Epidemiology and Genetics of Mucopolysaccharidoses

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Wiesbaden, 2nd November 2015
<table>
<thead>
<tr>
<th>Disease</th>
<th>No. / 100 000 Births</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS II</td>
<td>0.3 (0.6–0.6 (1.3))</td>
<td>Meikle et al (1999), Poorthuis et al (1999), Nelson (1997), Lowry and Renwick (1971), Lowry et al (1990), Applegarth et al (2000), Schaap and Bach (1980)</td>
</tr>
<tr>
<td>(non-Jewish population)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS IV B</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>MPS IX</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>

CLUSTERS

MPS IVA

Northern Ireland: 1,3/100 000 (J Hum Genet (1997) 101:355)
United Arab Emirates: 1,4/100 000 (JIMD Rep (2013) 10:1)

MPS VI

Northeast Brazil: 20/100 000 (Mol Genet Metab (2011) 104:603)
United Arab Emirates: 2,5/100 000 (JIMD Rep (2013) 10:1)
NEWBORN SCREENING
Mucopolysaccharidosis Type I

TAIWAN (Orphanet J Rare Dis (2013) 8:147)

- Fluorometric assay in dried blood spots
- 35,285 newborns were screened,
- Incidence MPS I: 1:17 643 = 5,7 : 100 000

MISSOURI, USA (J Pediatr (2015) 166:172)

- Multiplexed fluorometric assay in dried blood spots
- 43 701 newborns were screened for 4 LSDs
- Incidence MPS I: 1:14 567 = 6,9 : 100 000
Selective Screening in Columbia
(242 LSDs in 4700 Samples)

Uribe, A et al. JIMD Rep (2013) 11: 107
MPS I (α-Iduronidase Deficiency)

- IDUA gene: 4p16.3 / ~ 19kb / 14 exons
- More than 100, mostly missense mutations have been described
- Overall, most mutations are ‘private’, with only four mutations (p.W402X, p.Q70X, p.P533R, p.G51D) being common in specific populations
- MPS I-Hurler: 60% - 80% carry a non-sense mutation (suitable for read-through treatment !)

MPS II (Iduronate Sulfatase Deficiency)

- IDS gene: Xq27.3-q28 / ~ 24 Kb / 9 exons
- A pseudogene with homologous regions is located approximately 25 Kb telomeric to the functional gene
- About 500 mutations have been described, most (~ 70%) being private mutations
- 10–20% of MPS II patients: large gene alterations, including rearrangements and total IDS gene deletions
- 80–90% of MPS II patients: small gene alterations

http://www.hgmd.cf.ac.uk/ac/index.php
**Genes and Mutations**

**MPS IIIA (Sulfamidase Deficiency)**
- SGSH gene: 4p16.3 / ≈ 19kb / 14 exons
- About 80 different (missense) mutations

**MPS IIIB (α-N-Acetyl-Glucosaminidase Deficiency)**
- NAGLU gene: 17q21.1 / 8.2kb / 6 exons
- More than 100, mostly missense, mutations

**MPS IIIC (N-Acetyltransferase Deficiency)**
- HGSNAT gene: 8p11.1 / 62.4kb / 18 exons
  - More than 60 mutations

**MPS IIID (GlucNac-6-S Sulphotase Deficiency)**
- GNS gene: 12q14 / ≈ 43 kb / 14 exons
  - More than 20 mutations, 4 large deletions

http://www.hgmd.cf.ac.uk/ac/index.php
MPS IV A (GalNac-6-S Sulphatase Deficiency)
- GALNS gene: 16q24.3 / ~50 kb / 14 exons
- About different 200 mutations

MPS VI (GalNac-4-S Sulphatase Deficiency)
- ARSB gene: 5q11–q13 / ~44 kb / 8 exons
- About 150 different mutations

MPS VII (β-Glucuronidase Deficiency)
- GUS gene: 7q21.11 / ~20 kb / 12 exons
- About 60 different mutations

http://www.hgmd.cf.ac.uk/ac/index.php
The Diagnostic Future

MPS Type II (Hunter`s Disease)  
X-Linked Disorder!
<table>
<thead>
<tr>
<th>Sign and Symptom</th>
<th>Carriers (N = 40)</th>
<th>Non-carriers (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women presenting at least one abnormal finding in anamnesis/physical examination(^a)</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Prematurity</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Seizures during childhood</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myopia and/or astigmatism</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sleep obstructive apnoea syndrome (mild)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypoacusia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tumors(^b)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Prolapse of mitral valve</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Interventricular communication</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Short stature</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macrocephaly</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Palpebral ptosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Facial asymmetry</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Joint contractures</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pebbly skin lesion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Café au lait spots</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stiff joints</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Developmental delay (mild)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Learning problems</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Signs and Symptoms of MPS II Carriers

Iduronate-Sulphatase Activity

Absence of α-galactosidase cross-correction in Fabry heterozygote cultured skin fibroblasts

Maria Fuller \textsuperscript{a,b,*}, Natalie Mellett \textsuperscript{c,1}, Leanne K. Hein \textsuperscript{d,1}, Doug A. Brooks \textsuperscript{e,1}, Peter J. Meikle \textsuperscript{c,1}
MPS II in Females

I. Abnormal X-Chromosome (e.g. X;9 - Translocation)

MPS II in Femals

II. Unequal X-Inactivation (98:2)

MPS II in Females

III. Homozygosity

- 11 years old girl
- Daughter of consanguineous parents
- Small stature, hepatomegaly
- No dysmorphic signs
- No mental retardation

Mutation analysis: Homozygosity  p.L41P

Mucopolysaccharidosis Type II
Clinical Manifestation in Females

- Abnormalities of the X-Chromosome
- Unequal X-Inactivation (e.g. twins, Turner syndrome)
- Homozygosity
- Others?
Mutations of the IDS Gene

- About 500 mutations have been described, most (~70%) being private mutations
- MPS II is X-linked recessive
- Reproductive fitness of carriers = 1
- Reproductive of affected males is close to zero →
  ≈ 1/3 are new (de novo) mutations
Deletion of the IDS Gene and both DXS466 and DXS304 in a MPS II Patient

Which Way will we take in the Future?