This conference is part of the Educational Program of Excellence on CDG created by the Portuguese Association for CDG (APCDG, www.apcdg.com).

It is organized in partnership with several associations and/or country CDG patient advocates: CDG Australia, CDG Brazil, CDG Czech Republic, CDG Denmark, Foundation of Glycosylation (the FoG) Canada, CDG Denmark, CDG Italy/Ireland, CDG Israel, Les ptits CDG France, CDG Spain, CDG Sweden, CDG USA, CDG UK charity and CDG The Netherlands.
THE POWER OF ADVANCING PATIENT-ORIENTED RESEARCH UNITED
FAMILIES AND PROFESSIONALS

01 CDG IMPACT ON FAMILIES
02 RESEARCH
03 GOAL: CURE CDG
04 UNITED TO OVERCOME CHALLENGES
05 WHY YOU SHOULD ATTEND WORLD CONFERENCE ON CDG (WCCDG)?
06 OUTCOMES FROM THE CONFERENCE?
07 HOPE FOR PATIENTS AND THEIR FAMILIES

WORLD CONFERENCE CONGENITAL DISORDERS OF GLYCOXYLATION

This and other resources available at:
www.apcdg.com
Intellectual disability in congenital disorders of glycosylation

Marc C. Patterson, MD, FRACP
Professor of Neurology, Pediatrics and Medical Genetics
Mayo Clinic Children’s Center
8.29.2015, Lyon
Outline

• Intellectual disability – definition and concepts
• Intellectual disability – anatomy and physiology
• Intellectual disability in CDG
Intellectual disability – symptom complex

- *Intellectual disability* is characterized by significant limitations in both
  - *intellectual functioning* and in
  - *adaptive behavior*, which covers many everyday social and practical skills. This disability originates
- before the age of 18.

- [http://aaidd.org/intellectual-disability/definition#.VbEzivI9YVQ](http://aaidd.org/intellectual-disability/definition#.VbEzivI9YVQ)
Intellectual Functioning

• *Intellectual functioning*—intelligence—refers to general mental capacity, such as
  • learning, reasoning, problem solving, and so on.

• Measurement: IQ test. FSIQ of 70 -75 indicates a limitation in intellectual functioning.

Adaptive Behavior

- *Adaptive behavior* –
  - conceptual, social, and practical skills
  - learned and performed by people in their everyday lives.

http://aaidd.org/intellectual-disability/definition#.VbEzivl9YVQ
Adaptive behavior

• Conceptual skills—language and literacy; money, time, and number concepts; and self-direction.

• Social skills—interpersonal skills, social responsibility, self-esteem, gullibility, naïveté (i.e., wariness), social problem solving, and the ability to follow rules/obey laws and to avoid being victimized.

• Practical skills—activities of daily living (personal care), occupational skills, healthcare, travel/transportation, schedules/routines, safety, use of money, use of the telephone.

• [Link](http://aaidd.org/intellectual-disability/definition#.VbEzivl9YVQ)
ID – additional factors

• community environment typical of the individual’s peers and culture.

• linguistic diversity and cultural differences in the way people communicate, move, and behave.

• assume that limitations in individuals often coexist with strengths

• a person’s level of life functioning will improve if appropriate personalized supports are provided over a sustained period.

• http://aaidd.org/intellectual-disability/definition#.VbEzivl9YVQ
Neurological bases of intellectual disability

• Non-classical and non-localizable
• Multiple networks contribute to intellectual function:
  • Neurogenesis (proliferation)
  • Neuronal migration

• Cellular signalling cascades
• Regulation of transcription and translation
• Inter-neuronal connectivity
• (pre-synaptic vesicle formation, synaptogenesis, synaptic plasticity, dendrite morphogenesis, post-synaptic density)
Brain
Neuron

Dendrite

Cell body

Axon terminal

Node of Ranvier

Schwann cell

myelin

nucleus
Myelination
Common pathways in intellectual disability

• Synapse and ionotropic glutamate receptors
  • AMPA, NMDA, MAGUK proteins, SHANK2, SHANK3, SNARE complex

• Intracellular signalling cascades
  • RAS-MAPK (neuro-cardio-facio-cutaneous conditions); P13K- mTOR

• Epigenetic regulation of transcription
  • DNA methylation, Histone post-translational modification
The synapse

- Synaptic vesicle
- Voltage-gated Ca++ channels
- Post-synaptic density
- Neurotransmitters
- Neurotransmitter re-uptake pump
- Neurotransmitter receptors
- Axon Terminal
- Synaptic Cleft
- Dendritic Spine

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Glutamic acid – major excitatory neurotransmitter
Intracellular signalling cascades
RAS-MAPK

RAS pathway

RAS-GDP
(p120GAP, NF1) GAPs
GEFs (SOS1/2, RAS GRPs RAS GRFs)

RAS-GTP

RAF
PLCε
AKT
RAL

PI3K
RALGDS

PDK1
MEK
ERK

Membrane trafficking
Survival
Survival
Calcium signalling
Apoptosis

RASSF1
NORE1

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Syndromic disorders associated with RAS-MAPK pathway disruption

J Med Genet 2008;45:695-703 doi:10.1136/jmg.2007.055772
RAS-MAPk and P13K - mTOR
Syndromic disorders associated with mTOR pathway disruption

http://www.biomedj.org/article.asp?issn=2319-4170;year=2013;volume=36;issue=2;spage=40;epage=50;aulast=Wong
Epigenetic regulation of transcription
Control of gene expression

Gene on DNA → Primary transcript → mRNA → NUCLEUS → CYTOSOL → Protein

- transcriptional control
- RNA processing control
- RNA transport control
- translation control
Interaction between RNA, histone modification and DNA methylation in heritable gene silencing.

## Epigenetic diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Manifestation</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR-X</td>
<td>ID, thalasemia</td>
<td>ATRX mutations, hypomethylation</td>
</tr>
<tr>
<td>FRA-X</td>
<td>ID</td>
<td>FMR1 CGG repeat expansion</td>
</tr>
<tr>
<td>Angelman</td>
<td>ID, ataxia, microcephaly</td>
<td>15 q11-13 maternal imprinted genes deregulated</td>
</tr>
<tr>
<td>Prader-Willi</td>
<td>ID, obesity</td>
<td>15 q11-13 paternal imprinted genes deregulated</td>
</tr>
<tr>
<td>Rett</td>
<td>ID, seizures</td>
<td>MeCP2 mutations</td>
</tr>
<tr>
<td>Rubinstein-Taybi</td>
<td>ID, dysmorphism</td>
<td>CREB mutations (histone acetylation)</td>
</tr>
<tr>
<td>Coffin-Lowry</td>
<td>ID, dysmorphism</td>
<td>Rsk-2 mutation (histone phosphorylation)</td>
</tr>
</tbody>
</table>
Intellectual disability in CDG

- Intellectual disability occurs in most types and is
  - Developmental
  - Dose-related
  - Without clear anatomic correlate in many cases
  - Related to migrational disorders in O-linked forms
  - Non-syndromic in TUSC3-CDG
What can be done for intellectual disability in CDG?

- Early intervention
- Education
- Employment
- Health care
- Prevention
- Legal issues
  - Vulnerability, guardianship, protection, rights
Thank you!
Additional slides
Neuroanatomy basics

- Nervous system
  - Central nervous system (brain and spinal cord)
  - Peripheral nervous system
    - Autonomic nervous system (communicates with internal organs and glands)
      - Sympathetic division (arousing)
      - Parasympathetic division (calming)
    - Somatic nervous system (communicates with sense organs and voluntary muscles)
      - Sensory (afferent) nervous system (sensory input)
      - Motor (efferent) nervous system (motor output)
Normal myelination

Newborn 18 months 28 months
Cognition – “higher cortical function”

- Global impairment:
  - Intellectual disability
  - Dementia
  - Psychiatric symptoms

- Focal impairment:
  - Dysphasia
  - Learning disabilities
    - dyslexia
    - dyscalculia
Motor

- Corticospinal tracts
- Basal ganglia
- Cerebellum and connections
- Spinal cord
- Motor unit
  - roots, peripheral nerves, NMJ, muscle
Sensory

- General
  - Internal
  - External

- Special senses
  - Vision
  - Hearing
  - Taste
  - Smell
Foundation Glycosylation (FoG) is the official sponsor of the videos targeted to the “SSIEM Official Satellite Symposia – Second World Conference on Congenital Disorders of Glycosylation (CDG): a challenging story of sugar trees”:

The Foundation Glycosylation (FoG) founded by Duncan Webster (Canada), is the official sponsor of the videos of all oral session that will be given during the conference. This material will be available in the Youtube channel dedicated to “SSIEM Official Satellite Symposia – Second World Conference on Congenital Disorders of Glycosylation (CDG): a challenging story of sugar trees” at:

For more information about the work of this organization which is focused on research to ALG9 -CDG (CDG -1L), visit the following link:

http://www.thefog.ca/main.html

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