- **Psychomotor development**
- **Mental retardation**

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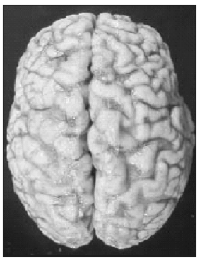
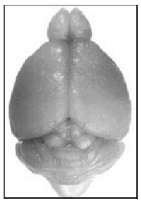
Semmelweis University,
Budapest

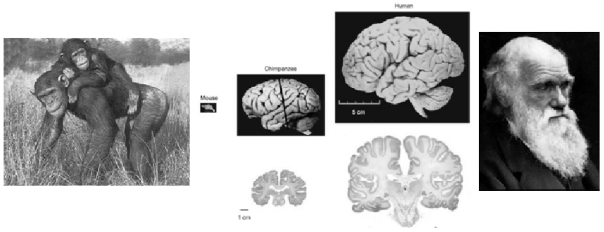
Human



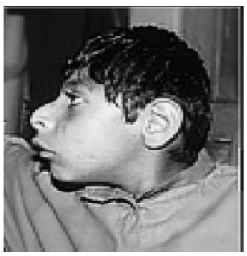
Mouse



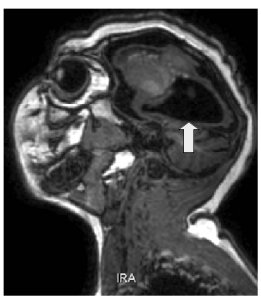
deeper thoughts…

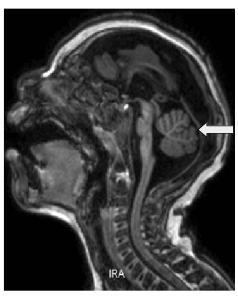


Microlissencephalia



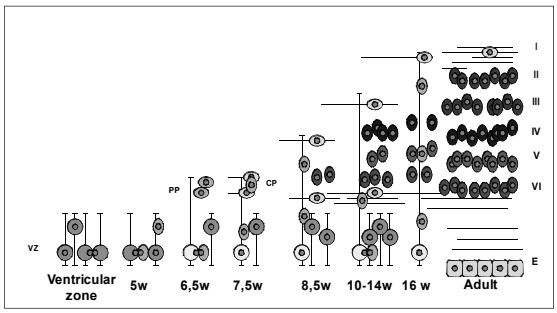
Gul et al., Neurogenetics 2006



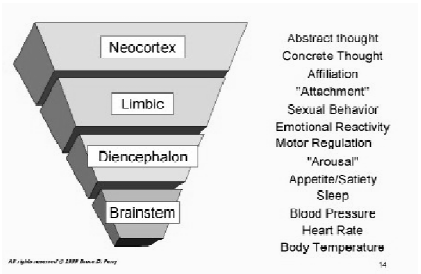


subarachnoideal space and ventricle enlargement
cerebellar and brainstem hyplasia

Development of the cerebral cortex

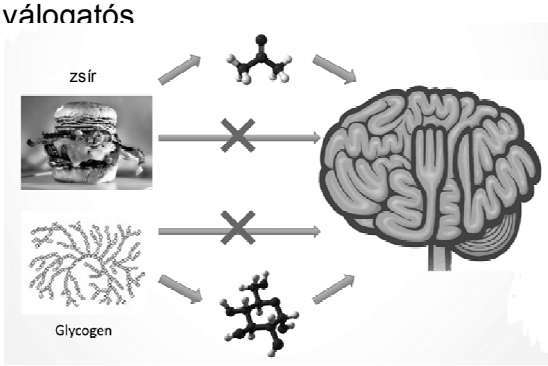


Couillard-Despres S *et al.* (2001) *Curr. Mol. Med.* 1: 677-688



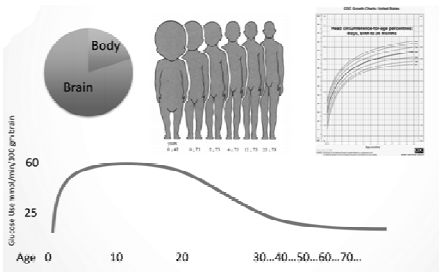
Functional Division	Constituent Parts	Developmental Division	Age of Functional Maturity	Functions
Neocortex	Cerebral cortex *Frontal Lobes* *Temporal Lobes* *Parietal Lobes* *Occipital Lobes* *Corpus Callosum*	Telencephalon	Puberty Childhood	Abstraction Self-image Socialization Affiliation Attachment
Limbic *Cingulate Cortex* *Amygdala* *Hippocampus* *Septum*	Amygdala Hippocampus Basal ganglia *Caudate Nucleus* *Putamen* *Globus Pallidus*		Early childhood	Mood regulation Fine motor Large motor Complex state regulation (e.g., sleep, appetite)
Diencephalon	Thalamus Hypothalamus	Diencephalon	Infancy	
Brainstem	Midbrain *Superior Colliculus* *Inferior Colliculus*	Mesencephalon	Six months	Primary state regulation
	Cerebellum Pons	Metencephalon	Third trimester	Core physiological reflexes and regulatory functions
	Medulla Oblongata	Myelencephalon		
Spinal Cord	Spinal Cord		Third trimester	

az agy energia ellátása: agyunk válogatós

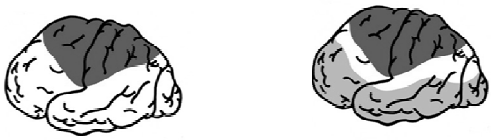


a **<u>gyermekkori agy</u>** energia ellátása:

a gyermekkori agy **<u>nagyon „önző”</u>**

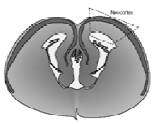


Development of Human Brain Myelinisation

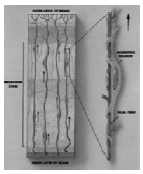


Disorders of cortical development

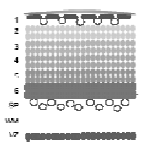
1. Disorders of proliferation and differentiation of the neuronal progenitor cells



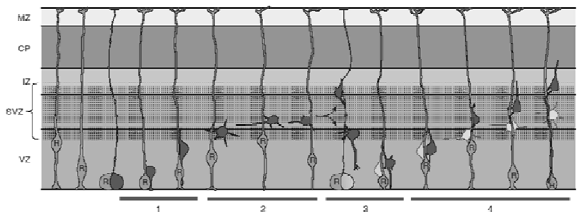
2. Disorders of migration



3. Disorders of cortical organisation (layering)

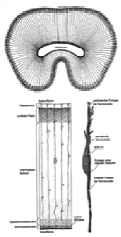


Pyramidal neurons undergo distinct phases of locomotion migration



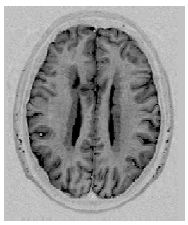
Kriegstein AR & Noctor *SC TINS* 2004

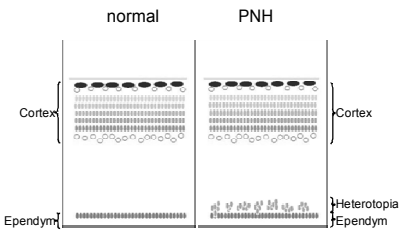
Genes involved in neuronal migration



FLNA	X-linked periventricular nodular heterotopia
ARFGEF2	a.-r. periventricular nodular heterotopia
LIS1	isolated lissencepahly (lissencephaly **type I**)
DCX	X-linked isolated lissencephaly (lissencephaly **type I**)
ARX	X-linked lissencepahly with abnormal genitalia (XLAG)
Reelin	lissencephaly with cerebellar hypoplasia (LCHb)
VLDLR	simplified gyration with cerebellar hypoplasia
POMT1	Walker-Warburg-Syndrome (lissencephaly **type II**)
POMT2	Walker-Warburg-Syndrome (lissencephaly **type II**)
POMGnT1	Muscle-Eye-Brain Disease (lissencephaly **type II**)
Fukutin	Fukuyama Congenital Muscular Dystrophy (liss. **type II**)
FKRP	congenital muscular dystrophy with cerebellar cysts
LARGE	congenital muscular dystrophy with cortical malformation
GPR56	bilateral frontoparietal polymicrogyria

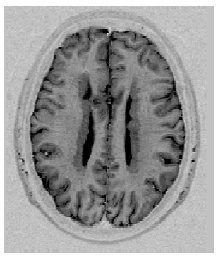
Periventricular Nodular Heterotopia (PNH)





ARFGEF2 gene	autosomal-recessive	microcephaly
FLNA gene	X-linked	

Periventricular Nodular Heterotopia (PNH)



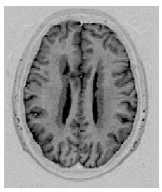
- associated with epilepsy
  - up to 80%
  - freq. begin after age 20
  - mostly focal seizures
- cognitive impairment
- coagulopathy / vasculopathy (stroke / patent ductus art. Botalli)
- abortions

Periventricular Nodular Heterotopia (PNH)

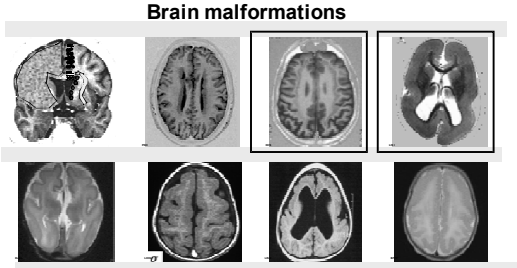
Mutations of ***Filamin A*** **gene (*FLNA*), Xq28**

$[X X_{mut}]$
- cause in **heterozygous females *PNH***

$[X_{mut} Y]$
- are in **hemizygous male fetuses** *lethal*

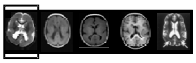


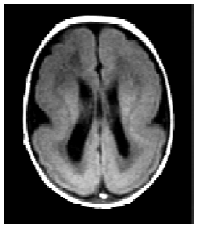
Brain malformations

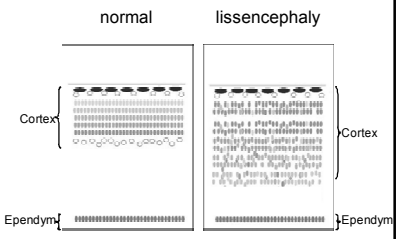


- subependymal / periventricular nodular heterotopia (PNH)
- lissencephaly type I (LIS I) / Double Cortex Syndrome (DCS)
- lissencephaly with abnormal genitalia (XLAG)
- lissencephaly with cerebellar hypoplasia (LCHb)
- lissencephaly type II (LIS II)
- bilateral frontoparietal polymicrogyria (BFPP)

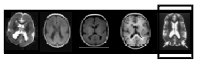
Lissencephaly Type I





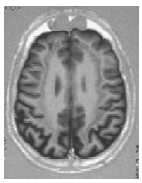


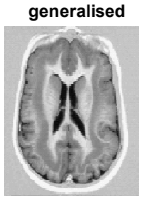
Subcortical bandheterotopia (SBH)

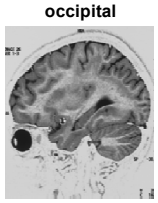


Cerebral imaging: heterotopic band of neurons under the cortex

frontal **generalised** **occipital**







♀ *DCX* mutations

LIS1 mutations

Doublecortin (*DCX*; Xq22.3-q23)

Mutations in ***Doublecortin*** **gene, Xq22.3-q23**

[X X_{mut}]

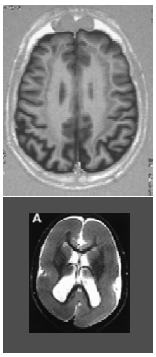
- Cause in **heterozygous females**

subcortical bandheterotopia

[X_{mut} Y]

- lead in **hemizygous males** to

lissencephaly type I

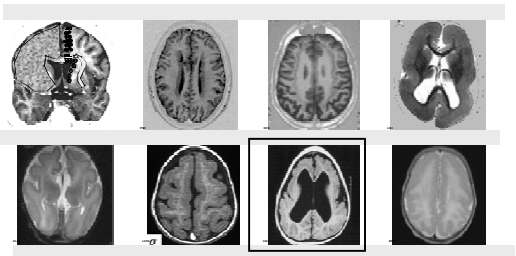


LIS1 (17p13.3)

21 patients with *LIS1*-mutations (*de novo*):

	truncating	missense/ in frame site	splice
Mutation	9	6	6
somatic mosaic		(2)	(1)
Seizures within 1st year of life		17	
Severe psychomot. retardation		14	
No walking		12	
Speech delayed / absent		13	
Autistic behaivior		2	

Brain malformations



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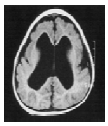
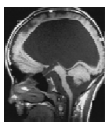
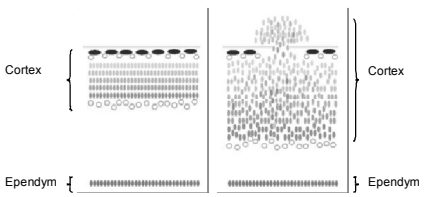
„Cobblestone“ lissencephaly (lissencephaly type II)

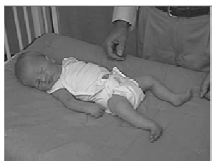






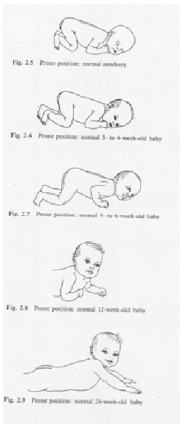
Ventral position: Abnormal newborn

Abnormal newborn



Development of locomotion

Prone position



Development of locomotion

- Sitting