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OD4RD GLOBAL REPORT ON ORPHANET-ERNs COLLABORATIONS
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Content summary

Introduction

The main scope of OD4RD Work Package 2 (WP2) is to improve the Orphanet nomenclature and classification of rare diseases in collaboration with European Reference Networks, to reflect the evolution of scientific and clinical knowledge.
This summary report will provide an overview of completed and ongoing collaborations with ERNs from January 2022 to March 2023. For every collaboration the following elements will be specified:

- The ERN involved and the composition of the working group;
- The group of diseases covered and the scope of the revision;
- A brief recapitulative of the advancement of the collaboration;
- For finalized and almost finalized collaborations: the list of entities that have been treated/revised up to now (as annex);
- For ongoing collaboration: an estimation of how many groups/entities will be revised and the expected timing to conclude the revision.

A final chapter will assess the lessons learned from the collaboration experiences, especially those that may benefit other ERN projects.
Annex 1 includes the lists of entities revised by activity.

Methodology

A collaboration project is usually initiated when Orphanet receives a request from an ERN to update the nomenclature and classification of a certain group of disorders. A collaboration can also be initiated by Orphanet if, during an internal quality control, the necessity for an update of the classification is identified. In this second case Orphanet will contact the ERN to ask experts' availability to begin a revision.
Generally speaking, any collaboration project established for the revision of a group of disorders involves the following roles:

- **Experts**: medical doctors contributing their knowledge and validating the scientific accuracy of the information provided by the Orphanet nomenclature; when updates are proposed, they help determine if these will appropriately answer the needs of clinicians dealing with patients suspected/confirmed to have a rare disease (RD).
- **Orphanet**: transposes the clinical knowledge provided by the experts and the scientific literature into a standardized terminological structure; prevents the introduction of inter- and intra-classification inconsistencies; anticipates any issue that may arise as a result of the proposed updates in regards to disease coding/data sharing, and in such case, finds and suggests alternatives.

Collaborations usually follow these main steps:

- Assessment of the work necessary:
  (i) the type of revision needed: only at the diagnosis level (ORPHAcodes missing, outdated, wrongly named, or misclassified); only at the structural level (classification to reorganize, subgroups missing or outdated); or both;
  (ii) a quantitative assessment: how many entities need to be analyzed, and the level of complexity of the issues at hand. A « weight » value is attributed to each project

according to its scale and complexity among these values: 0.5 - 1 - 1.5 - 2 (from smallest size/lowest complexity to larger size/highest complexity);

- Prioritization between different ERNs, or between different thematic groups within the same ERN, guided by the above-mentioned assessment and the criticality of the revision for ERN activities (e.g. registries, publications, etc.);
- Definition of the methodology: experts to be involved, working group(s) to be created, tools for the revision, timeline;
- Training of the involved experts on the Orphanet nomenclature standards and update process;
- Review of the nomenclature by ERN experts;
- Review by Orphanet of the updates proposed by experts, to ensure compliance with the nomenclature standards and state-of-the-art publications;
- Discussion to clarify scientific issues, solve problems, find alternatives, and reach a consensus;
- Validation of actions to be implemented by Orphanet and implementation of all validated decisions in the Orphanet database;
- Finalization of the project: a project summary report and a master file listing all clinical entities discussed (with the associated validated actions) are sent to the ERN representatives.

This methodology has been progressively established since 2017 and draws directly from past and ongoing experiences with ERNs. While it outlines a general structure and requirements for the collaboration, it is flexible enough to adapt to the specific challenges and scale of each project. This methodology has been formalized and published on the Orphanet website in June 2022 (link).

Finalized ERN collaborations

1. ERKNet: Renal tubular diseases and ciliopathies

ERN involved	ERKNet
Experts involved	the working group was composed of the ERN coordinator, an expert medical doctor acting as the primary contact person and collaboration leader, and a group of seven contributing expert medical doctors.
Assessment of the collaboration	Medium-low complexity (index 1), revision of around 60 ORPHAcodes and minimal changes to the classification structure. The complete list of revised codes is included in Annex 1.

In 2019 a first collaboration with ERKNet was carried out in order to revise the classification of Rare renal diseases, and in particular the groups of Thrombotic microangiopathies, Glomerular diseases, Renal or urinary tract malformations (CAKUT), and Rare causes of hypertension.

Following this first extensive revision, a more detailed revision of the classification of Rare renal tubular diseases was proposed by Prof. Rosa Vargas-Poussou. Moreover, this second revision also aimed to reply to the question of renal ciliopathies initially raised when ERKNet experts pointed out that a number of phenotypes included in the Rare renal tubular diseases classification were not really tubulopathies, but were rather considered as ciliopathies.

Rare renal tubular diseases are difficult to structure as a group, due to the close interrelations between different electrolytic parameters and pathological processes, and the resulting overlap between diseases that complicates the identification of clear-cut subclassification criteria when it comes to tubular dysfunction. In particular, the hypomagnesemia subgroup of disorders was challenged by the working group.

Taking all these into consideration and after extensive discussion with the experts it was decided to inactivate the Genetic primary hypomagnesemia group (ORPHA:34526), and reclassify all the entities it included directly under the upper main group Rare renal tubular diseases (ORPHA:93603), together with all the other tubulopathy-related phenotypes. Moreover, the phenotypes included in the Rare renal tubular disease and Familial cystic renal disease groups were reassessed in order to identify which ones were tubulopathies, which ones were cystic renal diseases, and which ones were ciliopathies.

At the end of the revision process, a final report was sent to ERKNet, recapitulating the steps of the collaborations and the decisions taken. All validated decisions were also provided in a Master file Excel document, which included the list of ORPHAcodes that were created, modified (including renamed diseases), or inactivated.

2. ERN CRANIO: Cranial malformations

ERN involved	ERN CRANIO
Experts involved	the working group was composed of the ERN coordinator acting as the primary contact person and collaboration leader, and a group of four contributing expert medical doctors.
Assessment of the collaboration	Medium-high complexity (index 1.5), revision of around 80 ORPHAcodes and their classification structure. The complete list of revised codes is included in Annex 1.

The classification of rare cranial malformations was revised following a request from ERN CRANIO, in anticipation of the setup of their patient registry, as the available ORPHAcodes no longer matched the current insights.
Notably, the diagnoses represented in the isolated craniosynostoses (CS) group were previously defined according to the shape of the skull (trigonocephaly, scaphocephaly, plagiocephaly…). The request was to shift to a classification defined according to the synostosis pattern (i.e. the cranial suture(s) involved), with explicit distinction between unisutural vs multisutural presentations. The revision also entailed the syndromic CS group, as well as the rest of clinical entities included in the cranial malformations group (other than CS).

The revision of the craniosynostoses group was guided by the following elements:

- The "isolated" vs "syndromic CS" structure was maintained, in line with the clinical practice: the diagnosis is typically clinical, with the presence of CS commonly identified in the first year of life, then assessment of possible additional features suggesting an underlying syndrome, usually leading to genetic testing;
- While "Isolated CS" has been renamed "Non-syndromic CS" as the logical alternative to "Syndromic CS", the term "isolated" has been incorporated in synonyms for all entities, as it is commonly used in this context and cannot be excluded;
- Non-syndromic CS diagnoses were all redefined according to the synostosis pattern, and in some cases skull shape terms were added as synonyms. Furthermore, the group was subdivided as "unisutural" (single-suture) CS vs "multisutural" CS, because this is an important element of the diagnosis associated with significant differences in clinical presentation and associated problems.
- Several clinical entities present in the Syndromic CS group have been suggested for inactivation. These issues will be progressively reviewed by the Orphanet nomenclature team as they are not blocking the finalization of the revision and can be solved later. Specific syndromic forms of craniosynostosis related to genes discovered in the recent years may need to be created as well.

At the end of the revision process, a final report was sent to ERN CRANIO, recapitulating the steps of the collaborations and the decisions taken. All validated decisions were also provided in a Master file Excel document, which included the list of ORPHAcodes that were created, modified (including renamed diseases), or inactivated.
The syndromic CS group will continue to be revised according to Prof Mathijssen's suggestions by the Orphanet nomenclature team, but this was not blocking for the finalization of the revision.

3. ERN-ITHACA: OrphaID - Intellectual disabilities

ERN involved	ERN-ITHACA
Experts involved	Experts involved: the working group was composed of the ERN coordinator, a project manager acting as the primary contact person, and an expert medical doctor and an IT manager of the SysID/SysNDD database.
Assessment of the collaboration	High complexity (index 2), revision and inclusion in OrphaID of around 800 ORPHAcodes. The complete list of revised codes is included in Annex 1.

Intellectual disability (ID) is a group of heterogenous disorders affecting up to 3% of worldwide population and characterized by variable impairment in cognition and behavior which can be associated with other syndromic or dysmorphic features. Most genetic intellectual disabilities result from mutations in single genes inherited in autosomal or X-chromosomes or in mitochondrial DNA.

The task of developing a comprehensive list of ID-related genes has first been tackled by Kochinke et al. (Kochinke et al., 2016) who developed the database of SysID (https://www.sysid.dbmr.unibe.ch/); which contains an updated catalogue of genes and phenotypes related to intellectual disabilities. This database has been very recently enlarged to include curated genes and phenotypes related to neurodevelopmental disorders (SysNDD: https://sysndd.org/Genes). However, this database is non-intuitive to navigate and unsuited for patients or ordinary users.

Orphanet has partnered with the European Reference Network on Rare Congenital Malformations, Autism and Rare Intellectual Disability (ERN-ITHACA) in order to develop a platform (OrphaID) for curated intellectual disability related genes and phenotypes. The list of ID entries in OrphaID contains all clinical entities currently classified in Orphanet under Rare genetic intellectual disability (ORPHA:183757).

The original list of intellectual disability-related genes has been curated in partnership with ERN-ITHACA and SysID/SysNDD. Orphanet and SysID/SysNDD have organized a common workflow for curating new ID-entries from peer-reviewed scientific literature under the sponsorship of ERN-ITHACA. OrphaID is a freely accessible database maintained in Orphanet and contains an updated list of ID-related genes and phenotypes. Currently (March 2023), the database contains 813 ORPHAcodes and 1,442 unique ID-related genes, of which 1,378 genes (95%) are disease-causing.

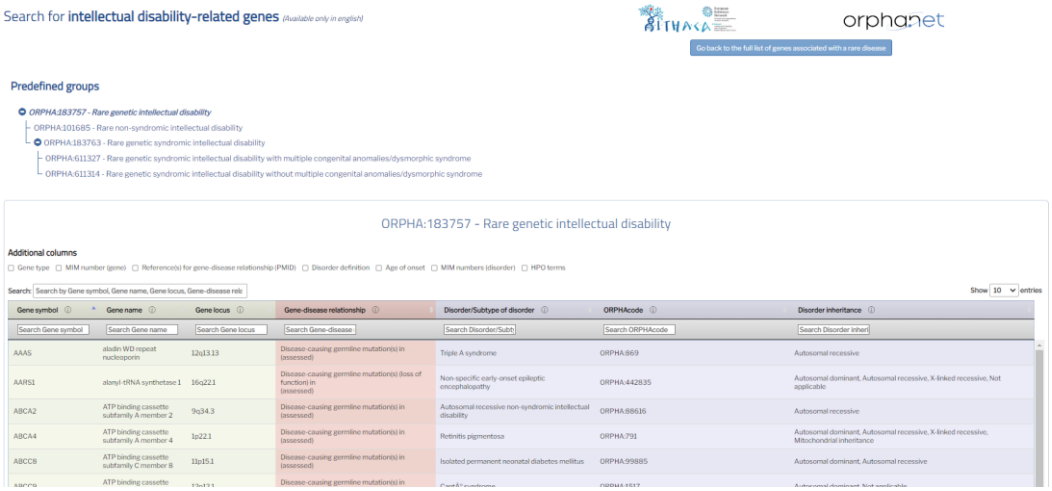

Figure1: OrphaID home page

OrphaID Is continuously updated with new genes and clinical entities from peer-reviewed scientific literature. In addition, Internal reclassification of entities under the Rare genetic intellectual disability (ORPHA:183757) is also being undertaken. Recently, 103 genes linked to 60 ORPHAcodes have been classified also under Rare genetic intellectual disability (ORPHA:183757).

At the end of the revision process, a final report was sent to ERN-ITHACA, recapitulating the steps of the collaborations and the decisions taken. The complete list of revised phenotypes is available through OrphaID at this link.

Finally, in order to objectify the decision of when to link gene(s) to a specific or non-specific ID entity (e.g. non-specific syndromic intellectual disability (ORPHA:528084)), Orphanet has developed a decisional diagram to assist in the process. This diagram defines syndromic IDs by the presence of congenital malformations, dysmorphic features and/or specific phenotypes (e.g. sensorineural deafness, obesity, etc.). Syndromic ID entities are considered specific if the combination of recognizable congenital anomalies and dysmorphic features or specific features are described in at least 30% of reported patients (with minimum of 2 patients). However, it's important to note that specific facial dysmorphic features when described should be interpreted cautiously taking into consideration the variable facial features of the background population. This decisional diagram can be accessed in the Orphanet's genes procedures which will be published soon in the Orphanet's webpage.

Ongoing ERN collaborations

1. ERN BOND: Primary bone dysplasias and Dysostoses

ERN involved	ERN BOND, in collaboration with the International Skeletal Dysplasia Society (ISDS)
Experts involved	the working group is composed of the ERN coordinator, an expert medical doctor acting as the primary contact person and collaboration leader, and a group of thirty-six contributing expert medical doctors.
Assessment of the collaboration	High complexity (index 2) revision of around 250 ORPHAcodes and their classification structure.

The collaboration, aimed at revising the Rare bone disease classification, and in particular the Primary bone dysplasias and Dysostoses groups, has been divided in two steps due to the complexity and the scale of the project:

- **Step 1** (ongoing) is focused on comparing the Orphanet disorder level with the Nosology and classification of genetic skeletal disorders (2019 edition and 2023 edition) published by the International Skeletal Dysplasia Society. This comparison revealed a large number of entities present in Orphanet that are not listed in the nosology. They are being reviewed to determine whether each phenotype should be kept as a real and distinct phenotype or inactivated.
- **Step 2** (planned for 2023/2024) will focus on the groups structure and the reclassifications of all phenotypes.

This collaboration was initiated in 2020 and the state of play of the collaboration together with the work accomplished and future planning has been presented to the ERN BOND plenary meeting in September 2022.

The file containing the entire classification to be revised (248 clinical entities) has been initially distributed between 11 groups of experts for a total of 38 experts from ERN BOND/ISDS involved. Despite the great impact of having a large number of experts involved, it has been challenging to validate the proposed actions and to arrive to consensual decisions between the experts, Orphanet, and the recent literature.

As of March 2023, 128 entities have been revised, leaving 120 entities/phenotypes to be revised. The estimated timeline for the end of Step 1 revision is August 2023. Step 2, dedicated to the revision of the classification groups, will be initiated in September 2023. We estimate the end of the revision process by early 2024. The complete list of the codes revised and implemented until March 2023 is included in Annex 1.

2. ERN-ITHACA and eUROGEN: Spina Bifida and other Dysraphisms

ERN involved	ERN-ITHACA and eUROGEN, working group on Spina Bifida and other Dysraphisms
Experts involved	the working group is composed of two expert medical doctors acting as the primary contact persons and collaboration leaders, and a group of eleven contributing expert medical doctors.
Assessment of the collaboration	Medium-low complexity (index 1), revision of around 55 ORPHAcodes and small changes to the classification structure.

In 2022 Orphanet has been contacted by the working group on Spina Bifida and other Dysraphisms to revise the group of disorders Isolated spina bifida and other dysraphisms present in Orphanet. The current Orphanet classification is in fact outdated and medical doctors face difficulties to code patients. This revision will consist to create new ORPHAcodes for missing clinical entities, inactivate entities that are not used in medical practice, update the definitions by improving the level of details and adapt to the current medical knowledge and propose a new classification structure.

No modification has been implemented yet as of March 2023. The revision is expected to be finalized approximately by May/June 2023.

3. ENDO-ERN: Pseudohypoparathyroidism and Pituitary tumors

ERN involved	Endo-ERN, European Registries for Rare Endocrine Conditions (EuRRECa)
Experts involved	the working group is composed of an expert medical doctor acting as the primary contact person and collaboration leader, a project manager, and a group of two contributing expert medical doctors.
Assessment of the collaboration	Medium-low complexity (index 1), revision of around 40 ORPHAcodes with changes to the classification structure.

The scope of the collaboration is to revise the classification of Pseudohypoparathyroidism and Pituitary tumors. The collaboration has been initiated in 2021, when experts from EuRRECa sent to Orphanet a proposition to revise the clinical entities affecting the PTH/PTHrp signaling pathway. According to the experts these disorders have been historically described as “pseudohypoparathyroidism” or “PHP” and divided in subgroups depending on their clinical presentation. However, a new classification has been proposed by the EuroPHP network. During the revision process, experts also expressed the will to revise Pituitary tumors.

At the moment Orphanet is awaiting the final decision of the experts regarding the classification changes proposed, after several exchanges, but no modifications have been finalized as of March 2023. The collaboration is expected to be finalized approximately by April/May 2023.

4. VASCERN: Vascular anomalies

ERN involved	VASCERN, Vascular Anomalies (VASCA) Working Group
Experts involved	the working group is composed of an expert medical doctor acting as the primary contact person and collaboration leader, a project manager, and a group of contributing expert medical doctors belonging to the VASCA Working Group.
Assessment of the collaboration	High complexity (index 2), revision of the vascular malformations and the vascular tumors groups (approximately 180 clinical entities) and their classification structure.

In 2019 a first collaboration with VASCERN, Pediatric and Primary Lymphedema (PPL) working group, was carried out in order to revise the classification of the Primary lymphedema group of disorders.

In 2022 a discussion has been rekindled with the VASCA Working Group to align the Orpha classification with the ISSVA classification for vascular anomalies (vascular malformations and vascular tumors). A brief presentation of the methodology of the collaboration has been given by Orphanet at the VASCERN meeting and the VASCA group meeting in Paris in October 2022.
Although discussion has been initiated on both the vascular malformations and the vascular tumors groups, no modifications have been finalized as of March 2023. The collaboration is expected to be finalized approximately by the end of 2023.

5. EpiCARE: Rare epilepsies

ERN involved	EpiCARE
Experts involved	the working group is composed of an expert medical doctor acting as the primary contact person and collaboration leader and a group of three contributing expert medical doctors.
Assessment of the collaboration	High complexity (index 2), revision of the rare epilepsy group (approximately 500 clinical entities) and its classification structure.

In 2022 several positions papers have been published by the International League Against Epilepsy (ILAE), restructuring and redefining the nomenclature and classification of rare epilepsies and epilepsy syndromes. Experts from EpiCARE have been working to reflect those changes into the Orphanet classification. At the beginning of 2023 an initial meeting has been conducted to structure the collaboration. It has been agreed that the project will be conducted in 3 phases:

- Phase 1: revision of the group of Epilepsy syndromes
- Phase 2: revision of the other epilepsy phenotypes
- Phase 3: restructuring the classification according to the ILAE recommendations

The collaboration is still in its early phase and is expected to be finalized approximately by the end of 2023/beginning of 2024.

Lessons learned

Drawing from past and ongoing collaboration projects, Orphanet has been able to improve its collaboration methodology and gain experience and knowledge, both positive and negative, that will help continuously improve the collaboration process. The following points are the most relevant lessons learned.

1. Communication with ERN experts

The dynamic of the revision process effectively relies on the reactivity of the two sides of the collaboration: the projects that Orphanet can absorb (given by the availability of Nomenclature project managers) and the ERN reactivity to Orphanet requests for expertise.

It is sometimes difficult to efficiently communicate and interact with ERN experts. Experts are usually medical doctors that are extremely busy between their clinical and research practice and ERN activities. Consequently, they might not be reactive when contacted by email, and organizing meetings with several experts at the same time might be difficult due to time constraints. This can also generate a delay in the starting of the collaboration, or a bottleneck during the revision process.

This need for improved communication has highlighted the importance of having a reactive ERN contact point, that could either be an ERN project manager in charge of soliciting experts' responses and organizing meetings with several participants, or an ERN medical doctor that acts as spokesman for all expert participants of the revision and is fully implicated in the revision process.

A revision process should not therefore be initiated if a full commitment of the ERN has not been obtained, together with an indication of the contact person that will follow the project on the ERN side.

If Orphanet is not able to obtain a timely follow-up on the ERN side, the collaboration might be paused and left on hold until the ERN has the adequate resources to dedicate to the project.

2. Importance of providing an adapted training to ERN experts

The importance of training the collaborating experts to the Orphanet nomenclature and classification rules and procedures was assessed very early during the first Orphanet-ERN collaborations. Training experts on the general Orphanet concepts (definition of the nomenclature and structure of the classification) and on the nomenclature update process makes sure that experts will have a full understanding of the different types of actions applicable in the Orphanet database and will compile their suggestions in the provided supports in a standardized and easy to understand format.

The training needs are generally assessed by the Orphanet nomenclature project manager, taking into consideration the eventual previous collaborations of the experts with Orphanet and the proportions of the revision.

Projects for which the experts started the work on their own before receiving the Orphanet training were generally slower and more complex to analyze on Orphanet side, due to the lack of

standardization and a general misunderstanding of the Orphanet nomenclature rules. This is why a training should always be proposed to experts, even at later stages of the collaboration, and in general every time that the Orphanet nomenclature manager perceives a need to guide the clinical experts in the methodology and the use of tools.

3. Treating high complexity collaborations

Out of the 8 initiated revision collaborations, 4 are High complexity (index 2) projects. These projects include the revision of large groups of clinical entities (ranging from 100 to up to more than 500 ORPHAcodes), together with entire classification restructuring. These projects also usually rely on the contribution of large groups of experts.

Taken together, the intrinsic characteristics of these high complexity revisions complicate the process and the timeline. Indeed, all 4 projects have been greatly delayed, either in their starting phase or during the active revision phase.

In order to avoid as much as possible this kind of complications, there are some solutions that seemed to work to speed up the process and render it more efficient:

1. Subdividing the workload by identifying smaller clinical blocs of entities/groups to be revised in a subsequent way during the collaboration;
2. Subdividing the workload by separating the ORPHAcodes revision process from the restructuring of the classification process in two consecutive phases;

Avoiding to work with large groups of clinical experts at the same time. A better approach is to work with a restricted group of 2/3 experts, and submit the final proposition for commentary and approval at the end to the entire ERN working group.