orphanet

orphadata

FREE ACCESS PRODUCTS DESCRIPTION

APRIL 2020

elixir Core Data Resource

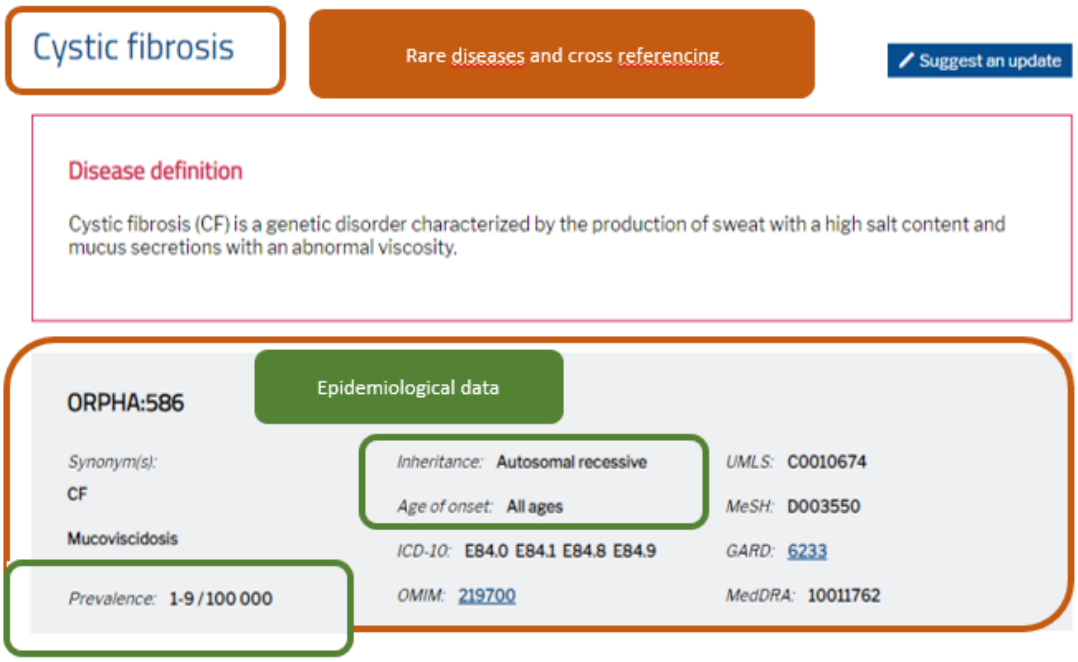
IRDiRC RECOGNIZED RESOURCES

THE HUMAN VARIOME PROJECT RECOMMENDED SYSTEM

Global Alliance for Genomics & Health
Collaborate. Innovate. Accelerate.

www.orphadata.org **www.orpha.net**

Table of contents

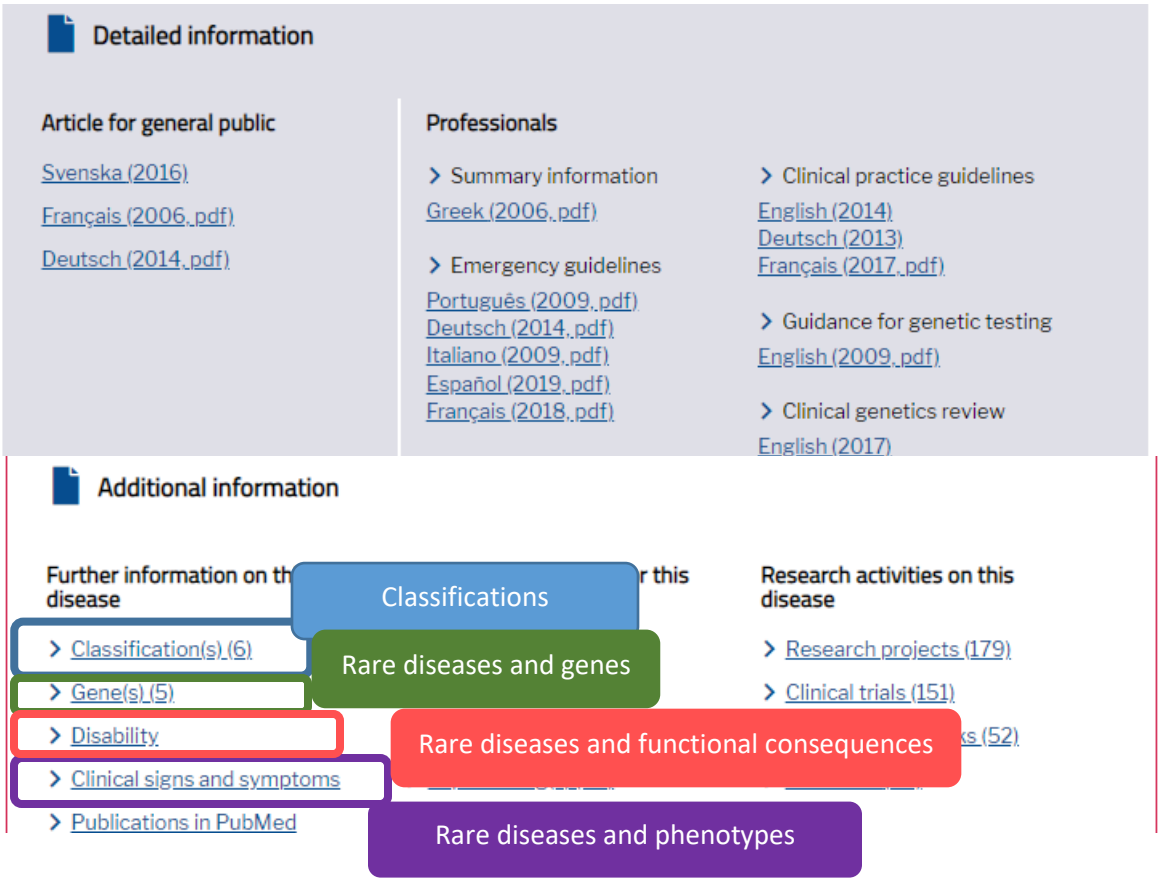


Epidemiology

It is the most common genetic disorder among Caucasian children. The incidence varies between populations: the condition is considerably less common in Asian and African populations than in the white populations of Europe and North America, with variation within each country. The exact prevalence in Europe is unknown, but estimates range between 1/8,000 and 1/10,000 individuals.

Clinical description

...



I. Rare diseases

1. Rare diseases and cross referencing

Orphanet has developed and maintains the Orphanet nomenclature of rare diseases, a multilingual, standardised, controlled medical terminology specific to rare diseases. Rare diseases within the Orphanet nomenclature affect less than five in 10,000 persons in Europe, as defined by the European Regulation on orphan medicinal products (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products).

Each clinical entity (generic technical term used to describe the clinical items included in the nomenclature of rare diseases) is associated with a unique numerical identifier named ORPHAcode, as well as a preferred term, synonyms, and a definition. The ORPHAcode provides a common language across healthcare and research systems for effective monitoring and reporting on rare diseases, thus improving their visibility.

The Orphanet nomenclature includes all disorders, subtypes of disorders, and groups of disorders that organise the Orphanet classification. A disorder in the database can be a disease, a malformation syndrome, a clinical syndrome, a morphological or a biological anomaly or a particular clinical situation (in the course of a disorder). They are organised into groups (category or clinical group), and further divided into clinical, etiological or histopathological subtypes.

The Orphanet nomenclature is cross-referenced with other international terminologies and reference databases (see below) in order to enable interoperability between different information systems:

- ICD-10 (10th International Classification of Diseases established by the World Health Organization - http://www.who.int/classifications/icd/en/),
- OMIM (Online Mendelian Inheritance in Man database - http://www.omim.org/),
- UMLS (Unified Medical Language System® - http://www.nlm.nih.gov/research/umls/),
- MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed - http://www.ncbi.nlm.nih.gov/mesh),
- MedDRa (Medical Dictionary for Regulatory Activities - http://www.meddra.org/)

For more definition, please consult the Annex of this document.

Description of the XML tags

- **DisorderList count**: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file
- **Orphanum**: named **ORPHAcode** – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- **ExpertLink**: stable URL pointing to the specific page of the given clinical entity on the Orphanet website
- **Disorder_Name:** preferred name of a given clinical entity. The most generally accepted

name according to the literature, and as adopted by the medical community

- **Lang:** ISO 639 code for language names
- **Name:** preferred name of a given clinical entity
- **SynonymList:** synonyms for a given clinical entity (Terms that are perfectly equivalent to the preferred term they are attached to. As many synonyms as necessary are added to a preferred term. Acronyms are included only when they are consistently used in the literature).
- **Definition**: short text stating the group of disorders that the clinical entity belongs to, and listing the major clinical characteristics (e.g. clinical, pathological, radiological, etc.) that define the entity and differentiate it from other entities classified within the same clinical group.
- **DisorderGroup**: can be either Group of disorders, Disorder or Subtype of disorder *(see definitions in annex)*
- **DisorderType**: can be either Disease, Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly, Category, Clinical group, Etiological subtype, Clinical subtype, Histopathological subtype or Particular clinical situation in a disease or syndrome *(see definitions in annex)*
- **DisorderFlag**: Most of clinical entities do not have a flag but for the other can be either head of classification, historical entity, deprecated entity, obsolete entity, obsolete entity with resources or non-rare disease in Europe *(see definitions in annex)*
- **ExternalReferenceList:** list of cross-references for a given clinical entity in the ICD-10, UMLS, MesH, MedDra, and OMIM systems
- **Source:** can be either OMIM, UMLS, MesH, MedDra or ICD-10
- **Reference:** listed reference for a given source associated with a clinical entity
- **DisorderMappingRelation:** characterisation of the alignment between a given clinical entity and one of the source. Can be either E, NTBT, BTNT, NTBT/E, BTNT/E, ND *(see explanations in annex)*
- **DisorderMappingICDRelation:** additional characterization used only for ICD-10. Can be either Specific code, Inclusion term, Index term or Attributed *(see explanations in annex)*
- **DisorderMappingValidationStatus**: Status validation between the given clinical entity and the ttreference. Can be either Validated or Not yet validated
- **DisorderDisorderAssociation**: Relationship between two clinical entities – Please note that in this file the relationship "Moved to" is only the relationship displayed and that the hierarchical relationships are given in the Orphanet classifications file.

Example

<DisorderList count="**XXXX**">

XXXX is the total number of clinical entities in this XML file

<OrphaNumber>61</OrphaNumber>
<Name lang="**en**">**Alpha-mannosidosis**</Name>

The concerned clinical entity has 61 as ORPHAcode and Alpha-mannosidosis as preferred term

<SynonymList count="**1**">

<Synonym lang="**en**">**Lysosomal alpha-D-mannosidase deficiency**</Synonym>

This entry name has one synonym “Lysosomal alpha-D-mannosidase deficiency”

<DisorderGroup id="36547">
<Name lang="**en**">**Disorder**</Name></DisorderGroup>

The entity is a disorder, not a group, not a subtype.

<DisorderType id="21394">
<Name lang="**en**">**Disease**</Name></DisorderType>

The entity is a disease, not a Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly or Particular clinical situation in a disease or syndrome.

<Source>**MeSH**</Source><Reference>**D00863**</Reference><DisorderMappingRelation id="21527"><Name lang="**en**">**E (exact mapping (the terms and the concepts are equivalent))**</Name></DisorderMappingRelation><DisorderMappingICDRelation/><DisorderMappingValidationStatus id="21611"><Name lang="**en**">**Validated**</Name></DisorderMappingValidationStatus></ExternalReference>

This clinical entity is exactly mapped with MeSH reference “D00863” and the relation between reference and entry is “Validated”.

<Source>**ICD-10**</Source><Reference>**E77.1**</Reference><DisorderMappingRelation id="21534"><Name lang="en">**NTBT (narrower term maps to a broader term)**</Name>
<DisorderMappingICDRelation id="21590"><Name lang="en">**Inclusion term (The term is included under a ICD-10 category and has not its own code)**</Name></DisorderMappingICDRelation><DisorderMappingValidationStatus id="21611"><Name lang="en">**Validated**</Name></DisorderMappingValidationStatus></ExternalReference>

The ICD-10 reference E77.1, the clinical entity is a narrower term that maps to a broader term. The term is included under an ICD-10 category and has not its own code. The relation between the reference and the clinical entity is “Validated”.

<Name lang="**en**"> **Aurocephalosyndactyly** </Name>
<Disorder1 id="**1465**">
<Orphanum>**1219**</Orphanum><DisorderDisorderAssociation>
<DisorderDisorderAssociation>
<Disorder1 id="**235**">
<Name lang="en">**Saethre-Chotzen syndrome**</Name>
</Disorder1>
<Disorder2 id="**1465**" cycle="true"/>
<DisorderDisorderAssociationType id="21471">
<Name lang="en">**Moved to**</Name>

The clinical entity named “Aurocephalosyndactyly” (ORPHAcode 1219) has been moved to “Saethre-Chotzen syndrome” (ORPHAcode 794).

<Name lang="**en**"> **Saethre-Chotzen syndrome** </Name>
<Disorder1 id="**235**">
<Orphanum>**794**</Orphanum><DisorderDisorderAssociation>

```
<DisorderDisorderAssociation>
        <Disorder1 id="235" cycle="true"/>
        <Disorder2 id="1465" >
         <OrphaNumber>1219</OrphaNumber>
          <Name lang="en"> Aurocephalosyndactyly </Name>
        </Disorder2>
        <DisorderDisorderAssociationType id="21471">
          <Name lang="en">Moved to</Name>
```

The clinical entity named "Aurocephalosyndactyly" (ORPHAcode 1219) has been moved to "Saethre-Chotzen syndrome" (ORPHAcode 794).

2. Rare diseases and classifications

Orphanet also maintains the Orphanet classification of rare diseases, a multi-hierarchical and polyparental system built on the Orphanet nomenclature and organised around the major medical specialties and based on clinical criteria according to diagnostic and therapeutic relevance. This structure reflects the multidimensional nature of rare diseases and enables to carry out epidemiological and statistical studies for research purposes.

Each clinical entity is assigned a classification level (Group, Disorder or Subtype of a disorder), and is included in as many classification groups as necessary depending on its clinical presentation and the medical specialties to which it is relevant, reflecting the current state of knowledge and the multidimensional nature of rare diseases.

The Disorder level is designated as the main typological level for data sharing and statistical reporting across the European Union. It is used to establish the total number of rare diseases that exist (to identify the disorder level in classification products, you must to use the product "Rare diseases and cross referencing").

Description of the XML tags

- DisorderList count: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file
- Orphanum: named ORPHAcode – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- ExpertLink: stable URL pointing to the specific page of the given clinical entity on the Orphanet website
- Disorder_Name: preferred name of a given clinical entity. The most generally accepted name according to the literature, and as adopted by the medical community
- Lang: ISO 639 code for language names
- Name: preferred name of a given clinical entity
- ClassificationNodeList count: number of clinical entities at the same level of the classification.
- ClassificationNodeChildList count: number of clinical entities under a given clinical entity

Example

<DisorderList count="**XXXX**">

XXXX is the total number of clinical entities in this XML file

<OrphaNumber>68334</OrphaNumber>
<Name lang="**en**"> **Rare hemorrhagic disorder due to a coagulation factors defect** </Name>

The concerned clinical entity has 68334 as its ORPHAcode and "Rare hemorrhagic disorder due to a coagulation factors defect" as preferred term

<ExpertLink lang="**en**">**http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=68334**</ExpertLink>

The stable URL pointing to information on this entry is http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=68334

<Name lang="**en**"> </Name>

The name of this entry in English is "Rare hemorrhagic disorder due to a coagulation factors defect"

<ClassificationNodeChildList count="**2**">

Two entries are present at this classification level

<Orphanum>**162949**</Orphanum>

The classification ORPHAcode is 162949

<Name lang="**en**">**Orphanet classification of rare hematological diseases**</Name>

This is the name of the classification

<ClassificationNodeChildList count="**15**">

There are 15 entries classified under the group of "Rare hemorrhagic disorder due to a constitutional coagulation factors defect"

3. Linearisation

The linearization is a process applied in the Orphanet database to attribute one classification group (called preferential parent) to each clinical entity, in order to enable the sorting out of all clinical entities by medical specialty and avoid multiple counting of multiclassified entities in statistical analysis. As some decisions could be made somewhat arbitrarily, we have written a set of rules to make sure attributions are consistent. The methodology can be found here.

Description of the XML tags

- DisorderList count: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file
- Orphanum: named ORPHAcode – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.

- ExpertLink: stable URL pointing to the specific page of the given clinical entity on the Orphanet website
- Disorder_Name: preferred name of a given clinical entity. The most generally accepted name according to the literature, and as adopted by the medical community
- Lang: ISO 639 code for language names
- Name: preferred name of a given clinical entity
- DisorderDisorderAssociation: Relationship between two clinical entities – Please note that in this file the relationship "Preferential parent" is only the relationship displayed

Example

<OrphaNumber>**166024**</OrphaNumber>
<ExpertLink lang="en">http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=166024</ExpertLink>
<Name lang="**en**">**Multiple epiphyseal dysplasia, Al-Gazali type**</Name>
<DisorderDisorderAssociationList count="1">
<DisorderDisorderAssociation>
<Disorder1 id="12333">
<OrphaNumber>**93419**</OrphaNumber>
<Name lang="**en**">**Rare bone disease**</Name>
</Disorder1>
<Disorder2 id="17601" cycle="true"/>
<DisorderDisorderAssociationType id="21485">
<Name lang="**en**">**Preferential parent**</Name>
</DisorderDisorderAssociationType>

The clinical entity "Multiple epiphyseal dysplasia, Al-Gazali type" has for preferential parent the clinical entity "Rare bone disease"

II. Rare diseases and genes

In order to better define rare disorders of genetic origin, Orphanet provides information on every gene related to a rare disorder. This information includes the genetic international nomenclature, the gene typology, the chromosomal location, the cross-mappings with other international genetic databases. Orphanet also defines the relationship between genes and their related rare disorders and provides the evidence for establishing these gene-disorder relationships.

The relationship between a gene and a disease is qualified according to the role that the gene plays in the pathogenesis of a disease. Genes are annotated as causative (from germline or somatic mutations), modifiers, major susceptibility factors or playing a role in the phenotype (for chromosomal anomalies). Candidate genes or biomarkers are included if a genetic test exists in the clinical setting.

Genes are indexed with:

- HGNC (http://www.genenames.org/) is a committee jointly funded by the US National Human Genome Research Institute (NHGRI) and the Wellcome Trust (UK). It operates

under the auspices of HUGO, with key policy advice from an International Advisory Committee. It is in charge of approving gene names and symbols (short-form abbreviations). All approved symbols are stored in the HGNC database. Each symbol is unique and each gene is only given one approved gene symbol.

- OMIM, Online Mendelian Inheritance in Man (http://www.omim.org/), is the database of human genes and genetic phenotypes.
- GenAtlas (http://www.genatlas.org/) is a database of genes and phenotypes. Only the objects with a known cytogenetic location are retained.
- UniProtKB (http://www.uniprot.org/) is the central hub for the collection of functional information on proteins, with accurate, consistent and rich annotation.
- Ensembl (http://www.ensembl.org/) is an EBI database that maintains automatic annotation on selected eukaryotic genomes.
- Reactome (http://www.reactome.org/) is an EBI open-source, open access, manually curated and peer-reviewed pathway database.
- IUPHAR (http://www.iuphar.org/) is The International Union of Basic and Clinical Pharmacology.

For more definition, please consult Annex of this document.

Description of the XML tags

- DisorderList count: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file
- Orphanum: named ORPHAcode – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- ExpertLink: stable URL pointing to the specific page of the given clinical entity on the Orphanet website
- Disorder_Name: preferred name of a given clinical entity. The most generally accepted name according to the literature, and as adopted by the medical community
- Lang: ISO 639 code for language names
- DisorderGroup: can be either Group of disorders, Disorder or Subtype of disorder *(see definitions in annex)*
- DisorderType: can be either Disease, Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly, Category, Clinical group, Etiological subtype, Clinical subtype, Histopathological subtype or Particular clinical situation in a disease or syndrome *(see definitions in annex)*
- Lang: ISO 639 code for language names
- GeneList count: number of genes associated with a given entry
- Symbol: official HGNC-approved gene symbol
- Synonym list: list of synonyms for a given gene, including past symbols
- GeneType: can be either gene with protein product, locus or non-coding RNA
- GeneLocus: gene chromosomal location
- DisorderGeneAssociationType: gene-disease relationships. Can be:
    - Role in the phenotype of;
    - Disease-causing germline mutation(s) (loss of function) in;
    - Disease-causing germline mutation(s) (gain of function) in;
    - Disease-causing germline mutation(s) in;

    - Disease-causing somatic mutation(s) in;
    - Modifying germline mutation in;
    - Part of a fusion gene in;
    - Major susceptibility factor in;
    - Candidate gene tested in;
    - Biomarker tested in.
- **DisorderGeneAssociationStatus:** can be either Validated or Not validated
- **External Reference List:** list of references in HGNC, OMIM, GenAtlas and UniProtKB, *Ensembl, Reactome and IU-PHAR* associated with a given gene
- **Source:** HGNC, OMIM, GenAtlas and UniProtKB, *Ensembl, Reactome and IU-PHAR*
- **Reference:** listed reference for a given source associated with a gene.

Example

<DisorderList count="**XXXX**">

XXXX is the total number of clinical entities in this XML file

<OrphaNumber>61</OrphaNumber>
<Name lang="**en**">**Alpha-mannosidosis**</Name>

The concerned clinical entity has 61 its ORPHAcode and "Alpha-mannosidosis as preferred term"

<DisorderGroup id="36547">
<Name lang="**en**">**Disorder**</Name></DisorderGroup>

The entity is a disorder, not a group, not a subtype.

<DisorderType id="21394">
<Name lang="**en**">**Disease**</Name></DisorderType>

The entity is a disease, not a Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly or Particular clinical situation in a disease or syndrome.

<GeneList count="**1**">

The entry is associated with one gene

<Symbol>**MAN2B1**</Symbol>
<Name lang="**en**">**Mannosidase, alpha, class 2B, member 1**</Name>

Its official symbol and name are MAN2B1 and Mannosidase, alpha, class 2B, member 1, respectively

<SynonymList count="**2**">
<Synonym lang="**en**">**LAMAN**</Synonym>
<Synonym lang="**en**">**MANB**</Synonym>

There are two synonyms for this gene: *LAMAN* and *MANB*

<GeneType id="24110">
<Name lang="en">**gene with protein product**</Name></GeneType>

The type of the given entry is a gene with protein product

<Locus id="7379">

<GeneLocus>**7q31-q32**</GeneLocus >

The given gene is located on 7q31-32

<DisorderGeneAssociationType id="17949">
<Name lang="**en**">**Disease-causing germline mutation(s) in**</Name>
</DisorderGeneAssociationType>

The relationship between a given entry and the given gene is “Disease-causing germline mutation(s) in”

<DisorderGeneAssociationStatus id="17991">
<Name lang="**en**">**Validated**</Name>

The status of the relationship between a given entry and the given gene is Validated

<ExternalReferenceList count="**4**">

This gene is mapped with 4 other references

<Source>**GENATLAS**</Source>
<Reference>**MAN2B1**</Reference>

The reference for this gene in GenAtlas is MAN2B1

<Source>**HGNC**</Source>
<Reference>**6826**</Reference>

The reference for this gene in HGNC is 6826

<Source>**OMIM**</Source>
<Reference>**609458**</Reference>

The reference for this gene in OMIM is 609458

<Source>**UNIPROTKB/SWISSPROT**</Source>
<Reference>**O00754**</Reference>

The reference for this protein in UniProtKB is O00754

III. Rare diseases and functional consequences

The Orphanet inventory of rare diseases is annotated with activity limitation/participation restriction (functional consequences), using the Orphanet Functioning Thesaurus, derived and adapted from the International Classification of Functioning, Disability and Health – Children and Youth (ICF-CY, WHO 2007).

The information provided is assessed taking into account the whole patient population affected by the disease, receiving standard care and management (specific and/or symptomatic management, prevention and prophylaxis, devices and aids, care and support). Functioning is divided into different abilities, tasks and activities. Disability therefore involves limitation of activity or restriction of participation, described as functional consequences.

Each functional consequence is annotated with the following:

- Frequency in the patient population:
    - Very frequent: more than 80%
    - Frequent: between 30% and 80%
    - Occasional: fewer than 30%
- Temporality:
    - Permanent limitation/restriction: the functional consequence is present throughout the life of the patient. It can be congenital, secondary to loss of a skill or a participation. It can be a direct or indirect consequence of the disease or of its treatment.
    - Transient limitation/restriction: the functional consequence occurs during acute episodes, periodic crises or relapses. It resolves or reduces spontaneously or by the action of a treatment or care.
    - Delayed acquisition: a skill or a participation is performed later than by a healthy person.
- Degree of severity:
    - Low: activity or participation can be carried out with little difficulty by the patient alone.
    - Moderate: activity or participation can be carried out with some technical and/or human assistance
    - Severe: activity or participation cannot be carried out without substantial technical and/or human assistance.
    - Complete: activity or participation cannot be carried out, even with technical and/or human assistance.
    - Unspecified: limitation/restriction is difficult to quantify or highly variable between patients (ranging from 'Low' to 'Complete').
- Loss of ability when relevant, defined by the progressive and definitive loss of a skill or participation over the course of the disease.

A functional limitation is stated to be « undefined » when the current knowledge does not enable information about the extent of the consequences on daily life to be provided.

The unaffected activities and participation are not listed.

Environmental factors that may have an impact on the daily activities of the patients are also identified and listed when possible.

Description of the XML tags

- DisorderDisabilityRelevanceList count: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file.
- Orphanum: named ORPHAcode – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- ExpertLink: stable URL pointing to the specific page of the given clinical entity on the Orphanet website

- Disorder_Name: preferred name of a given clinical entity. The most generally accepted name according to the literature, and as adopted by the medical community
- Lang: ISO 639 code for language names
- DisorderGroup: can be either Group of disorders, Disorder or Subtype of disorder *(see definitions in annex).*
- DisorderType: can be either Disease, Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly, Category, Clinical group, Etiological subtype, Clinical subtype, Histopathological subtype or Particular clinical situation in a disease or syndrome *(see definitions in annex).*
- DisabilityDisorderAssociationList count: total number of functional consequences or environmental factors identified for a given clinical entity.
- DisabilityCategory: the category can be either "Activity limitation/participation restriction", "No functional disability" or "Not applicable". Functional consequences are identified only if the category "Activity limitation/participation restriction" is relevant for the given clinical entity. If the category "Not applicable" is indicated, see the "ReasonForNotApplicable" field.
- ReasonForNotApplicable: for a given disease, if the category is "Not applicable", a reason is identified and can be either "Hypervariable functioning", "Early death-causing disease" or "Not applicable for another reason".
- DisabilityID: unique identifying number assigned to a functional consequence or an environmental factor.
- AnnotationDate: date of the annotation of the given clinical entity.
- StatusDisability: status of the validation of the given clinical entity's annotation. Can be either Validated or Not yet validated.
- FrequenceDisability: frequency of the functional consequence in the given population. Can be either "very frequent", "frequent" or "occasional".
- TemporalityDisability: temporality of the functional consequence in the given population. Can be either "permanent limitation/restriction", "transient limitation/restriction" or "delayed acquisition".
- SeverityDisability: severity of the functional consequence in the given population. can be either "low", "moderate", "severe", "complete" or "Unspecified".
- LossOfAbility: defined as a progressive and definitive loss of a skill or ability over the course of the disease. Can be either "yes" or "no".
- SourceOfValidation:s ource of validation of the given clinical entity's annotation.
- SpecificManagement: can be either "yes" or "no". The functional consequences or environmental factors are evaluated based on the average limitation of all patients (infants, children, adolescents, adults) receiving standard care and management (specific treatment, symptomatic treatment). If specific management protocol is known for the given disease, this field will indicate "y" for yes and all the annotations will have been conducted considering this specific management protocol.
- Type: can be either "Disability" (functional consequence) or "Environmental factor".
- Defined: If the relationship between the given clinical entity and the functional consequences or the environmental factor is defined by a severity, temporality and frequency then the value given will be "y" (for yes). If the relationship is not defined, the

value will be “n” (for no).

Example

<DisorderDisabilityRelevanceList count="**XXXX**">

XXXX is the total number of clinical entities in this XML file

<OrphaNumber>**893**</OrphaNumber>
<Name lang="**en**">**WAGR syndrome**</Name>

The main name of the clinical entity is “WAGR syndrome” with 893 as its ORPHAcode

<DisorderGroup id="**36547**">
<Name lang="**en**">**Disorder**</Name></DisorderGroup>

The entity is a disorder, not a group, not a subtype.

<DisorderType id="21401">
<Name lang="**en**">**Malformation syndrome**</Name></DisorderType>

The entity is a malformation syndrome, not a Disease, Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly or Particular clinical situation in a disease or syndrome.

<SourceOfValidation>Expert</SourceOfValidation>
<SpecificManagement>n</SpecificManagement>
<Online>y</Online>
<AnnotationDate>2018-06-29 00:00:00.0</AnnotationDate>
<StatusDisability id="27327">
<Name lang="en">Validated</Name>
</StatusDisability>
<DisabilityCategory id="27278">
<Name lang="en">Activity limitation/participation restriction</Name>
</DisabilityCategory>
<ReasonForNotApplicable/>
</DisorderDisabilityRelevance>

The entity was annotated on 29/06/2008. The annotation was validated by an expert and described as an “Activity limitation/participation restriction” for the given disease.

<DisabilityDisorderAssociationList count="91">

The entity was annotated with 91 functional consequences and/or environmental factors.

<DisabilityDisorderAssociation id="74963">
<Disability id="4">
<Name lang="en">Seeing/watching</Name>
</Disability>
<FrequenceDisability id="27201">
<Name lang="en">Very frequent</Name>
</FrequenceDisability>
<TemporalityDisability id="27180">
<Name lang="en">Permanent limitation</Name>

```
  </TemporalityDisability>
  <SeverityDisability id="27236">
    <Name lang="en">Moderate</Name>
  </SeverityDisability>
  <LossOfAbility>n</LossOfAbility>
  <Type>Disability</Type>
  <Defined>y</Defined>
</DisabilityDisorderAssociation>
```


The given entity has been annotated with a functional consequence (disability) named "Seeing/watching". This limitation appears to be very frequent, of moderate severity and of permanent temporality in the given entity. It is not progressive (the loss of capacity is indicated as "no").


```
<DisabilityDisorderAssociation id="74964">
  <Disability id="5">
    <Name lang="en">Hearing/listening</Name>
  </Disability>
  <FrequenceDisability id="27208">
    <Name lang="en">Frequent</Name>
  </FrequenceDisability>
  <TemporalityDisability id="27187">
    <Name lang="en">Acquisition delay</Name>
  </TemporalityDisability>
  <SeverityDisability id="27271">
    <Name lang="en">Unspecified</Name>
  </SeverityDisability>
  <LossOfAbility>n</LossOfAbility>
  <Type>Disability</Type>
  <Defined>y</Defined>
</DisabilityDisorderAssociation>
```


The given entity has been annotated with a functional consequence (disability) named " Hearing/listening". This limitation appears frequent, of unspecified severity and leads to a delay in acquisition in the given entity. It is not progressive (the loss of capacity is indicated as "no").

IV. Rare diseases and phenotypes

The Orphanet inventory of rare diseases is annotated with **Human Phenotype Ontology** (HPO) terms, a standardised and controlled terminology covering phenotypic abnormalities in human diseases. This product contains rare diseases listed in Orphanet annotated with HPO phenotypes. The annotation is characterized by frequency (obligate, very frequent, frequent, occasional, very rare or excluded) and whether the annotated HPO term is a major diagnostic criterion or a pathognomonic sign of the rare disease. Source (PMID references), the date and the validation's status of the association between the rare disease and HPO terms is also made available.

The frequency in the patients' population can be:

- always present: 100 %
- very frequent: 99%-80%
- frequent: 79%-30%
- occasional: 29%-5%
- rare: 4%-1%
- excluded : 0%

The phenotypic abnormality can be defined as one of the following:

- Pathognomonic sign: a sign whose presence indicates that a particular disease is present beyond any doubt. The absence of this sign does not exclude the possibility of the presence of the disease, but the presence of the pathognomonic sign affirms it with certainty.
- Diagnostic criterion: phenotypic abnormalities noted as « diagnostic criterion » are those included in established sets of criteria to establish the diagnosis of a particular disease having been published in a peer-reviewed journal.

Description of the XML tags

- DisorderList count: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file
- Orphanum: named ORPHAcode – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- ExpertLink: stable URL pointing to the specific page of the given clinical entity on the Orphanet website
- Disorder_Name: preferred name of a given clinical entity. The most generally accepted name according to the literature, and as adopted by the medical community
- Lang: ISO 639 code for language names
- DisorderGroup: can be either Group of disorders, Disorder or Subtype of disorder *(see definitions in annex)*
- DisorderType: can be either Disease, Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly, Category, Clinical group, Etiological subtype, Clinical subtype, Histopathological subtype or Particular clinical situation in a disease or syndrome *(see definitions in annex)*
- HPODisorderAssociationList count: number of HPO phenotypes associated with a given clinical entity
- HPOID: unique identifying number assigned by HPO to a given phenotype
- HPOTerm: preferred name of HPO phenotype
- HPOFrequency: estimated frequency of occurrence for a given phenotype in a given clinical entity. Five different frequency groups have been defined
- DiagnosticCriteria: indicate if the given phenotype is a pathognomonic sign or a diagnostic criterion in a given clinical entity.

Example

<DisorderList count="**XXXX**">

XXXX is the total number of clinical entities in this XML file

<OrphaNumber>**2331**</OrphaNumber>
<Name lang="**en**">**Kawasaki disease**</Name>

The main name of the clinical entity is "Kawasaki disease" with 2331 as its ORPHAcode

<DisorderGroup id="36547">
<Name lang="**en**">**Disorder**</Name></DisorderGroup>

The entity is a disorder, not a group, not a subtype.

<DisorderType id="21394">
<Name lang="**en**">**Disease**</Name></DisorderType>

The entity is a disease, not a Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly or Particular clinical situation in a disease or syndrome.

< HPODisorderAssociationList count="**6**">

There are 6 HPO phenotypes associated with this clinical entity

<DiseaseSign>
<Name lang="en"> **Kawasaki disease** </Name>
<HPOID>**HP:0001945**</HPOID>
<HPOTerm>**Fever**</HPOTerm>
<DiagnosticCriteria>**Pathognomonic sign**</ DiagnosticCriteria >

Fever is a pathognomonic sign seen in patients with Kawasaki disease

<OrphaNumber>**2331**</OrphaNumber>
<Name lang="**en**">**Kawasaki disease**</Name>
</Disorder>
<Source>**15505111[PMID]**</Source>
<ValidationStatus>**y**</ValidationStatus>
<ValidationDate>2016-05-31 11:48:46.583</ValidationDate>

The annotation with HPO terms of Kawasaki disease was based on the article (PMID 15505111) and was made the 31/05/2016

V. Epidemiological data

This product contains two different files. The first one contains epidemiological data on disorders, group of disorders or sub-type: point prevalence, birth prevalence, lifelong prevalence and incidence, or the number of cases/families reported together with their respective intervals per geographical area (country, continent) are available. The second one contains type of inheritance, interval average age of onset and interval average age of death of entries.

The data are extracted from the literature as to reflect the situation in Worldwide. The validity

of the published studies is taken for granted and not re-assessed, although there is a low level of consistency between studies and usually poor documentation of methods used.
For more definitions, please consult Annex of this document.

1. Rare diseases epidemiology

Description of the XML tags

- **DisorderList count**: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file
- **Orphanum**: named **ORPHAcode** – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- **ExpertLink**: stable URL pointing to the specific page of the given clinical entity on the Orphanet website
- **Disorder_Name:** preferred name of a given clinical entity. The most generally accepted name according to the literature, and as adopted by the medical community
- **Lang:** ISO 639 code for language names
- **DisorderGroup**: can be either Group of disorders, Disorder or Subtype of disorder *(see definitions in annex)*
- **DisorderType**: can be either Disease, Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly, Category, Clinical group, Etiological subtype, Clinical subtype, Histopathological subtype or Particular clinical situation in a disease or syndrome *(see definitions in annex)*
- **PrevalenceList count:** total number of epidemiological data for a given clinical entity
- **PrevalenceType:** can be "Point prevalence", "birth prevalence", "lifelong prevalence", "incidence", "cases/families"
- **PrevalenceQualification:** can be either "Value and Class", "Only class", "Case" or "Family"
- **PrevalenceClass:** estimated prevalence of a given clinical entity. There are eight possible values:
    - >1 / 1,000,
    - 1-5 / 10,000,
    - 6-9 / 10,000,
    - 1-9 / 100,000,
    - 1-9 / 1,000,000
    - or <1 /1,000,000,
    - Not yet documented,
    - Unknown
- **ValMoy:** Mean value of a given prevalence type. By default, the mean value is 0.0 when only a class is documented
- **PrevalenceGeographic:** Geographic area of a given prevalence type
- **Source:** Source of information of a given prevalence type for a clinical entity
- **PrevalenceValidationStatus:** can be either: "Validated" or "Not yet validated"

Example

<DisorderList count="**XXXX**">

XXXX is the total number of clinical entities in this XML file

<OrphaNumber>**2331**</OrphaNumber>
<Name lang="**en**">**Kawasaki disease**</Name>

The main name of the clinical entity is “Kawasaki disease” with 2331 as its ORPHAcode

<DisorderGroup id="36547">
<Name lang="**en**">**Disorder**</Name></DisorderGroup>

The entity is a disorder, not a group, not a subtype

<DisorderType id="21394">
<Name lang="**en**">**Disease**</Name></DisorderType>

The entity is a disease, not a Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly or Particular clinical situation in a disease or syndrome

<PrevalenceList count="1">

1 is the total number of prevalence type data for the given entry

<PrevalenceType id="23515">
<Name lang="en">**Annual Incidence**</Name></PrevalenceType>

The type of the given prevalence type is “Annual incidence”

<PrevalenceQualification id="23550">
<Name lang="en">**Value and class**</Name></PrevalenceQualification>

The qualification of the given prevalence type is “Value and class”

<PrevalenceClass id="23599">
</OrphaNumber><Name lang="en**"><1 / 1 000 000**</Name></PrevalenceClass>

Estimated disorder prevalence is < 1 / 1,000,000

<ValMoy>**0.037**</ValMoy>

Exact disorder prevalence is 0.037 / 100,000

<PrevalenceGeographic id="24957">
<Name lang="en">**England**</Name></PrevalenceGeographic>

The given prevalence is for England

<Source>**PMID:21533827**</Source>

The source of information of the given prevalence type is PMID:21533827

<PrevalenceValidationStatus id="24075"><Name
lang="en">**Validated**</Name></PrevalenceValidationStatus>

The given prevalence type is validated

<PrevalenceQualification id="23704">
<Name lang="en">C**lass only**</Name></PrevalenceQualification>
<PrevalenceClass id="23760">
<Name lang="en**"><1 / 1 000 000**</Name></PrevalenceClass>
<ValMoy>**0.0**</ValMoy>

Estimated disorder prevalence is < 1 / 1,000,000 and no prevalence figure is documented.

2. Natural history

Description of the XML tags

- **DisorderList count**: total number of clinical entities (disorders, group of disorders or subtypes) in the Xml file
- **Orphanum**: named **ORPHAcode** – a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- **ExpertLink**: stable URL pointing to the specific page of the given clinical entity on the Orphanet website
- **Disorder_Name:** preferred name of a given clinical entity. The most generally accepted name according to the literature, and as adopted by the medical community
- **Lang:** ISO 639 code for language names
- **DisorderGroup**: can be either Group of disorders, Disorder or Subtype of disorder *(see definitions in annex)*
- **DisorderType**: can be either Disease, Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly, Category, Clinical group, Etiological subtype, Clinical subtype, Histopathological subtype or Particular clinical situation in a disease or syndrome *(see definitions in annex)*
- **AverageAgeOfOnset:** classes based on the estimated average age of clinical entity onset. There are ten different population age groups: Antenatal, Neonatal, Infancy, Childhood, Adolescence, Adult, Elderly, All ages and No data available *(see definitions in annex).*
- **AverageAgeOfDeath:** classes based on the estimated average age at death for a given clinical entity. There are twelve different population age groups *(see definitions in annex)*:
    - Embryofoetal,
    - Stillbirth,
    - Infantile,
    - Early Childhood,
    - Late Childhood,
    - Adolescent,
    - Young adult,
    - Adult,
    - Elderly,
    - Any age,
    - Normal life expectancy, and

    - No data available
- TypeOfInheritance: type(s) of inheritance associated with a given clinical entity. There are thirteen different types of inheritance *(see definitions in annex)*:
    - Autosomal dominant,
    - Autosomal recessive,
    - X- linked dominant,
    - X-linked recessive,
    - Chromosomal,
    - Mitochondrial inheritance,
    - Multigenic/multifactorial,
    - Oligogenic,
    - Semi-dominant,
    - Y-linked,
    - No data available,
    - Not applicable,
    - Not yet documented

Example

<DisorderList count="**XXXX**">

XXXX is the total number of clinical entities in this XML file

<OrphaNumber>**2331**</OrphaNumber>
<Name lang="**en**">**Kawasaki disease**</Name>

The main name of the clinical entity is “Kawasaki disease” with 2331 as its ORPHAcode

<DisorderGroup id="36547">
<Name lang="**en**">**Disorder**</Name></DisorderGroup>

The entity is a disorder, not a group, not a subtype

<DisorderType id="21394">
<Name lang="**en**">**Disease**</Name></DisorderType>

The entity is a disease, not a Clinical syndrome, Malformation syndrome, Biological anomaly, Morphological anomaly or Particular clinical situation in a disease or syndrome

<Name lang="**en**">**Neonatal**</Name></AverageAgeOfOnset>

Class of average age of disease onset is during the neonatal/infancy period

<Name lang="**en**">**All age**</Name></AverageAgeOfDeath>

Class of average age of death can be at any age

<Name lang="**en**">**Autosomal recessive**</Name></TypeOfInheritance>

The entry is inherited as an autosomal recessive trait

VI. Annexes

Table 1: Definition of clinical entities group of type

Group of type of Clinical Entity	Definition
Group of disorders	Collection of clinical entities sharing a set of common features. It can be a category or a clinical group.
Disorder	Clinical entity characterised by a set of homogeneous phenotypic abnormalities and evolution allowing a definitive clinical diagnosis. It can be a disease, a malformation or clinical syndrome, a morphological or biological anomaly or a particular clinical situation in a disease or a syndrome.
Subtype of disorder	Subdivision of a disorder according to a positive criterion. It can be a clinical subtype, an etiological subtype or a histopathological subtype.

Table 2: Definition of clinical entities type

Type of Group of disorders	Definition
Category	A group of clinically heterogeneous disorders sharing one general feature, used to organise the classification. Example: ORPHA:68385 Neurometabolic disease
Clinical group	A group of clinically homogeneous disorders that share a similar etiology, course, outcome, and/or management. Example: ORPHA:216 Neuronal ceroid lipofuscinosis.
Type of Disorders	**Definition**
disease	A disorder with homogeneous therapeutic possibilities and an identified physiopathological mechanism. Developmental anomalies are excluded. Example: ORPHA:848 Beta-thalassemia.
clinical syndrome	A disorder with homogeneous therapeutic possibilities, regardless of the physiopathological mechanism involved. Example: ORPHA:529799 Acute bilirubin encephalopathy.
malformation syndrome	A disorder resulting from a developmental anomaly involving more than one morphogenetic field. Malformative sequences and associations are included. Example: ORPHA:648 Noonan syndrome
morphological anomaly	A disorder characterised by a morphological alteration resulting from a development anomaly involving a single morphogenetic field. Example: ORPHA:617 Congenital primary megaureter

biological anomaly	A disorder defined by a set of physiological abnormalities without clearly associated clinical manifestations. Example: ORPHA:440731 L-ferritin deficiency.
particular clinical situation in a disease or syndrome	A set of phenotypic abnormalities presenting in a subset of patients under particular circumstances. Example: ORPHA:567983 Parenteral nutrition associated cholestasis.
Type of Disorders subtypes	**Definition**
clinical subtype	Subdivision of a disorder according to distinct clinical characteristics (severity, age of onset, particular clinical signs, etc.). Example: - Mild Canavan disease (ORPHA:314918) - Severe Canavan disease (ORPHA:314911) are subtypes of Canavan disease (ORPHA:141).
etiological subtype	Subdivision of a disorder according to distinct causes resulting in a similar clinical presentation. Example: - Cystinuria type A (ORPHA:93612) - Cystinuria type B (ORPHA:93613) are subtypes of Cystinuria (ORPHA:214), caused by mutations in SLC3A1 and SLC7A9 respectively.
histopathological subtype	Subdivision of a disorder according to characteristic histological patterns. Example: - Protoplasmic astrocytoma (ORPHA:251598) - Fibrillary astrocytoma (ORPHA:251601) - Gemistocytic astrocytoma (ORPHA:251604) are subtypes of Diffuse astrocytoma (ORPHA:251595).

Table 3: List of flags

Concepts	Definition
Head of classification	Top level of a given classification (For instance, Rare cardiac disease for Orphanet classifications of rare cardiac diseases)
Historical entity	Clinical entity that was described long time ago, most of the time before the genetic era, and for which the princeps article is still available but no further literature exists that confirms its existence.

Deprecated entity	Clinical entity that was initially considered as an independent diagnosis, but is now considered as part of another diagnosis as a result of the evolution of knowledge, and is therefore removed from the Orphanet nomenclature. The deprecated ORPHAcode is “moved to” the recognised ORPHAcode that is now in use.
Obsolete entity or Obsolete with ressources	Clinical entity that has been removed from the Orphanet nomenclature for one of the following reasons: - Exact duplicate of another existing clinical entity - Unclear entity that cannot be precisely characterized - Only one published case in the literature - Organisational category that is no longer in use Whenever possible, the obsolete ORPHAcode is “referred to” an active ORPHAcode.
Non-rare disease in Europe	Disease that does not meet the European definition of a rare disease (less than 5 affected individuals per 10,000 in Europe) in light of current epidemological knowledge, and has therefore been removed from the Orphanet nomenclature.

Table 4: Characterization of the alignments between disorders and external terminologies or resources

Concepts	Definition
E	exact mapping - the terms and the concepts are equivalent
NTBT	narrower term maps to a broader term
BTNT	broader term maps to a narrower term
NTBT/E	narrower term maps to a broader term because of an exact mapping with a synonym in the target terminology
BTNT/E	broader term maps to a narrower term because of an exact mapping with a synonym in the target terminology
ND	not yet decided/unable to decide

Table 5: Added characterization of the alignments between disorders and ICD-10

Concepts	Definition
Specific term	the term has its own code in the ICD10
Inclusion term	the term is included under a ICD10 category and has not its own code
Index term	the term is included in ICD10 index pointing to a code that is not specific for the term
Attributed	the term does not appears at all in ICD10 and a code was attributed according to rules

Table 6: Type of genes

Type of gene	Definition
disorder-associated locus	Chromosomal region associated with a hereditary disorder but without any precision on the possible associated gene.
gene with protein product	DNA sequence translated into protein.
non coding RNA	RNA transcript not translated into protein.

Table 7: Relationships between genes and clinical entities

Relationships	Definition
autosomal dominant	Pattern of inheritance in which a single mutated allele located on one of the 22 autosomes (non-sex chromosomes) is sufficient to express the phenotype.
autosomal recessive	Pattern of inheritance in which two mutated alleles of the same gene located on one of the 22 autosomes (non-sexual chromosomes) are needed to express the phenotype.
mitochondrial	Pattern of inheritance in which a mutation in one of the mitochondrial genes is sufficient to express the phenotype. The transmission is exclusively maternal.
multigenic/multifactorial	The combination of one or more genes and/or environmental factors contributes to the expression of the phenotype.
no inheritance data available	No information is available in the scientific literature on heredity of the clinical entity.
not genetically inherited	clinical entity without genetic inheritance.
oligogenic	The combination of mutated alleles of two or more genes is necessary to express the phenotype.
semi-dominant	Pattern of inheritance in which a single mutated allele located on one of the 22 autosomes (non-sex chromosomes) suffices to express the phenotype, the phenotype of the homozygous individual being more severe, when both alleles are mutated.
unknown inheritance	Hereditary clinical entity whose mode of inheritance is unknown.
X-linked dominant	Pattern of inheritance in which a single mutated allele on the X chromosome is sufficient to express the phenotype. The phenotype is more consistently and severely expressed in hemizygous boys (having only one copy of the gene) than in heterozygous girls.
X-linked recessive	Pattern of inheritance in which two mutated alleles on the X chromosome are needed to express the phenotype. The phenotype is expressed in hemizygous boys (having only one copy of the gene) and homozygous girls.

Y-linked	Pattern of inheritance in which a single mutated allele on the Y chromosome is sufficient to express the phenotype. The transmission is exclusively paternal.

Table 8: categories of onset

Categories of onset	Definition
adolescent	From 12 to 18 years.
adult	From 19 to 65 years.
all ages	From birth to adulthood without peak of onset.
antenatal	Before birth.
childhood	From 2 to 11 years.
elderly	After 65 years.
infancy	From the end of the fourth week to the 23rd month of life.
neonatal	From birth to the fourth week of life.
no age of onset data available	No information is available in the scientific literature on the age of onset of the first clinical manifestations.

Tab 9: Concepts for “epidemiology”

Class/value	Definition	Type of data	Definition	categories	Definition
annual incidence	Number of newly diagnosed cases in a population in 1 year.				
cases/ families	Number of cases or family (ies) published in the literature.	case	Number of cases published in the literature.		
		family	Number of family(ies) published in the literature.		
prevalence	Number of cases scaled up to the general population at a given time or during a given period. Prevalence can be observed at birth (prevalence at birth), at a point in time (point prevalence), or in a lifetime (lifetime prevalence).	birth prevalence	Number of cases observed at birth relative to the number of children born alive at a given moment.	<1 / 1 000 000	Interval of prevalence or annual incidence of less than 1 case per 1,000,000 in the population.
				>1 / 1000	Interval of prevalence or annual incidence greater than 1 case per 1,000 in the population.
				1-5 / 10 000	Interval of prevalence or annual incidence of between 1 and 5 cases per 10,000 in the population.
				1-9 / 1 000 000	Interval of prevalence or annual incidence of between 1 and 9 cases per 1,000,000 in the population.
				1-9 / 100 000	Interval of prevalence or annual incidence of between 1 and 9 cases per 100,000 in the population.
				6-9 / 10 000	Interval of prevalence or annual incidence of between 6 and 9 cases per 10,000 in the population.
				Unknown_ epidemiological_range	No information is available in the scientific literature to inform prevalence or annual incidence.
		lifetime prevalence	Number of cases presenting or having presented the clinical entity during their lifetime scaled up to the general population.	<1 / 1 000 000	Interval of prevalence or annual incidence of less than 1 case per 1,000,000 in the population.
				>1 / 1000	Interval of prevalence or annual incidence greater than 1 case per 1,000 in the population.
				1-5 / 10 000	Interval of prevalence or annual incidence of between 1 and 5 cases per 10,000 in the population.
				1-9 / 1 000 000	Interval of prevalence or annual incidence of between 1 and 9 cases per 1,000,000 in the population.
				1-9 / 100 000	Interval of prevalence or annual incidence of between 1 and 9 cases per 100,000 in the population.
				6-9 / 10 000	Interval of prevalence or annual incidence of between 6 and 9 cases per 10,000 in the population.

				Unknown_ epidemiological_range	No information is available in the scientific literature to inform prevalence or annual incidence.
		point prevalence	Number of cases scaled up to the general population at a given time.	<1 / 1 000 000	Interval of prevalence or annual incidence of less than 1 case per 1,000,000 in the population.
				>1 / 1000	Interval of prevalence or annual incidence greater than 1 case per 1,000 in the population.
				1-5 / 10 000	Interval of prevalence or annual incidence of between 1 and 5 cases per 10,000 in the population.
				1-9 / 1 000 000	Interval of prevalence or annual incidence of between 1 and 9 cases per 1,000,000 in the population.
				1-9 / 100 000	Interval of prevalence or annual incidence of between 1 and 9 cases per 100,000 in the population.
				6-9 / 10 000	Interval of prevalence or annual incidence of between 6 and 9 cases per 10,000 in the population.
				Unknown_ epidemiological_range	No information is available in the scientific literature to inform prevalence or annual incidence.

For any questions or comments, please contact contact the Orphadata team: data.orphanet@inserm.fr

The correct form when quoting this document is :

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http://www.orphadata.org/cgi-bin/img/PDF/OrphadataFreeAccessProductsDescription.pdf

Version 2

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