X-linked Intellectual deficiency: Current research and impacts of genetics

NB: There are specific associations of parents for FMR1 (Fragile X) and Rett syndrome,
Chromosome X and Syndromal XLID genes

- Oral-facial-digital I (OFD1)
- X-linked VACTERL-hydrocephalus (FANCB)
- Turner, XLID-hydrocephaly-basal ganglia calcification
- Coffin-Lowry (RSK2)
- Nance-Horan (NHS)
- Pyruvate dehydrogenase deficiency (PDHA1)
- Glyceraldehyde kinase deficiency (GKD)
- Duchenne muscular dystrophy (DMD)
- Ornithine transcarbamylase deficiency (OTC)
- XMRE (Renin receptor; ATP6AP2)
- Arts, PRPP synthetase superactivity (PRPS1)
- Ornithine transcarbamylase deficiency (OTC)
- Creatine transporter deficiency (SLC6A8)
- *XLID-hypotonia-recurrent infections (MECP2 dup)
- Autism (NLGN4)
- Telecanthus-hypospadias (MID1)
- MIDAS (HCCS)
- XLID-infantile seizures, Rett like (CDKL5, STK9)
- Spermine synthase deficiency (SMS)
- Ichthyosis follicularis, atrichia, photophobia (MBTPS2)
- Partington, West, Proud, XLAG (ARX)
- Norrie (NDP)
- OFCD, Lenz microphthalmia (BCOR)
- Monoamine oxidase-A deficiency (MAOA)
- Turner macrocephaly, XLID macrocephaly (HUBWE1)
- Cantagrel spastic paraplegia (KIAA2022)
- Duchenne muscular dystrophy (DMD)
- Round cell macrogoliosis (ARHGEF9)
- X-linked macrocephaly-hypotonia-facies (RAB39B)
- Menkes disease (ATP7A)
- Phosphoglycerate kinase deficiency (PGK1)
- Allan-Herndon (MCT8, SLC16A2)
- Cantagrel spastic paraplegia (KIAA2022)
- XLID-macrocephaly-large ears (BRWD3)
- XLID-hyperekplexia-seizures (ARHGEF9)
- Mohr-Tranebaerg (DPP, TIMM8A)
- Pelizaeus-Merzbacher (PLP)
- Arts, PRPP synthetase superactivity (PRPS1)
- Mitochondrial encephalopathy (NDUFA1)
- Danon cardiomyopathy (LAMP2)
- FG/Lujan phenotype (UPF3B)
- Chionobu XLID (GRIA3)
- Lowe (OCRL1)
- Simpson-Golabi-Behmel (GPC3)
- Christianson, Angelman-like (SLC9A6)
- Fragile XA (FMRI)
- Mucopolysaccharidosis IA (IDS)
- Adrenoleukodystrophy (ABCD1)
- Rett, PPM-X (MECP2)*
- Autism (RPL10)
- Autism (NLGN4)
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Syndromal XLID genes

- Autism (NLGN4)
- Telecanthus-hypospadias (MID1)
- MIDAS (HCCS)
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Greenwood Genetic Center, updated Oct 2010
Large-scale identification of XLID genes within the last 15 years

- In the last 10 – 15 years, a great number of mutations have been identified in genes. But from Xtraordinaire point of view, main ones regarding the number of patients are:
  - ARX,
  - RSK2 / Coffin-Lowry syndrome
  - PQBP1 / Renpenning syndrome
  - SLC6A8 / Deficiency carrier of X-linked creatine
  - MECP2 duplication (different from Rett syndrome)
  - ATRX
  - OPHN1, MCT8, FGD1, and many others…

  NB : Different mutations on the same gene can cause different MR syndromes (for example, ARX : Partington syndrome and ‘XLAG’)

- Prevalence : From recent studies, X-linked factors are responsible from 8 to 12% of Intellectual Deficiencies,
  - Actually, for each “main” disorders, we believe only 10 to 80 patients are known to have one of the diagnosis listed above in France,
Xtraordinaire: The scope

- Founded in 2006, by a small group of parents.
  - 1 to 2 conferences each year to recruit parents concerned with a specific syndrome
  - Initiatives to extend solidarity between parents,
  - Direct partnership with expert doctors
  - Communication to inform families and professionals about those disorders
  - Representation of patients
  - Fund raising

- Specific aims:
  - X-Linked Inheritance: Family stories with boys being patients and mother carriers (Rarely, Female carriers manifest a less crucial phenotype)
  - 1 association for several groups, each group being dedicated to one syndrome
    - Board members, Parents leaders for each syndromes, Caring individuals for the administration and the organization of events …
  - No such association with the same scope exists outside France ➔ How to export this approach?

- 2012:
  - 60 to 80 families either being members or in contacts with Xtraordinaire
  - Around 200 followers
  - Member of Alliance Maladies Rares,
X-chromosome experts in France

- Geneticists:
  - Pr. Jamel Chelly, in Inserm, expert on XLID, member of the European XLMR Consortium, founded in 1995,

- Clinicians:
  - From Plan Maladies Rares 1 (National plan for Rare Disorders): ‘Defiscience’ network: 2 complexes dedicated to rare genetic intellectual diseases, in Lyon (Pr. des Portes), and in Paris (Dr. Delphine Héron)
  - A “clinical” research program dedicated to XLID:
    - One hospital and one of its practitioners is responsible to identify pathophysiological functions of one gene and impacts on functionalities and capabilities of patients,
    - Examples: Dr. Curie on ARX, Dr. Germanaud on PQBP1 …

- Geneticists and partly clinicians: a few experts specialized in one of the syndromes, with international opening:
  - Dr. Vassili Valayannopoulos, in Necker Hospital, for ‘deficiency carrier of X-linked creatine’
  - Pr. André Hanauer, in Igbmc Strasbourg, for Coffin Lowry Syndrome
‘PHRC’ : French clinical research program

Rare disorders
Only a few families

Opportunities for therapeutic research

No process for diagnosis in laboratories

Diagnosis in laboratories

XLDI rare diseases

No request for diagnosis

Description of Specific Clinical phenotypes

New clinical practices

• Regional network of clinicians

• Regional network of laboratories
• Screening of the full family

• More patients with diagnosis
• Common Database
• Standardized medical record

• Cohorts of well-characterized families
• Analysis of sporadic cases
• Clinical surveys
• Therapeutic tests

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Increase diagnosis?

1. Identifying genetic etiology still remains an important task if cognitive impairment is the only manifestation,

   Today, only families with more than one disabled boy benefit of a diagnosis

2. Patient diagnosis, actually a challenge, will be possible at a larger scale:
   1. Today, need to combine physical examination, laboratory investigation and brain imaging
   2. Extension of automated mutation-detection protocols, sequencing many genes in a single experiment, will arise soon:
      1. Right now? high-resolution array CGH
      2. In the near future? Full Exome sequencing

   The exponential increase of the number of genes diagnosis is a perplexing challenge for our parents organization,

3. Benefit of diagnosis:
   1. Genetic counseling, including reproductive options
   2. Knowledge of the possible performances of the patients, even if it is highly relative to variability of patients, and submitted to environmental factors,
   3. Vindication of the Rights of the patients

Diagnosis is a strong opportunity for families if sufficient information about the disease can lead to health care
Toward therapeutic approaches?

1. Behavioral and cognitive therapies can help patients reach their maximum potential.
   1. Priority is to develop targeted treatment and assessment services from diagnosis to social integration into society,
   2. In parallel, promote guidance of the families to allow them to realize effective personal project for the child or the adult patient.

2. Pathways? Defects happens to be often a consequence of the synaptic structure and/or function and neuronal connectivity, hampering the ability of the brain to process information
   1. New and unexpected possibilities for drug treatment of similar disorders are leading to opportunities for therapy program, looking for the right molecule,
   2. This approach can be even more fantastic if it means that therapeutic intervention might be possible even after birth,

3. Actually, No resources dedicated in France to develop this type of programs:
   1. Regarding the number of patients, need to know what is done in all countries,
   2. Parents’ association need to cooperate together

How to push for international cooperation in clinical research and pharmacogenetics?