2nd Virtual OIFE Investigator Meeting

Introduction

On the 17th of November 2023, the Osteogenesis Imperfecta Federation Europe (OIFE) hosted the second Virtual OIFE Investigator Meeting for the OI research community. 277 people from 48 countries signed up and more than 160 individuals attended the online event. Attendees were a mix of health professionals, scientists, OI clinicians and a small number of representatives from industry and patient groups.

The Osteogenesis Imperfecta Federation Europe (OIFE) is an umbrella association for organizations dealing with the rare condition Osteogenesis Imperfecta (OI) also known as brittle bone disease. The federation was established in 1993 by six founding OI-organizations and is registered as a nonprofit in Belgium. Because of logistical reasons, OIFE was reestablished in Belgium in 2022 by four founding organizations and is now registered as a nonprofit in Belgium.

The meeting's objectives aimed to highlight recent advances in OI research, providing a collaborative space for researchers in Europe and beyond, attracting fresh talent to European OI research, and offering support to the younger generation of OI researchers. With a focus on fostering a spirit of cooperation and innovation, this meeting wished for contributing to the growth and development of OI research globally.

In this report we summarize the invited talks and list the presentations and authors of the oral presentations selected from the submitted abstracts.

Research collaboration in Europe: hurdles and opportunities

European Rare Disease Research Coordination and Support Action (ERICA) and the European Rare Disease Research Coordination and Support Action (ERDERA)

Luca Sangiorgi (Bologna, Italy)

ERICA (The European Rare Disease Research Coordination and Support Action)

ERICA (The European Rare Disease Research Coordination and Support Action) aims to increase collaboration, by bringing together all 24 European Reference Networks (ERNs). ERICA provides a platform that integrates all ERNs research and innovation capacities.

At its core, ERICA functions as a rare disease competitive network, with a commitment to enhance the quality and impact of clinical trials, increase patient involvement with the goal to develop safe and efficient therapies for patients with rare diseases.

Currently, the involvement of ERNs in clinical trials still faces challenges in implementation. One of the obstacles is that the wide geographical distribution of Health Care Providers (HCPs) in different European countries with different national regulations and legislations makes uniform decisions difficult. Navigating these complexities is imperative for streamlined trial implementation. Another hurdle is the lack of knowledge, opportunities, procedures, and methodological solutions for trial implementation.

To address this, ERICA has organized a series of webinars to help ERNs and their researchers in their clinical trial activities. These webinars provide ERNs and their researchers with the necessary insights and tools to navigate the intricacies of clinical trial activities. The goal is to foster a more cohesive and informed approach across the diverse European landscapes represented within the ERNs.

ERICA performed a survey in 2023, to investigate the status quo of ERNs and clinical research, which was conducted among ERN coordinators (42) and HCP members (134). This survey delves into the current state-of-the-art of ERNs and clinical research. Notably, 66% of participants revealed the existence of transversal Working Groups on research activities, particularly focused on diagnostic research studies and observational and interventional clinical trials. 85% of ERN/HCPs want to include clinical trials in their activities and they developed some clinical research on the disorders treated by their ERN (74%).

Looking forward, ERICA aims to advance clinical research, by addressing priorities such as guidelines, outcome measures, registries, resources/funding, identification of biomarkers, diagnostic tools, supporting disease-specific networks and many more. The overarching goal is to ensure the development of safe therapies and efficient access for patients grappling with rare diseases.

In the future two separate surveys targeting ERN coordinators and HCP members will be conducted, with a specific focus on clinical trials. This strategic approach aims to collect more comprehensive information about the evolving aspects and issues that have surfaced since the last survey.

The European Rare Diseases Research Alliance (ERDERA)
The European Rare Diseases Research Alliance (ERDERA) is a co-funded partnership between the European Commission, European Member States, and beyond. It aims to improve the health and well-being of the 30 million people living with a rare disease in Europe, by making Europe a world leader in RD research and innovation, to support concrete health benefits to rare disease patients, through better prevention, diagnosis, and treatment. The programmes that come out of this, will probably replace the European Joint Programme on Rare Diseases (EJP RD).

Research advances/What's new in basic science?

Presentations: New animal models in OI by Roy Morello (Little Rock, USA)
Endoplasmatic Reticulum (ER) Stress by Antonella Forlino (Pavia, Italy)

New animal models in OI
Roy Morello

A new conditional knock-in mouse model of osteogenesis imperfecta (OI) was introduced. Current available OI murine models express mutations globally (i.e. in all tissues), the idea of this new conditional knock-in mouse model is to be able to assess the role of a severe type I collagen mutation in a specific cell type and/or tissue.

To achieve this goal, a conditional mouse model was generated by inserting a *COL1A1* point mutation causing a gly substitution in the murine genome. The mutant allele is expressed only after Cre-specific recombination of the floxed *COL1A1* allele.

This new mouse model allows tissue-specific expression of the mutation only following its breading with different Cre-recombinase expressing strains. To assess the role of an OI mutation on respiratory function in the context of a healthy skeleton, these mice will be crossed with mice expressing Cre recombinase in lung fibroblasts. A mouse model that has a healthy skeleton and only expresses the mutation in the lung, makes it easier to isolate the impact of the mutation on the lung versus the effects of the mutation on the skeleton, as a whole.

To determine the potential contribution of osteocytes to OI disease manifestations (since they produce type I collagen which is mutated) compared to osteoblasts, the conditional knock-in mice will be bred with mice expressing Cre in osteocytes. The goal is to express the mutation only in osteocytes, but not in osteoblasts to clarify how it contributes to disease manifestation and possibly to identify new therapeutic targets. In addition, these mice will be used to study the impact of a severe type I collagen mutation at different developmental time points.

In summary, this conditional knock-in model for *COL1A1* was successfully generated to fill the gap of knowledge on the specific effect of collagen I mutation in different tissue. The model will be a unique tool to better dissect OI pathogenesis and identify new therapeutic targets.

Endoplasmatic Reticulum (ER) Stress
Antonella Forlino

The endoplasmic reticulum (ER) is important for the proper folding and processing of type I collagen, which is impaired in OI due to the *COL1A1/COL1A2* mutation. It has been demonstrated that in OI, an accumulation of mutated type I collagen in the ER induces ER stress in osteoblasts, causing osteoblast dysfunction leading to bone fragility (Scheiber et al., 2019). Thus, the endoplasmic reticulum (ER) has emerged as a novel therapeutic target for osteogenesis imperfecta (OI). Targeting the ER stress response through chemical chaperones is thought to improve collagen processing and bone properties in OI mouse models and eventually patients.

4-phenylbutyric acid (4PBA) is a chemical chaperone FDA approved for Urea cycle disorders as ammonia scavenger and known to have chaperone function. 4-phenylbutyric acid (4PBA) has been shown to normalize the excessive production of type I collagen, reduce ER retention, partially improve misfolding of the type I collagen helix in the extracellular matrix (ECM), and improve osteoblast mineralization.

It has also been shown, that 4PBA treatment decreased apoptotic cells, reduced the expression of unfolded protein response (UPR) genes, improved osteogenic phenotype by improving *RUNX2*, *SPP1*, *BGLAP*, and *IBPS* expression, as well as stimulating mineralization. In vitro and in vivo studies support the use of 4PBA as novel drug for OI. The downsides are the short half-life of the molecule, which require high daily doses and the difficulty to specifically deliver it to the bone in proper amount. Furthermore, some side effects may occur that may need medical attention and the taste of the drug is quite disgusting.

In conclusion, ER stress represents a good target for OI treatment. Specifically, chemical chaperones are appealing drugs and in the future new chaperones other than 4PBA with higher stability and/or bone specific targeting are needed.

The summaries of the following presentations conducted during the OIFE Investigator Meeting were omitted, as they involved the dissemination of unpublished research:

Characterization of tendon properties in the murine model of severe osteogenesis imperfecta
Presented by Antoine Chretien (Leuven, Belgium)

Crispant analysis in zebrafish as a tool for rapid functional screening of disease-causing genes for bone fragility
Presented by Sophie Debaenst (Ghent, Belgium)

Deciphering phenotypic and mechanistic variability in Bruck syndrome and Osteogenesis imperfecta, through a zebrafish model with loss of fkbp10
Presented by Tamara Jarayseh (Ghent, Belgium)

Absence of TRIC-B from type XIV osteogenesis imperfecta osteoblasts alters cell adhesion and mitochondrial function - A multi-omics study
Presented by Milena Jovanovic (Bethesda, USA)

Methods and tools to evaluate outcomes in clinical trials/Techniques to assess bone density, structure, strength, and mobility in OI

Presentations: HR-pQCT to assess bone density, structure, and strength in OI by Enrico Schileo (Bologna, Italy)
Assessing mobility in OI – the role of movement analysis by Andreas Kranzl (Vienna, Austria)
Assessing bone in adults with OI – a 10 year follow up study Bente Langdahl (Aarhus, Denmark)

HR-pQCT to assess bone density, structure, and strength in OI
Enrico Schileo

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a noninvasive imaging modality that measures volumetric bone mineral density (vBMD) and measures/estimates microarchitectural bone parameters in OI (Mikolajewicz et al., 2020). Currently, the gold standard for clinical imaging of bone mass is dual-energy X-ray absorptiometry (DXA). DXA-derived areal bone mineral density (aBMD) is a significant predictor of fracture risk. However, it is far from perfect, and many people still have bone fractures despite scoring high on their DXA bone scan.

HR-pQCT can predict fractures beyond what is seen with DXA-aBMD and FRAX (Fracture Risk Assessment Tool). However, HR-pQCT is limited to measuring peripheral bones (i.e. arms and legs). HR-pQCT assessment may be valuable in longitudinally monitoring disease progression and treatment efficacy. But more research is still needed to fully validate and optimize its use in evaluating bone status and outcomes for patients with OI.

Dr. Schileo leads a working group around the use of HR-pQCT OI. If you are interested in joining the working group or collaborating with him, please contact Enrico Schileo via email at enrico.schileo@ior.it .

Assessing mobility in OI – the role of movement analysis
Andreas Kranzl

Motion analysis in osteogenesis imperfecta (OI) is a valuable tool for improving clinical decision-making, particularly in the assessment and treatment of gait issues. Through objective data gathered through the Motion Analysis Laboratory, clinicians can determine the appropriate surgery or other treatments to correct a person's gait issue or other movement disorder.

Motion can be analyzed through different methods, including video-based analysis (2D, 3D), optical motion capture systems (3D), inertial sensor-based systems, markerless motion capture systems (2D, 3D), and activity trackers.

Markerless motion capture uses standard video to record movement without markers, often relying on deep learning-based software to identify body segment positions and orientations (pose). While this method has potential benefits, its slow adoption in biomechanics may be attributed to the requirement for advanced coding skills and in-depth computer science knowledge.

Wade et al., 2022 discuss the applications and limitations of current markerless motion capture methods for clinical gait biomechanics, emphasizing the need for informed use of these technologies in research, clinical, and coaching settings.

The evaluation of individuals with OI by means of motion analysis and selected functional assessments, along with an accurate biomechanical model of the lower and upper extremities is an effort to better understand and predict OI disability and improve quality of life. It has been noted, that there is a need for more studies on upper extremity motion, larger participant samples, and research on OI types beyond Type I.

Assessing bone in adults with OI – a 10 year follow up study
Bente Langdahl

Disclaimer: This study is still in the planning phase.

Plans for a 10-year follow-up study assessing bone status in adults with OI were discussed. The planned study aims to reevaluate approximately 80-100 adults with OI, that participated in a clinical trial 10 years ago.

The methods to conduct skeletal studies, reevaluate bone health and identify fractures include: Dual-energy X-ray Absorptiometry (DXA) to measure areal BMD for lumbar spine, hip and the entire body, High-resolution peripheral quantitative computed tomography (HRpQCT) to measure volumetric BMD of the distal radius, distal tibia, and investigate bone architecture, and spine X-rays. Combining data from multiple assessment methods may help better understand fracture risk long-term.

The summaries of the following presentations conducted during the OIFE Investigator Meeting were omitted, as they involved the dissemination of unpublished research:

Investigation into the development and progression of coxa vara after intramedullary rodding in children with osteogenesis imperfecta
Kamron Zand (Omaha, USA)

Effect of antiresorptive agent on exfoliation of primary dentition in children with osteogenesis imperfecta medicated with bisphosphonates
Clara Garcete (Madrid, Spain)

Midterm outcomes of multimodal approach to treating severe scoliosis in patients with osteogenesis imperfecta
Yusuke Hori (Wilmington, USA)

Asynchronous healing at the proximal and distal sites in limb osteotomies of osteogenesis imperfecta
Peikai Chen (Shenzhen, China)

Nosology and classification in OI: finding a common language/can we find a common language? Why is it important to find a common language? Implications for treatment

Presentations:
Nosology of genetic skeletal disorders: 2023 revision – implications for OI by Valérie Cormier-Daire (Paris, France)
Classification systems for OI – which path to choose? by Dimitra Micha (Amsterdam, Netherlands)
Genetics first by Joan Marini (Bethesda, USA)

Nosology of genetic skeletal disorders: 2023 revision – implications for OI
Valérie Cormier-Daire

The purpose of nosology (classification of diseases) is to create a common naming system to facilitate diagnosis for the growing number and variety of skeletal phenotypes with a genetic basis.

The 2023 revision of the Nosology of genetic skeletal disorders was published:

*"The **Nosology of genetic skeletal disorders** has undergone its 11th revision and now contains **771 entries** associated with **552 genes** reflecting advances in molecular delineation of new disorders thanks to advances in DNA sequencing technology. The most significant change as compared to previous versions is the adoption of the **dyadic naming system**, **systematically associating a phenotypic entity with the gene it arises from."** (Unger et al., 2023)*

The most significant change to the previous version of 2019 (Mortier et al., 2019) is the adoption of the dyadic naming system which associates the clinical description with the gene.

The 2023 version presents 41 groups of disorders which have been categorized based on clinical, radiographic and molecular criteria. In this revision 310 novel disorders were defined reporting 771 disorders overall. 115 new genes were defined, reporting 552 genes overall. In the previous edition 42 groups of disorders were reported, meanwhile here 41 groups are reported since the group of "perlecan and agregan" and "neonatal osteosclerotic dysplasias and other sclerosing bone disorders » were fused into "osteosclerotic disorders". A new group called "skeletal disorders of parathyroid hormone signaling cascade" was introduced.

OI is group 26 and the naming of disorders including OI has changed from "Osteogenesis Imperfecta and decreased bone density group" to "OI and bone fragility group". While in 2019, the classification was mainly based on the type (Type 1-5), in 2023, 55 disorders were reported overall of those 37 were OI types and 18 "bone fragility" disorders. The renaming of the group was supposed to reflect the fact that skeletal fragility is a hallmark of these disorders irrespective of the bone mineral density (since a small subset of osteogenesis imperfecta patients can have high bone mass).

The organization of disorders in groups is helpful for pediatricians, geneticists (clinical and molecular), radiologists etc. who are not experts in skeletal dysplasia, since it helps in finding the disorders relevant for specific findings.

Over the last decade, there have been significant advances in our understanding of rare and ultrarare disorders due to Next-Generation Sequencing (NGS) technologies. Some key insights and developments include:

- The identification of the molecular basis of previously unrecognized rare and ultrarare disorders
- Major phenotypic heterogeneity arising from a single locus and genetic heterogeneity for a single entity

Classification systems for OI – which path to choose?
Dimitra Micha

Sillence clinical classification

Osteogenesis imperfecta was initially classified by type according to a scheme developed by David Sillence, an Australian clinical geneticist, based mainly on family history, clinical presentation and radiologic findings. The advantages are that it describe skeletal presentation and can help determine treatment.

Genetic classification system of Osteogenesis Imperfecta

In the genetic classification system of Osteogenesis Imperfecta every gene is allocated to an OI type. The advantage of this system is that it describes the genetic defect in the patient very accurately but in the clinical setting, it is less practical because there is clinical variability within each OI gene.

OI Classification based on mechanism identifies gene defects such as

- Primary collagen structure: COL1A1, COL1A2, BMP1
- Collagen modification: CRTAP, LEPRE1, PPIB, TMEM38B

- Collagen folding/crosslinking: SERPINH1, FKBP10, PLOD2, MBTPS2
- Ossification/mineralisation: IFITM5, SERPINF1
- Osteoblast development: WNT1, CREB3L1, SP7, CCDC134, SPARC, FAM46A
- Osteoclast activity: PLS3
- Vesicle transport: KDELR2

Taken from: Lancet. 2016 Apr 16;387(10028):1657-71
Hum Genet. 2021 Aug;140(8):1121-1141

All classification systems are important, each for their own reason. Sillence is very important for the accurate description of disease, which is very important in clinical settings. Genetic classification is useful to confirm the disease, the disease mechanism and eventually develop personalized treatments. The OI classification based on the underlying mechanis combines the genetic with the clinical presentation. This helps understand the prognosis of the disease and to explain the clinical variation.

The most recent system introduced in 2023, the dyadic nomenclature system associates the phenotype with the genetic defect. The advantages of this system are that it is suitable for monogenic diseases characterized by clinical and genetic variability.

This system aims to associate phenotypes with specific genetic defects, facilitating accurate reporting of OI characteristics in both clinical and laboratory settings. With 35 NOS codes, it provides flexibility to accommodate the discovery of new OI genes. The use of this system promotes uniformity and consensus in the literature when describing OI-related information.

OI Nosology – Genetics first
Joan Marini

There are varying nosologies for OI:

- Modified Sillence - essentially phenotypic
- ISDS – basically an updated Sillence classification
- Genetic
- OMIM – essentially genetic but assigns a number at first report resulting in some type numeration assignments that differ from Genetic Nosology

Genetics first – Nosology approach:

The advantages of the “Genetics first” approach are that it prioritizes OI etiology and mechanism, rather than outcome. In addition, it unifies medical classification for individuals and within families since the individual always stays the same type. Having groups based on genes makes it easier to create a unified group for treatment trials. It also makes phenotypic variability/modifiers easier to understand since the diagnosis is based on the gene and not on the phenotype. The downsides are that it retains the phenotypic “Sillence types” for collagen genes.

Phenotypic Classification:

The issues are that current molecular and genetic advances are secondary, if only the phenotype is considered. It is also internally inconsistent since the same gene is now in multiple types, family members have different types, the type of same individual changes during lifetime, the same type has variable inheritance pattern etc. In addition, it is confusing for research, since mechanism and response to drugs are more likely to be based on the defective gene than the phenotype.

The advantage is that in clinical settings similar groups for physical medicine and orthopedics are created. This advantage can be retained by having parallel classifications for molecular genetics and clinical severity.

Dual Nosology – preserving the advantages of both phenotypic and genetic classification?

Dual Nosology is a possible solution which would start with genetics and then add a clinical notation, which could change over lifetime and within families, could denote skeletal severity (i.e. mild (M), intermediate (I), severe (S), lethal (L)), and could contain add-ons, e.g. for mobility, respiratory, hearing, (others).

Nosology is a moving target, not a scientific or clinical fact.

Discussion/Debate among OI experts

Question 1: All these systems are creating confusion about types (clinical, genetic) types. What is the next step forward? What is the perfect classification system?

Lena Lande Wekre (Oslo, Norway)
"I think this question is getting more and more difficult. And today, I feel I have more questions than answers. I think we need a nosology that describes all the various types new and old based on mutation and heredity. This is important for the diagnostics and the coming treatment. When it comes to the phenotypes or clinical descriptions, I think that it is more or less impossible due to the large clinical variation, both between the different types and the difference within the different types. So, before we start to divide our people with OI into different groups of any kind, genetical or clinical, I think we have to define why we have to make groups, when it is useful, who needs it, and so on. The most important thing for me as a clinician will be to map the phenotype, the clinical changes in their entirety to give the best treatment, the best follow up the best advice. And that will always have to be individually, not based on OI, type or gene or anything. "

Fleur van Dijk (London, UK)
I would say, I don't believe in perfect classifications. I think it is really important that the classification is understandable and informative for patients, but also for their family members. I'm quite pleased with the dyadic system, where you have a combination of clinical and genetic info. I think, yes, I can understand from the researcher's point of view, genetic first, and then clinical, I think for the clinicians, it probably will be the other way around."

Valérie Cormier-Daire (Paris, France)
"We will not have a perfect classification. And so the approach, in some ways, is simplistic. So it's really not the best classification. I do think that it is really still helpful to have a classification. Between type one and type phi, we see a genetic basis is mandatory, and we have no choice in 2023. But combining some clinical data with a genetic basis. I don't think that we need more mechanistic classification which is quite helpful for other research for personalized medicine. So maybe we will have to think that clinical and genetic classification on one side and the more mechanistic classification on the other side, because for clinical geneticists, we need to have something easy, easy, understandable for patients. And maybe we need to improve the clinical part, because it's not detailed, and it's not a precise, but we still need to have some clinical information.

Dimitra Micha (Amsterdam, Netherlands)
"I think, for a while there is no perfect classification system, it is too complicated to achieve perfection. I think it is not realistic anymore to use the Sillence types or the genetic classification, by itself, because in this way, we miss too much information. I think they're both important for the effective communication of the disease, for the patients, and for research.
For me, the dyadic system represents a very nice, let's say, compromise between the the genetic and the Sillence classification. I know that there are some people who think that it is still a little bit too complex with all these different nosology codes. So maybe it can still be simplified, but I think it provides a good basis for what we want to achieve."

Joan Marini (Bethesda, USA)
"The reason there's no ideal is that nosology is a moving target, when we know more, we will reorganize it some more. Now we're at a point where the genetics of OI is essentially well defined. And that makes it a fortuitous point to you know, consider re groupings. I do think, one of the disadvantages of genetics first, is that 22 types is a bit unwieldy. I think there needs to be a smaller number of mechanistic groupings that can be rearranged. For me, obviously dyadic genetics first, would be the ideal but rearranged a bit."

Question 2: Do you think after all this discussion it is possible/useful to have a common classification that allow all and that's beneficial for all the stakeholders (geneticists, clinicians, patients)?

Lena Lande Wekre (Oslo, Norway)
"I'm not sure if it's going to be possible to have a common system, but if so, they will have to work a lot on it. And I think we have to go further into the genotype phenotype descriptions. I liked the five groups based on the mechanism. I think it's useful for several reasons. But I think we need to know much more about the phenotype to use the registries, the talks and the service to get the broader information about the phenotype."

Fleur van Dijk (London, UK)
"I would involve the patients more, have patient representation in the workshops to discuss this. "

Valérie Cormier-Daire (Paris, France)
"I think that it will be possible. I think that the dyadic approach is a major change. I also agree that we need to involve patients, and that workshop will be great."

Dimitra Micha (Amsterdam, Netherlands)
"I don't believe in a perfect system. But I believe in a common system. I think it is important to promote interactions between all the different specialists to solve this very complicated problem. This is why I really support the dyadic system, because there is something for everybody there is the clinical type, that clinicians can relate to. There's the genetics, which is perfect for the scientists. And it is not too complicated for the patients to understand."

Joan Marini (Bethesda, USA)

"I think it's really important to have a common dyadic system. I think it's important because if we're at the stage of understanding phenotypic variability, which is where I think the next great black box is, then we need to be making precisely that connection. And if you separate the two systems, you're not going to facilitate that connection."

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