Cerebral dysgenesis

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Disclosure

• Dr. Mochida has no relevant financial relationship to disclose.
Agenda

• Introduction

• Examples of brain malformations
  – Microcephaly
  – Lissencephaly
  – Polymicrogyria
  – Hemimegalencephaly and focal cortical dysplasia
  – Brain malformations due to congenital Zika virus infection
Phenotypes of human developmental brain disorders

- Developmental delay and intellectual disability
- Epilepsy
- Focal neurological signs
- Microcephaly
- Macrocephaly
- Learning disorders
- Autism
- Psychiatric disorders
Cerebral cortical development

Preplate Stage (proliferation) 6-7wk

Cortical Plate Stage (migration, patterning) 7-24?wk

Late Embryonic Stage (layering, axon growth) 5-7mo~

Adult
Microcephaly: overview

• Microcephaly = “small head”, failure of brain to achieve normal size
• Head circumference >2SD below the mean for the person’s age and sex
• Highly heterogeneous (environmental vs. genetic, congenital vs. postnatal)
• ~300 genes in OMIM (Online Mendelian Inheritance in Man)
• Etiology remains unidentified in about 40% of cases [von der Hagen et al., Dev Med Child Neurol (2014)]

[Normal brain](a) [Microcephaly (normal gyral pattern)](b) [Microcephaly (abnormal gyral pattern)](c)

[Mochida and Walsh, Curr Opin Neurol (2001)]
Microcephaly vera (primary autosomal recessive microcephaly)

- Literary means “true” microcephaly [Giacomini 1885]
- A clinical subtype of microcephaly, and is characterized by:
  - Severe microcephaly present at birth (congenital microcephaly)
  - Relatively normal early motor development
  - Intellectual disability, often moderate
  - Epilepsy uncommon

A child with microcephaly vera
[Dr. Anna Rajab]
Genetics of microcephaly vera

- To date, 15 loci/genes have been reported
- Most common genes are *ASPM* (40-50%) and *WDR62* (10-15%)
- Many proteins encoded by microcephaly vera genes, including ASPM and WDR62, are implicated in mitotic spindle and centrosome function, and are thought to regulate cell division of neural progenitor cells
Brain MRI of individuals with ASPM mutations

a: axial brain MRI; individual with an ASPM mutation (13 y)
b: axial brain MRI; control (11 y)
c: sagittal brain MRI; individual with an ASPM mutation (8 y)
d: sagittal brain MRI; control (11 y)

[C. G. Woods, P. E. Grant, K.S. Krishnamoorthy and G. H. Mochida]
WDR62 mutations are associated with a wide range of cortical malformations

[Yu, Mochida et al., Nat Genet (2010)]

[Nicholas et al., Nat Genet (2010)]
ASPM and WDR62 proteins localize to the mitotic centrosome/spindle pole

[Kouprina et al., Hum Mol Genet (2005)]

[Yu, Mochida et al., Nat Genet (2010)]
Lissencephaly ("smooth brain")

- Abnormally smooth and thick cerebral cortex
- Often with intractable epilepsy, severe developmental delay, microcephaly
- Four genes \((LIS1, DCX, TUBA1A, ARX)\) can cause similar lissencephaly
  - \(LIS1\) = lissencephaly 1
  - \(DCX\) = doublecortin
  - \(TUBA1A\) = tubulin, alpha-1a
  - \(ARX\) = aristaless-related homeobox, X-linked
Clinically distinguishing different lissencephaly genes

• Family history
  – Autosomal dominant (de novo) in \(LIS1^*/TUBA1A\), and X-linked in \(DCX\) and \(ARX\)
  * Some cases are due to balanced translocation in parents

• Brain imaging
  – \(LIS1\): P (posterior) > A (anterior)
  – \(DCX\): A>P
  – \(TUBA1A\)**: P>A (may be centered in the perisylvian region), small cerebellum, abnormal anterior limb of the internal capsule
  – \(ARX\)**: P>A, cortex not as thick, absent corpus callosum

*\(TUBA1A\) and \(ARX\) may cause a wide range of imaging findings
Anterior-posterior gradient of gyral abnormalities in *LIS1* and *DCX* mutations

*LIS1* mutations

*DCX* mutations

[Pilz et al., Hum Mol Genet (1998)]
MRI findings of ARX mutations

Hydranencephaly

Lissencephaly, callosal agenesis, basal ganglia abnormalities (classic presentation)

Lissencephaly, callosal agenesis, posterior fossa abnormalities

[Kato et al., Hum Mut (2004)]
**TUBA1A mutations: a wide range of radiological presentations**

- Lissencephaly to polymicrogyria (often most severe in the perisylvian region)
- Abnormal anterior limb of the internal capsule (fused basal ganglia)
- Callosal agenesis/hypoplasia
- Small cerebellum


TUBA1A = tubulin, alpha-1a; Autosomal dominant (de novo)
Lissencephaly as a disorder of microtubules

Microtubules regulate migration of neurons during brain development
- Both LIS1 and DCX regulates microtubules
- TUBA1A is a structural component of microtubules
- Exception: ARX is a homeobox protein involved in migration of GABAergic interneurons
Polymicrogyria

- Cortical malformation characterized by numerous small meandering gyri
- Genetic and environmental (e.g., congenital infection) causes polymicrogyria
- One of the most common malformations of cortical development
- Often epileptogenic
  - Seizure in 78% (mean age of onset: 4.9 years; median: 2 years) [Leventer et al. Brain (2010)]
**TUBB2B** mutations can cause asymmetric polymicrogyria

- Abnormalities of corpus callosum, basal ganglia, internal capsule and posterior fossa (similar to **TUBA1A** mutations)
- Tubulins polymerize into microtubules, which are a major component of cytoskeleton
- “Tubulinopathies”

[Jaglin et al., Nat Genet (2009)]

TUBB2B=tubulin, beta-2b; Autosomal dominant (de novo)
Clinical spectrum of *TUBB2B* mutations

- *TUBB2B* mutations have also been found in cases of diffuse polymicrogyria

- However, the frequency of *TUBB2B* mutations in polymicrogyria may be relatively low (~2%)

[Guerrini et al., Eur J Hum Genet (2012)]
Chromosomal abnormalities and polymicrogyria

• Polymicrogyria with DiGeorge syndrome first reported in 1996 [Cramer et al., J Child Neurol (1996)]
• Since then, many patients with 22q11.2 (DiGeorge/velocardiofacial syndrome critical region) deletion have been reported
• Subsequently other loci (e.g., 1p36) were implicated [Dobyns et al., Am J Med Genet Part A (2008)]
• Testing by chromosomal microarray is often indicated, but there is no good data about its yield
Somatic mosaicism and cortical dysgenesis

- Mutations are present only in some cells of the body
- Recently found in various cortical malformations
- DNA sequencing may fail to identify mutations

[Campbell et al., Trends Genet (2015)]
Cortical malformations could be due to somatic mosaic mutations

[Jamuar et al., New Eng J Med (2014)]
Mosaic mutations may not be detected by traditional (Sanger) sequencing

Table 2. Phenotypes and Distributions of Types of Pathogenic Mutations Detected.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Participants</th>
<th>Mutations</th>
<th>Mosaic Mutations Missed by Sanger Sequencing</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>All</td>
<td>Germline</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>--------------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Double-cortex syndrome</td>
<td>30</td>
<td>9 (30)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Polymicrogyria with megalencephaly</td>
<td>20</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Periventricular nodular heterotopia</td>
<td>61</td>
<td>8 (13)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Pachygyria</td>
<td>47</td>
<td>8 (17)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Total</td>
<td>158</td>
<td>27 (17)</td>
<td>19 (12)</td>
</tr>
</tbody>
</table>

* Mosaic mutations account for 30% of the 27 mutations detected in the study participants.

[Jamuar et al., New Eng J Med (2014)]
Genetic mechanism of hemimegalencephaly

• Mutations of genes in the PI3K-AKT-mTOR pathway have been reported [Poduri et al., Neuron (2012); Riviére et al., Nat Genet (2012); Lee et al., Nat Genet (2012)]

• Some of these mutations were detected only in the brain tissue sample (i.e., somatic mosaicism)

[Poduri et al., Neuron (2012)]
PI3K-AKT-mTOR pathway and brain malformations

- PI3K-AKT-mTOR pathway regulates cell proliferation and growth
- Mutations in PIK3CA, AKT1, AKT3, PTEN and MTOR have been associated with hemimegalencephaly
- Hemimegalencephaly may be seen in individuals with tuberous sclerosis

PI3K = phosphoinositide 3-kinase  
AKT = protein kinase B  
MTOR = mechanistic target of rapamycin  
PTEN = phosphatase and tensin homolog

[Hevner, Semin Perinatol (2015)]
Focal cortical dysplasia and the PI3K-AKT-mTOR pathway

- $DEPDC5$ and $NPRL3$ are regulators of mTOR

Germline mutations in $DEPDC5$

[D’Gama et al., Ann Neurol (2015)]
Global distribution of Zika virus vector mosquitoes

Global map of the predicted distribution of *Aedes aegypti*

Global map of the predicted distribution of *Aedes albopictus*

[Kraemer et al. (2015) eLife]
Clinical characteristics of congenital Zika syndrome

- Congenital microcephaly
- Abnormal neuroimaging findings
  - Intracranial calcification (primarily subcortical)
  - Ventriculomegaly
  - Cortical gyral abnormalities (polymicrogyria, lissencephaly [agyria])
- Seizures
- Retinal lesions
- Sensorineural hearing loss
- Arthrogryposis/hip dysplasia
- Hydrocephalus

Spectrum of head CT findings in congenital Zika syndrome

- Calcification (often subcortical)
- Ventriculomegaly
- Gyral abnormalities (polymicrogyria, lissencephaly?)

[Drs. Vanessa van der Linden, Adriano Hazin, Fatima Vasco Aragão]
Spectrum of brain MRI findings in congenital Zika syndrome

- Calcification (often subcortical)
- Ventriculomegaly
- Gyral abnormalities (polymicrogyria, agyria)
- White matter signal abnormalities
- Progressive hydrocephalus

[Drs. Vanessa van der Linden, Adriano Hazin, Fatima Vasco Aragão]
Neuroimaging of congenital cytomegalovirus infection

- Agyria
- Calcification

- Polymicrogyria

- White matter signal abnormalities
- Calcification

- Polymicrogyria
- Calcification

[Barkovich and Lindan (1994) AJNR]
Clinical approach to cortical dysgenesis

1. Etiological work-up
   - Detailed history and examination
   - Imaging (MRI) analysis
   - Genetic (or other laboratory) testing

2. Intervention
   - Epilepsy
   - Development (Early Intervention)
   - Other neurological and non-neurological complications

3. Counseling
   - Clinical course
   - Genetic counseling
Options and strategies for genetic testing

1. Specific gene testing (sequencing, deletion/duplication analysis)
   – Usually the method of choice if the condition is associated with a small number of genes

2. Panel testing for a disease group
   – Important to know which genes and tests are included in the panel (e.g., sequencing only or including deletion/duplication testing)

3. Whole-exome/whole-genome sequencing
   – Variability among labs in analysis and reporting
   – May identify incidental findings
   – Referral to a geneticist/genetic counselor recommended
   [American College of Medical Genetics policy statement]
Database of available clinical genetic tests and disease information

http://www.genetests.org


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