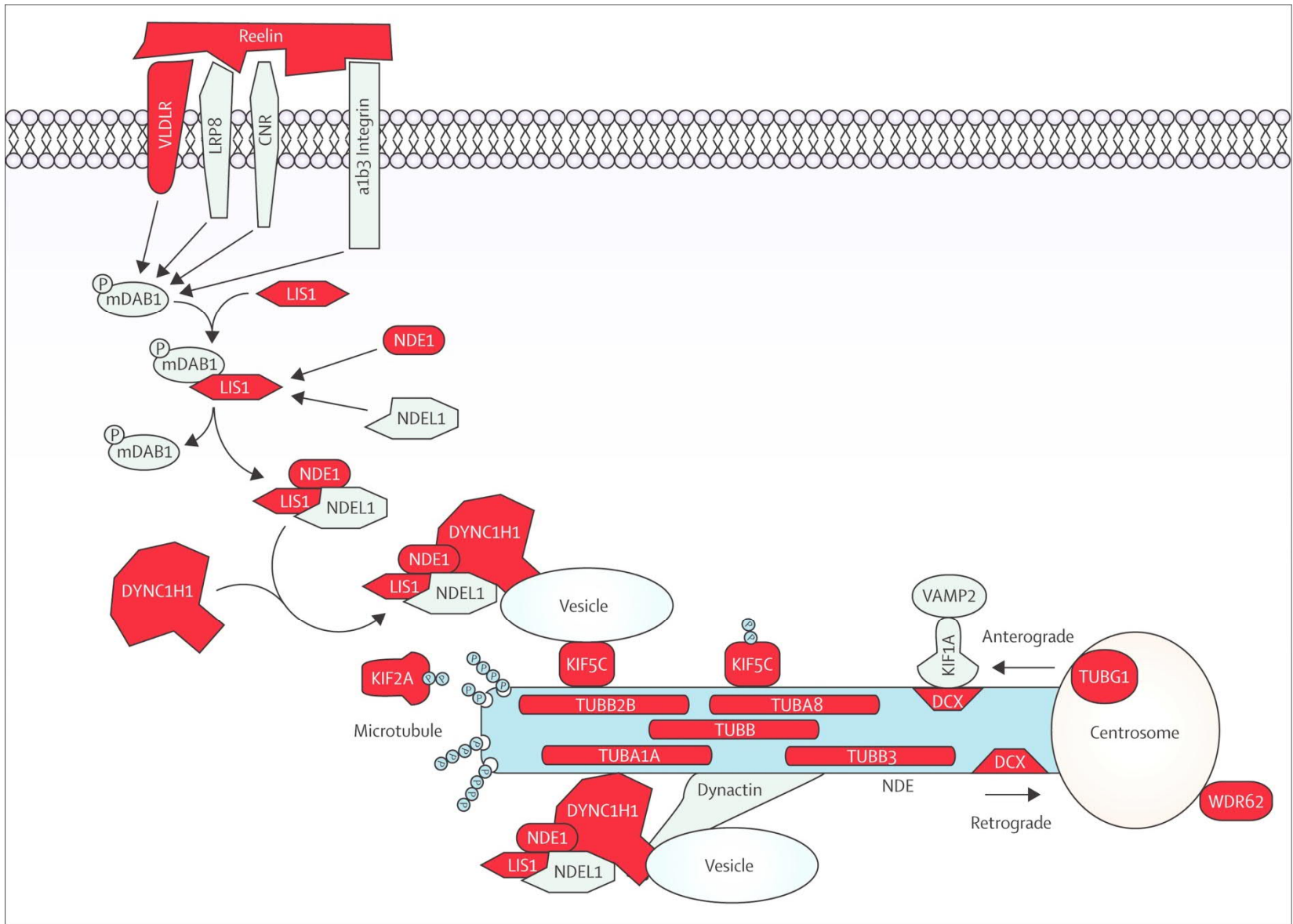
Inhibition of calpain increases LIS1(PAFAH1B1) and partially rescues *in vivo* phenotypes in a mouse model of lissencephaly

Masami Yamada^{1,*}, Yuko Yoshida^{1,*}, Daisuke Mori¹, Takako Takitoh¹, Mineko Kengaku², Hiroki Umeshima², Keizo Takao^{3,4,5}, Tsuyoshi Miyakawa^{3,4,5}, Makoto Sato^{6,7}, Hiroyuki Sorimachi⁸, Anthony Wynshaw-Boris⁹, and Shinji Hirotsune^{1,#}

Post-natal treatment by a blood-brain-barrier permeable calpain inhibitor, SNJ1945 rescued defective function in lissencephaly

Shiori Toba^{1*}, Yasuhisa Tamura^{2*}, Kanako Kumamoto^{1*}, Masami Yamada¹, Keizo Takao^{3,4}, Satoko Hattori^{3,5}, Tsuyoshi Miyakawa^{3,4,5}, Yosky Kataoka², Mitsuyoshi Azuma⁶, Kiyoshi Hayasaka⁷, Masano Amamoto⁸, Keiko Tominaga⁹, Anthony Wynshaw-Boris¹⁰, Hideki Wanibuchi¹¹, Yuichiro Oka^{12,13,14}, Makoto Sato^{12,13,14}, Mitsuhiro Kato⁷ & Shinji Hirotsune¹

LIS1 is essential for the regulation of cytoplasmic dynein und facilitates intracellular transport during the whole life



1. LIS - genetic disorder with the diagnostic yield > 80%
2. LIS1 (40%) and DCX (23%) are the most frequently mutated genes
3. Standard and expert diagnostic strategies
4. Genotype-phenotype correlation allows prediction of the causative genes or inheritance pattern
5. Therapy possible - > LIS-associated genes function through the whole life

