Malformations of Cerebral Cortex - OUTLINE

- Cortical development
- Lissencephaly
- Polymicrogyria
- Cortical dysplasia

“The smooth brain”

- Heterotopia
TERMINOLOGY

• Macroscopic appearance of smooth brains:
  – Completely smooth = agyria, lissencephaly
  – Fewer coarser convolutions = macrogyria, pachygyria
  – Cobblestone pattern

• Microscopic pattern:
  – Lissencephaly type I....agyria,pachygyria w/wo 4 layers
  – Lissencephaly type II...cobblestone cortex/ cerebro-ocular dysplasia
  – Polymicrogyria... 2 or 4 layers
  – Cortical Dysplasia with cytomegaly
Development of the cerebral cortex.

Lissencephaly

• Neuronal migration disorder characterized by abnormal gyri
• Varies from agyria to pachygyria
• Severe mental retardation, hypotonia, intractable seizures
• Type 1 - cortex usually has 4 (instead of 6) layers, poorly organized
<table>
<thead>
<tr>
<th>Disease</th>
<th>CNS</th>
<th>Gene</th>
<th>Function of product</th>
<th>Chromosome</th>
<th>Mouse model</th>
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<tbody>
<tr>
<td>Lissencephaly (type I): autosomal recessive</td>
<td>Lissencephaly with low sloping forehead and prominent nasal bridge</td>
<td><em>RELN</em></td>
<td>Reelin: extracellular matrix protein produced by Cajal-Retzius cells required for neuronal migration</td>
<td>7q22</td>
<td>reeler mutant mouse causes cerebellar and cerebral cortical lamination anomalies</td>
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<td>(Norman-Roberts type)</td>
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<td>Lissencephaly (type I): Miller-Dieker syndrome Dominant (haploinsufficiency)</td>
<td>Lissencephaly, cerebral heterotopias, facial dysmorphism</td>
<td><em>LIS1</em> and <em>14-3-3ɛ YWHAE</em> ; (contiguous gene deletion)</td>
<td>LIS1: Non-catalytic subunit of brain platelet-activating factor acetyl hydrolase (PAFAH)</td>
<td>17p13.3</td>
<td>Targeted loss of function alleles of <em>Pafah1b1</em> gene and <em>14-3-3ɛ</em></td>
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<td>Lissencephaly (type I): isolated lissencephaly sequence (ILS) AD</td>
<td>Lissencephaly</td>
<td><em>LIS1</em> deletion alone</td>
<td>LIS1: as above</td>
<td>17p13.3</td>
<td>Targeted loss of function alleles of <em>Pafah1b1</em> gene causes neuronal migration disorders</td>
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<td>Lissencephaly (type I): X-linked isolated</td>
<td>Lissencephaly with agenesis of corpus callosum in males; subcortical band heterotopia in females</td>
<td><em>DCX</em></td>
<td>Doublecortin: microtubule-associated protein that interacts with non-receptor tyrosine kinases, including Abl</td>
<td>Xq22.3-q23</td>
<td>suppression of doublecortin expression by RNAi inhibits neuronal migration in rat neocortex</td>
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<td>Lissencephaly (type I): X-linked (XLAG)</td>
<td>Lissencephaly with ambiguous genitalia</td>
<td><em>ARX</em></td>
<td>Aristalless-related homeodomain transcription factor</td>
<td>Xp22.13</td>
<td>Targeted mutation of <em>Arx</em></td>
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<td>Lissencephaly (type III)</td>
<td>Agyria, pachygyria or laminar heterotopia, abnormalities of corpus callosum, hippocampus, cerebellar vermis and brainstem</td>
<td><em>TUBA1A</em></td>
<td>Tubulin, alpha 1a</td>
<td>12q12-q14</td>
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Layer

I
II
III
IV
V
VI
wm

Normal

Layer

Lis1
DCX
ARX
TUBA1A

Mutations

3 layer cortex
2 layer cortex
4 layer cortex with Anterior predominance
4 layer cortex with Posterior predominance

3 layer cortex
2 layer cortex

Courtesy of Forman MS et al. J Neuropathol Exp Neurol 2005
Lissencephaly type I

- Miller-Dieker syndrome
  - Microcephaly, bitemporal narrowing, vertical ridging in forehead, micrognathia
  - Cryptorchidism, heart/kidney anomalies can be seen
  - Contiguous gene deletion syndrome of 17p13.3
  - Most of the deletions are cytogenetically visible
  - Lissencephaly due to deletion of LIS1
  - Facial features due to other genes on 17p13
  - More severe lissencephaly due to gene encoding 14-3-3ε YWHAE
Isolated Lissencephaly

- **LIS1 - 17p13 - PAFAH1B1** *(Platelet-activating factor acetylhydrolase, isoform 1B, alpha subunit)*
  - Isolated lissencephaly
  - Autosomal dominant
  - More severe occipital/posterior parietal

- **DCX - Xq22 - Doublecortin**
  - X-linked dominant
  - In males, isolated lissencephaly
  - More severe anteriorly
Syndromic Lissencephaly

• *RELN*-7q22- Reelin
  – Lissencephaly with severe ataxia
  – Mental retardation, seizures
  – Cerebellar hypoplasia
  – Autosomal recessive
Syndromic Lissencephaly

• XLAG - ARX - Xp22
  – Lissencephaly with ambiguous genitalia
  – Agenesis of the corpus callosum, severe seizures, temperature dysregulation, microcephaly
  – Immature white matter
  – Posterior-anterior gradient
  – X-linked recessive
  – Mutations also associated with infantile spasms, MR with dystonia
Lissencephaly II - Cobblestone Dysplasia
AR

- cortex unlayered disorganized with cobblestone surface and thickened meninges
- can be partly polymicrogyric,
- variable muscular and ocular involvement with CNS disorder

- Dystroglycanopathies

- Walker-Warburg syndrome
- Muscle-eye-brain disease
- Fukuyama muscular dystrophy (Japan 3/10000)
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<td>Lissencephaly (type II): Fukuyama congenital muscular dystrophy</td>
<td>Cobblestone lissencephaly, polymicrogyria</td>
<td>FCMD</td>
<td>Fukutin: gene interrupted by retro-transposon insertion. A secreted protein, which may function as a glycosyl transferase in the Golgi</td>
<td>9q31</td>
<td>Targeted mutation of FCMD gene causes muscular dystrophy and cortical dysplasia</td>
</tr>
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<td>Lissencephaly (type II): muscle-eye-brain disease, type A, 5; type B, 5; type C, 5</td>
<td>Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus</td>
<td>FKRP</td>
<td>Protein targeted to the medial Golgi apparatus and necessary for posttranslational modification of dystroglycan</td>
<td>19q13.3</td>
<td></td>
</tr>
<tr>
<td>Lissencephaly (type II): Walker-Warburg syndrome</td>
<td>Agyria, cobblestone lissencephaly, cerebellar dysplasia and vermal agenesis, hydrocephaly, occipital encephalocele</td>
<td>POMT1, POMT2</td>
<td>O-mannosyl transferase 1: first enzyme in synthetic pathway of O-mannosyl glycans</td>
<td>9q31-q33, 14q24.3</td>
<td>Large \textsuperscript{myd} mutant and targeted mutation of ( \alpha ) dystroglycan gene provide models of Walker-Warburg syndrome</td>
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<td>Lissencephaly (type II): muscle-eye-brain disease</td>
<td>Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus</td>
<td>POMGnT1</td>
<td>O-mannose ( \beta-1,2-N)-acetyl glucosaminyl transferase: second enzyme in synthetic pathway of O-mannosyl glycans</td>
<td>1p34-p33</td>
<td>Targeted mutation of POMGnT1 gene causes phenotype resembling muscle-eye-brain disease</td>
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<td>Lissencephaly (type II): muscle-eye-brain disease</td>
<td>Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus</td>
<td>LARGE</td>
<td>Interacts directly with dystroglycan to allow glycosylation</td>
<td>22q12</td>
<td></td>
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</table>
α-Dystroglycanopathy - pathomechanisms

Lisi MT, Cohn RD. Biochim Biophys Acta 2007;1772:159-172

Saito F, Matsumura K. Skeletal Muscle 2011; 1.22
Walker-Warburg syndrome
Lissencephaly II
excessive migration

Vimentin
MUSCLE-EYE BRAIN DISEASE - LARGE
Grey Matter Heterotopia

• Clusters of neurons and glia that form a nodule of grey matter in an abnormal location
• May be single or multiple, line ventricles, in deep white matter, subcortical white matter, leptomeninges
• Overlying cortex can be normal or disrupted
• May have normal intelligence, and normal neurologic exam
Band Heterotopia

- Bilateral bands of heterotopic grey matter in the white matter between the lateral ventricular walls and the cortex
  - Overlying cortex may be normal or have simplified gyral pattern
  - Mild to moderate mental retardation
  - Seizures, often with later onset
Band Heterotopia

- Predominantly in females
  - Rarely in males
- DCX mutations detected in many patients
Nodular Heterotopia

• Bilateral periventricular nodular heterotopia (BPNH)
  – Varying degrees of severity
  – Associated with seizures in some patients
  – Intelligence - normal to mild mental retardation
Nodular Heterotopia
Genetics

• Most cases consistent with X-linked dominant
  – Strong skewing toward females in sporadic cases
  – Increased rate of pregnancy loss
  – Rare males with BPNH
  – Mutations detected in females affected with epilepsy
  – FLNA- Filamin1, actin binding protein associated with cytoskeleton - Xq28

• Periventricular nodular heterotopia with microcephaly
  – ARFGEF2 Brefeldin A-inhibited GEF2 protein (BIG2), involved in vesicular trafficking from Golgi - 20q13.13
Polymicrogyria (PMG)

- Multiple abnormally small gyri
- Several patterns of regional distribution
- Etiologically heterogeneous
- May be due to intrauterine insult (e.g. infection, hypoxia/ischemia)
- Very variable presentation
- Often associated with seizures, mental retardation, swallowing problems
Polymicrogyria Genetics

- Usually sporadic
  - Occasionally familial
- Bilateral perisylvian polymicrogyria
  - Usually sporadic
  - X-linked form described
- Bilateral fronto-parietal PMG
  - GPR56, G-protein coupled receptor (16q13)
- Tubulin genes, TUBA8, (22q11) TUBB2A & 2B (6p25.2)
Band-like Calcification with Simplified Gyration and Polymicrogyria (BLCPMG) syn. Pseudo-Torch syndrome

- early onset seizures, developmental arrest, progressive microcephaly
- Intracranial calcification, cortical malformation, esp PMG
- Autosomal recessive, mutations in OCLN gene 5q13.2, encoding occludin a tight junction protein

Cortical Dysplasia with Cytomegaly

- Unilateral dysplasia – hemimegalencephaly
- Focal cortical dysplasia
- Tuberous Sclerosis
<table>
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<tr>
<th>FCD Type I</th>
<th>Focal Cortical Dysplasia with abnormal radial cortical lamination (FCD Ia)</th>
<th>Focal Cortical Dysplasia with abnormal tangential cortical lamination (FCD Ib)</th>
<th>Focal Cortical Dysplasia with abnormal radial and tangential cortical lamination (FCD Ic)</th>
</tr>
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<tr>
<td>FCD Type II</td>
<td>Focal Cortical Dysplasia with dysmorphic neurons (FCD IIA)</td>
<td>Focal Cortical Dysplasia with dysmorphic neurons and balloon cells (FCD IIB)</td>
<td></td>
</tr>
<tr>
<td>FCD Type III</td>
<td>Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD IIIa)</td>
<td>Cortical lamination abnormalities adjacent to a glial or glio-neuronal tumor (FCD IIIb)</td>
<td>Cortical lamination abnormalities adjacent to vascular malformation (FCD IIIc)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD IIIId)</td>
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The clinico-pathological spectrum of Focal Cortical Dysplasias: a consensus classification proposed by an *ad hoc* Task Force of the ILAE Diagnostic Methods Commission.
Tuberous Sclerosis
Tuberous Sclerosis

NF

GFAP
• Locus heterogeneity with disease-determining genes mapped to chromosome 9q34 (TSC1 gene; product – hamartin) and 16p13.3 (TSC2 gene; product – tuberin).

• Allelic loss (i.e. loss of heterozygosity) for 16p13.3 has been demonstrated in hamartomas, a cortical tuber, and a giant cell astrocytoma from tuberous sclerosis patients. This is consistent with the hypothesis that TSC2 acts as a tumor suppressor gene.

• TSC1 and 2 gene products are strategically important in cell growth and turnover

Hydrocephalus

• Enlargement of cerebral ventricles due to increased CSF
• Distinguish from “hydrocephalus” due to decreased brain volume
• Etiologically heterogeneous
**Hydrocephalus**

- CSF overproduction
- Compromised absorption
Ventricular System

Arachnoid granulations
Superior sagittal sinus
Choroid plexus of lateral and third ventricles
Lateral ventricle
Third ventricle
Fourth ventricle
Lateral recesses of fourth ventricle

Major sites of CSF block

i  Foramen of Monro  
ii  Third ventricle   
iii Aqueduct of Sylvius  
iv  Foramina of Luschka and Magendie  
v  Basal cisterns/subarachnoid spaces
Hydrocephalus - Aqueduct obstruction

- The Aqueduct is the narrowest part of ventricular system, irregular curved tube with 2 constrictions either side of central ampulla
- Narrowest part in children 0.15mm$^2$ (mean 0.5mm$^2$)

Obstruction can result from
- Stenosis: sporadic, rarely recessive, X-linked form is the most common type of genetic hydrocephalus,
- Atresia
- Gliosis/ septum
- Vascular malformation (Galen)
Septum
Stenosis
X-linked hydrocephalus: absent medullary pyramids
Hydrocephalus and L1CAM

• L1CAM (cell-adhesion molecule)
• Xq28
• Mutations in this gene may cause up to 25% of congenital hydrocephalus in males
• Loss-of-function (»failed interaction with cytoskeletal protein, ankyrin)
• Not all cases of aqueductal stenosis/hydrocephalus are due to L1CAM mutations
L1CAM Diseases

- X-linked hydrocephalus
  - Stenosis of aqueduct of Sylvius
- MASA syndrome (MR, aphasia, shuffling gait, adducted thumbs)
- Complicated spastic paraparesis 1
- Corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia (lower limbs), hydrocephalus
- All can occur in same family: CRASH syn
Holoprosencephaly (HPE)

- Developmental defect of the forebrain (prosencephalon)
- Incomplete separation of the cerebral hemispheres into distinct right and left halves
  - Other brain findings that can be seen in association with HPE do not necessarily indicate HPE (ACC, absent septum pellucidum)
- Prevalence: 1:16,000 live births
  1:250 conceptuses
Alobar HPE
Semilobar HPE
HPE Clinical Features

- Cleft lip/palate
- Eye anomalies
- Pituitary dysfunction (including SIADH)
- Congenital nasal pyriform aperture stenosis
- Seizures
- Hypotonia
HPE Microforms

- Anosmia
- Single central maxillary incisor
- Cleft lip/palate
- Congenital nasal pyriform aperture stenosis (presents like choanal atresia)
- Ocular hypotelorism
- Microcephaly
- Developmental delay / mental retardation
- Seizures
HPE Etiology

• Genetic and etiologic heterogeneity
• Teratogens
  – Diabetes, Ethanol, retinoic acid, cholesterol synthesis inhibitors
• Genetic factors
  – Cytogenetic abnormalities - Trisomy 13
  – Genetic defects
  – Syndromes - Smith-Lemli-Opitz
  – Incomplete penetrance
  – Variable expressivity
HPE Genes

- 7q36 SHH
- 13q32 ZIC2
- 2p21 SIX3
- 18p11 TGIF
- 9q22 PTCH
- 3p23 TDGF1
- 2q14 GLI2
- Other loci have been described
HPE Genes

• Many PHE patients do not have a defined genetic cause
• Patients with detected mutations in the HPE genes to date have alterations in one allele
• HPE may be due to the interactions of multiple genetic and environmental influences
Agenesis of the Corpus Callosum

- Isolated (silent clinically, or subtle)
- Syndromic, Aicardi, Andermann, Meckel,
- Inborn errors of metabolism, chromosomal defects
- Possible pathogenetic mechanisms
  - Probst bundle of misdirected fibers
  - Midline glial sling: exptal manipulation, acallosal mice
  - Mechanical defect suggested by hamartoma/ lipoma
Agenesis of the Corpus Callosum

Normal

Probst bundles