Rare Diseases
Nomenclature and classification

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Using standards and embedding good practices to promote interoperable data sharing in ERNs
26 Apr 2017
## Orphanet RD nomenclature

<table>
<thead>
<tr>
<th>ORPHA number</th>
<th>Preferred label</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORPHA:93545</td>
<td>Renal or urinary tract malformation</td>
<td>CAKUT</td>
</tr>
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<td></td>
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<td>Congenital anomalies of kidney and urinary tract</td>
</tr>
<tr>
<td>ORPHA:216</td>
<td>Neuronal ceroid lipofuscinosis</td>
<td>NCL</td>
</tr>
<tr>
<td>ORPHA:586</td>
<td>Cystic fibrosis</td>
<td>CF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucoviscidosis</td>
</tr>
<tr>
<td>ORPHA:355</td>
<td>Gaucher disease</td>
<td>Acid beta-glucosidase deficiency</td>
</tr>
<tr>
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<td>Glucocerebrosidase deficiency</td>
</tr>
<tr>
<td>ORPHA:77259</td>
<td>Gaucher disease type 1</td>
<td>Non-cerebral juvenile Gaucher disease</td>
</tr>
</tbody>
</table>

- The only clinical terminology specific for rare diseases
- Unique, stable ORPHA number
- Definitions
- 8 languages (En, Fr, Es, It, Nl, De, Pt, Pl)
- Peer-reviewed publications only (2 cases<RD<1/2000)
Usher syndrome

Disease definition

Usher syndrome (US) is characterized by the association of sensorineural deafness (usually congenital) with retinitis pigmentosa and progressive vision loss.

ORPHA:886

Synonym(s):
Retinitis pigmentosa-deafness syndrome

USH

Prevalence: 1-9 / 100 000
Inheritance: Autosomal
RD classification

- Why?
  - Improve information
  - Epidemiology and statistics studies

- How?
  - Organized by medical specialties

- Particularity
  - Systemic disorders
Multi-classification

Multi-dimensional

- X-linked adrenoleukodystrophy

- Orphanet classification of rare inborn errors of metabolism
- Orphanet classification of rare genetic diseases
- Orphanet classification of rare neurological diseases
- Orphanet classification of rare endocrine diseases
- Orphanet classification of rare infertility disorders

Multi-hierarchical

- Rare neurologic disease ORPHA:98006
  - Rare epilepsy ORPHA:101998
    - Metabolic diseases with epilepsy ORPHA:166481
      - Peroxisomal disease with epilepsy ORPHA:225686
        - X-linked adrenoleukodystrophy ORPHA:43
    - Adrenomyeloneuropathy ORPHA:139399
      - X-linked cerebral adrenoleukodystrophy ORPHA:139396
- Rare neurologic disease ORPHA:98006
  - Neurometabolic disease ORPHA:68385
    - X-linked adrenoleukodystrophy ORPHA:43
    - Adrenomyeloneuropathy ORPHA:139399
      - X-linked cerebral adrenoleukodystrophy ORPHA:139396
- Rare neurologic disease ORPHA:98006
  - Leukodystrophy ORPHA:68356
    - X-linked adrenoleukodystrophy ORPHA:43
    - Adrenomyeloneuropathy ORPHA:139399
      - X-linked cerebral adrenoleukodystrophy ORPHA:139396
Logical structure

Group

Category: clinically heterogeneous
Clinical group: clinically homogeneous

Disorder:
• Disease, clinical syndrome, malformation syndrome, morphological anomaly, biological anomaly, particular clinical situation

Subtype:
• Clinical, etiological, histopathological

• Every entity is meaningful
• Entities are disjointed
• Parts are added to form the wholes
• Transitivity applies at every level
Rare cardiac diseases

Rare cardiac tumors

Rare cardiac rhythm diseases

Unclassified cardiomyopathies

Arrhythmogenic right ventricular cardiomyopathies

Restrictive cardiomyopathies

Dilated cardiomyopathies

Hypertrophic cardiomyopathies

Non-familial hypertrophic cardiomyopathies

Hypertrophic cardiomyopathies

Rare familial disorders with hypertrophic cardiomyopathy

Mitochondrial diseases with hypertrophic cardiomyopathy

Lysosomal diseases with hypertrophic cardiomyopathy

Fatty acid oxidation and ketogenesis disorders with hypertrophic cardiomyopathy

Syndromes with hypertrophic cardiomyopathy

Glycogen storage disorders with hypertrophic cardiomyopathy

GSD due to GDE deficiency

GSD due to LAMP-2 deficiency

GSD due to glycogen synthase deficiency

GSD due to acid maltase deficiency

GSD due to acid maltase deficiency, infantile-onset

GSD due to acid maltase deficiency, late-onset
Update process

Orphanet DB verification, literature search, expert advice

Verification of prevalence, database and classification consistency

Decision Disease committee

Creation

New entry
Reject
+ info

Modification

Nomenclature
Obsolescence
Deprecation

Qualify the demand

Expert advice

Impact on the inventory
New Orpha numbers, Status modification

Impact on the classification
New hierarchy including new orpha numbers consistency inter- and intra-classification
Some figures

9,958 Orpha numbers

32 classifications

9,521 Orpha

Groups
2,215 Orpha

Rare disorders
6,247 Orpha

Subtypes
1,059 Orpha

Deprecated
185 Orpha

Obsolete
437 Orpha

www.orpha.net
Mappings with other terminologies

<table>
<thead>
<tr>
<th>Terminology</th>
<th>mapped</th>
<th>RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-10</td>
<td>Manually</td>
<td>All</td>
</tr>
<tr>
<td>OMIM</td>
<td>Manually</td>
<td>4,390</td>
</tr>
<tr>
<td>Snomed-CT</td>
<td>Manually</td>
<td>3,800</td>
</tr>
<tr>
<td>GARD</td>
<td>Semi-automatically</td>
<td>2,998</td>
</tr>
<tr>
<td>UMLS</td>
<td>Semi-automatically</td>
<td>2,885</td>
</tr>
<tr>
<td>MeSH</td>
<td>Semi-automatically</td>
<td>1,763</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Semi-automatically</td>
<td>1,224</td>
</tr>
</tbody>
</table>

**Qualifier**

<table>
<thead>
<tr>
<th>E</th>
<th>exact mapping (the terms and the concepts are equivalent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTBT</td>
<td>narrower term maps to a broader term</td>
</tr>
<tr>
<td>BTNT</td>
<td>broader term maps to a narrower term</td>
</tr>
<tr>
<td>W</td>
<td>incorrect mapping (two different concepts)</td>
</tr>
<tr>
<td>ND</td>
<td>not yet decided/unable to decide</td>
</tr>
</tbody>
</table>

**ICD10 codes only :**

<table>
<thead>
<tr>
<th>Specific code</th>
<th>The term has its own code in the ICD10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion term</td>
<td>The term is included under a ICD10 category and has not its own code</td>
</tr>
<tr>
<td>Index term</td>
<td>The term is included in ICD10 index and refers to one more general code</td>
</tr>
<tr>
<td>Attributed code</td>
<td>The term does not exist in ICD10 and a code was attributed by Orphanet</td>
</tr>
</tbody>
</table>
## Coding perspective

<table>
<thead>
<tr>
<th>Orpha number</th>
<th>Preferred label</th>
<th>Synonyms</th>
<th>Typology</th>
<th>Status</th>
<th>ICD-10</th>
<th>Definition/relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORPHA:93545</td>
<td>Renal or urinary tract malformation</td>
<td>CAKUT, Congenital anomalies of kidney and urinary tract</td>
<td>Category</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>ORPHA:216</td>
<td>Neuronal ceroid lipofuscinosis</td>
<td>NCL</td>
<td>Clinical group</td>
<td>_</td>
<td>E75.4</td>
<td>Yes</td>
</tr>
<tr>
<td>ORPHA:586</td>
<td>Cystic fibrosis</td>
<td>CF, Mucoviscidosis</td>
<td>Disease</td>
<td>_</td>
<td>E84.0, E84.1, E84.8, E84.9</td>
<td>Yes</td>
</tr>
<tr>
<td>ORPHA:355</td>
<td>Gaucher disease</td>
<td>Acid beta-glucosidase deficiency, Glucocerebrosidase deficiency</td>
<td>Disease</td>
<td>_</td>
<td>E75.2</td>
<td>Yes</td>
</tr>
<tr>
<td>ORPHA:1245</td>
<td>BIDS syndrome</td>
<td>Amish brittle hair syndrome, Trichothiodystrophy type D</td>
<td>Disease</td>
<td>Deprecated</td>
<td>_</td>
<td>moved to Trichothiodystrophy</td>
</tr>
<tr>
<td>ORPHA:77259</td>
<td>Gaucher disease type 1</td>
<td>Non-cerebral juvenile Gaucher disease</td>
<td>Subtype</td>
<td>_</td>
<td>E75.2</td>
<td>yes</td>
</tr>
<tr>
<td>ORPHA:101042</td>
<td>Taussig-Bing syndrome</td>
<td>Subtype</td>
<td>Obsolete</td>
<td>_</td>
<td>_</td>
<td>Referred to Double outlet right ventricle with subpulmonary ventricular septal defect</td>
</tr>
</tbody>
</table>

### Orpha Code

\[
\text{Orpha Code} = \text{Orpha numbers used to be assigned to a patient within an information system}
\]
Users and information media

Health professionals
Patients
Public health stakeholders

Information on a specific disorder

R&D
Public health stakeholders
HIS

Computational use
subset of disorders/data

R&D

Computational analysis
logical inference
Similarities and differences

- Orpha numbers in use
- **deprecated** disorders

Updated daily

- Orpha numbers in use
- **deprecated** disorders

Updated monthly

- Orpha numbers in use
- **deprecated** disorders
- **obsolete** disorders

Updated bi-annually

- Orpha numbers in use
- **deprecated** disorders
- **obsolete** disorders
- Versioning with change log

xml format

owl format
Where to find a gene?

Search for a gene

**USH2A** - usherin

- **Synonym(s):** RP39
- **Chromosomal location:** 1q41
- **Genetics:** USH2A
- **OMIM:** 608400
- **HGNC:** 12601
- **UniProtKB:** 075445
- **Diseases list:**
  - Disease-causing germline mutation(s) in *Retinitis pigmentosa*
  - Disease-causing germline mutation(s) in *Usher syndrome type 2*
Genes-RD relationships

- Qualified
  - Disease **causing germline** mutation(s) in (+/- loss of function/gain of function)
  - Disease **causing somatic** mutation(s) in
  - **Modifying germline** mutation in
  - Major **susceptibility factor** in (multifactorial diseases)
  - Part of a **fusion gene** in (cancers)
  - **Role in** the phenotype of (chromosomal anomalies)
  - Biomarker tested in
  - Candidate gene tested in

- **Standardized** decision process

- **Manually curated**: 6,500 PMID

- **7030 Gene-RD** relationships (4449 genes – 3624 RD)
Search for a rare disease

Usher syndrome

Disease definition

Usher syndrome (US) is characterized by the association of sensorineural deafness (usually congenital) with retinitis pigmentosa and progressive vision loss.

Additional information

Further information on this disease
- Classification(s) (15)
- Gene(s) (16)
- Publications in PubMed
- Other websites (15)

Specialised Social Services
- Eurodis directory

Health care resources for this disease
- Expert centres (258)
- Diagnostic tests (59)
- Patient organisations (73)
- Orphan drugs (2)

Research activities on this disease
- Research projects (34)
- Clinical trials (0)
- Registries/biobanks (38)
- Networks (20)
Phenotype annotations

- 2,583 annotated RD with **HPO** phenotypes
- **Manually curated**: 2,000 PMID
- Feed **Orphamizer**

<table>
<thead>
<tr>
<th>Frequencies</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obligate (100%)</td>
<td>Pathognomonic sign</td>
</tr>
<tr>
<td>Very frequent (99-80%)</td>
<td>Diagnostic criterion</td>
</tr>
<tr>
<td>Frequent (79-30%)</td>
<td></td>
</tr>
<tr>
<td>Occasional (29–5%)</td>
<td></td>
</tr>
<tr>
<td>Very rare (1-4%)</td>
<td></td>
</tr>
<tr>
<td>Absent 0%</td>
<td></td>
</tr>
</tbody>
</table>
This is Orphamizer
- Orphamizer and used data updated on April 18th, 2017
- This tool is maintained and developed by Sebastian Körner, Peter Robison, and the Orphanet team
- This tool is funded by the HIPPO-RD project
- The algorithm used is SOIA.
To know more about...

Orphanet process

Sources / Procedures

ICD-10 coding rules for rare diseases
Creation and Update of Disease Summary Texts for the Orphanet Encyclopaedia for Professionals
Orphanet Standard Operating Procedures
International Advisory Board rules of procedure
Orphanet Advisory Board on Genetics Rules of procedures
Glossary and representation of terms related to diagnostic tests
How to contribute to Orpha terminology, definitions, ...

Browse, Discover, Contribute.

curation.orphanet.org is an interactive expert community-driven curation platform for the Orphanet database of rare disorders co-developed by Orphanet and Garvan Institute.

to classifications...

- Publish consensus on restricted domain or medical speciality
To know more about...

Orphanet (www.orpha.net) is the reference resource on rare diseases and orphan drugs. You can view a number of videos that explain... Plus
Thank you for your attention!