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Six at Sixty. Commentary on osteogenesis imperfecta 1975–2025

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ABSTRACT

Between 1975 and 1977, my collaborators and I conducted a whole-of-population study in Victoria, Australia, examining the various presentations and clinical manifestations of osteogenesis imperfecta (OI) and familial forms of bone fragility. In 1975, the prevailing view was that all presentations of OI reflected variable expression of pathogenic genomic variants at a single gene locus—possibly involving the recently identified protein, type I collagen. We concluded that OI was in fact genetically heterogeneous, setting the scene for future biochemical and genomic discoveries. Currently, OI is recognised to result from pathological variants in >20 genes, with variants in many further loci resulting in related forms of familial osteoporosis or special syndromes characterised by bone fragility. A dyadic nosology has been adopted to help clinicians, researchers and affected individuals in accessing OI diagnosis, treatment and research with a focus on precision medicine.

In 1979, we published *Genetic Heterogeneity in Osteogenesis Imperfecta in the Journal of Medical Genetics (JMG)*, a report of a 3-year clinical genetic study of all presentations and manifestations of the familial bone fragility disorders known as osteogenesis imperfecta (OI), ascertained in Victoria, Australia.[1] The paper compressed 267 pages of data and analysis from my doctoral thesis into a detailed 16-page scientific contribution. The thesis recorded an in-depth clinical, epidemiological, morphological and radiographic study of 190 subjects with many and varied presentations of OI.[2] My colleagues and I were presented with a unique opportunity to investigate the relationship between a common familial disorder known at the time as OI tarda and severely affected infants known at the time as OI congenita. The latter frequently died in the perinatal period and their genetic basis was a vital question for health professionals delivering genetic counselling at the time. Victoria had established a Consultative Committee on Perinatal Mortality in 1961. Every infant who died in the perinatal period had a complete perinatal autopsy including anthropometric measurements, photographic, radiographic and histopathological studies. Permission was given for our research group to review all documentation on each of these babies. Our senior investigator approached the attending medical practitioner at the time of birth for each family and offered a genetic consultation. This meant that in most cases we were able to document the family history and examine both parents as well as siblings. Most families were interviewed at their home. In some instances, particularly where various branches of the family reported bone fragility, multiple family members attended a single venue, so that we were able to review successive generations on the same day. With the assistance of a senior paediatric radiologist, we were also able to obtain a copy of the radiology on each baby and document the radiographic findings and count the total number of reported fractures.

Ascertainment and documentation for most probands was enhanced by the centralisation of paediatric consultative and orthopaedic management services in Melbourne. Children and adults had a medical record at a central Melbourne hospital, predominantly the Royal Children's Hospital in Parkville. The observation and documentation of clinical findings and lived experience of children and adults was enhanced by the educational arrangements at the time of the study. Most children with mobility aids and many young adults with impairment of mobility participated in integrated education and allied health schooling, such as that offered by the Yooralla Society and the Victorian Society for Crippled Children and Adults.

We concluded that virtually all the affected individuals could be grouped into one of four broad categories of clinical findings and inheritance. These categories were dominantly inherited OI with distinctly blue sclerae and postpubertal hearing loss, perinatally lethal OI, progressively deforming OI and dominantly inherited OI with normal sclerae. Finally, there were individuals with familial bone fragility, with one family in particular suggesting X linked inheritance of bone fragility.

OI RESEARCH AT THE UNIVERSITY OF CALIFORNIA, LOS ANGELES

Soon after my arrival as a postdoctoral fellow in 1977 in the Division of Medical Genetics, Harbor-University of California, Los Angeles Medical Center, Torrance California, Dr Victor McKusick visited. He reviewed my findings with me and suggested that the four initial syndrome groups proposed in the thesis be numbered using Roman numerals, to facilitate gene mapping of these traits. The published *JMG* paper incorporated table 7, which gave a numerical value to the four syndrome groups we had delineated, OI types 1–4. These were incorporated into *Mendelian Inheritance in Man* as four types of OI.[3] I was reluctant to limit the number to four types, as we had postulated further genetic heterogeneity in the paper and even an X linked type of OI, based on a pedigree analysis. The latter family has been confirmed as segregating a pathogenic variant in *PLS3*. Furthermore, prior to our Victorian study, I was aware of a paper

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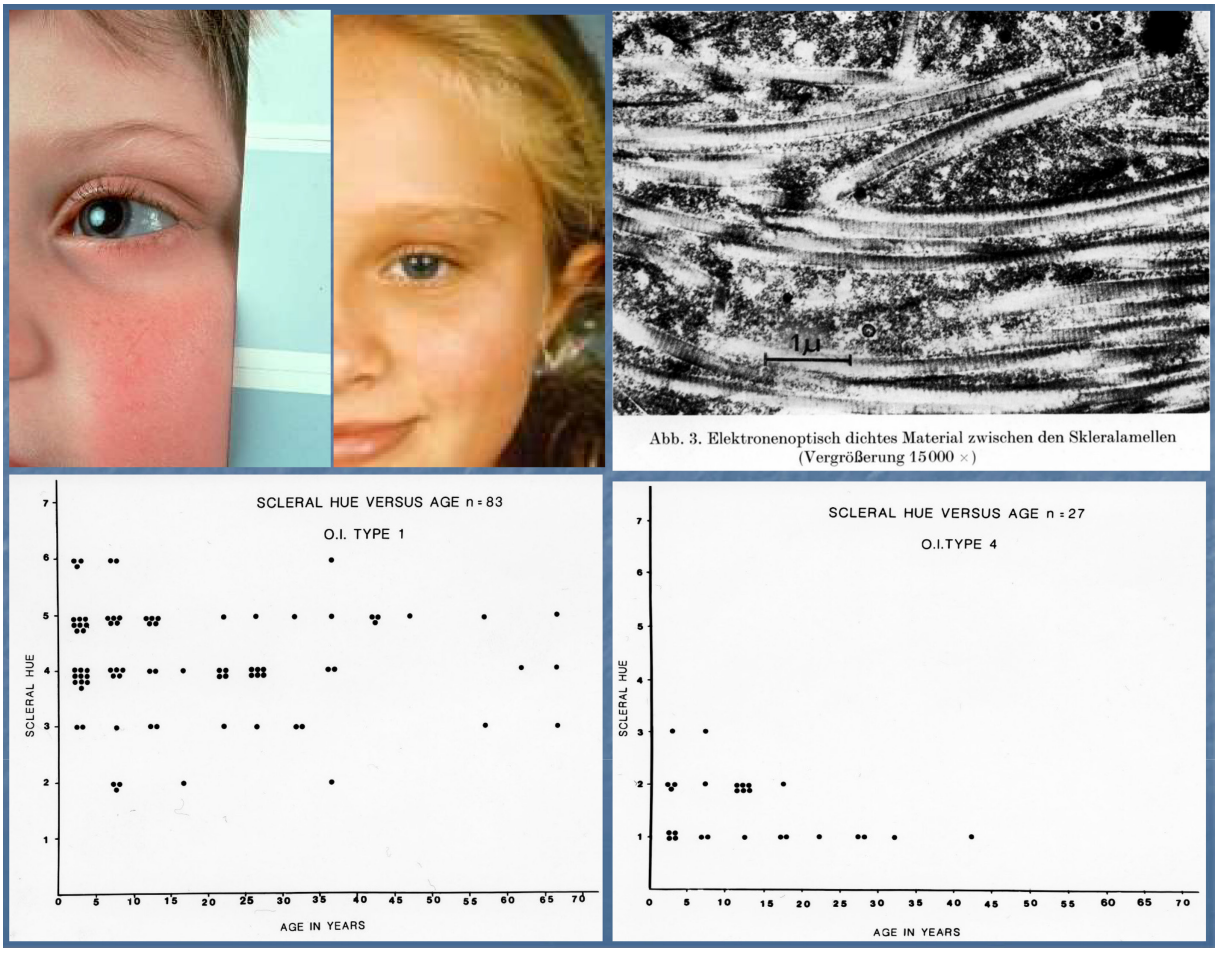

Figure 1 Scleral photographs of a subject with osteogenesis imperfecta (OI) type 1 and distinctly blue sclera (left) compared with normal sclera in a subject with OI type 4 (right). Mapping of scleral hue in cohorts of subjects at different ages is taken from Sillence[13] and the electron micrograph showing electron dense aggregates between the scleral lamellae.[9]

published in 1974 by an Australian colleague, Dr Robert Bauze, reporting on the clinical experience of OI from the clinics of the Nuffield Department of Orthopaedic Surgery in Oxford. A careful reading of his paper could be interpreted as suggesting that the hyperplastic callus form of OI—now recognised as OI type 5 was a distinct autosomal dominant type.[4]

During my Fulbright Fellowship, with funding from the OI Foundation (USA), my collaborators and I—working alongside genetic counsellor Dr Ann Garber-Rimoin—ascertained a further 250 families in the Western USA, primarily through Orthopedic and Shriners Hospitals for Crippled Children.[5] These included additional perinatally lethal probands (OI type 2) and further sibships with progressively deforming OI (OI type 3).[6 7] I had convincing clinical and radiographic evidence that there were two groups of people with dominantly inherited OI, one with distinctly blue sclerae (OI type 1) and a group with normal sclerae (white or just faintly blue grey), which we have now grouped as common variable OI with normal sclerae (OI type 4)[8 9] (figure 1).

We now know that OI type 1, *COL1A1*-related results primarily from nonsense mutations and/or single nucleotide deletions/duplications that cause a frameshift resulting in premature termination of transcription in the *COL1A1* gene.[10] Genomic variants, including multiexon deletions in *COL1A2*, have also been reported in subjects with OI type 1, *COL1A2*-related.[11]

OI type 4, *COL1A1*-related and *COL1A2*-related are commonly characterised by missense coding genomic variants, usually glycine substitution variants which disrupt triple helical assembly.[10] There are at least seven other related genomic variant disorders with overlapping phenotypes. In addition, another large X-linked kindred was ascertained but declined permission for publication. These observations were reported to the Scientific Advisory Committee of the OIF (USA) in my final research report. Once the seminal paper was published in the *JMG*, I prepared my thesis for publication in 1980 through University Microfilms (now Clarivate) and provided a supplementary preface detailing the additional observations noted above.[2] The classification and nosology were adopted by Dr Victor McKusick in 1978, and by clinicians, scientists and people with OI and is now used in most countries of the world.

FURTHER OI RESEARCH IN AUSTRALIA

In 1980, I took up a Senior Lectureship in Human Genetics in the School of Public Health in the University of Sydney. Soon afterwards, I was joined by Dr Kristine Barlow-Stewart, who joined me as a research counsellor for OI Australia and an honorary genetic associate (counsellor) at the Children's Hospital, Camperdown.[12] Over a period of several decades, we ascertained several hundred further families comprising 530 affected children and adults with OI.[13] We were ably supported

Figure 2 The author with Dr Eva Åström, Astrid Lindgren Children's Hospital, Karolinska Institute, alongside the hospital's mascot, Pippy Longstockings.

in developing a multidisciplinary clinic for people with OI by allied health departments, rehabilitation consultants, orthopaedic surgeons, paediatric endocrinologists and Dr Kazimierz Kozlowski—a distinguished paediatric radiologist and member of the International Nosology Consultative Group for Genetic Skeletal Dysplasias.

We have contributed to the literature on genetics, matrix biology, biochemistry and genomics through published works and presentations at the International OI Conferences, which began in 1979 and have been held approximately every 3–4 years since.[13] At the 1993 International OI Conference in Oxford, Åström and Söderhäll presented a paper on the treatment of OI with cyclic intravenous pamidronate combined with multidisciplinary care, which inspired multiple research centres to investigate this approach[14] (figure 2). Our centre was a pioneer in Australia in the use of dual-energy X-ray absorbtiometry (DXA) for assessing paediatric bone mineral density.[15 16] We trialled growth hormone and several different regimens of cyclic intravenous pamidronate in over 200 subjects, resulting in a marked reduction in fracture frequency, skeletal deformity and improved quality of life. Dr Lanie Alcausin reported our experience in treating infants during the first 3 years of life.[16] We also enrolled the largest single cohort of children in the international randomised trial of oral risedronate, which has significantly contributed to the therapeutic options for children with mild-to-moderate OI.[17] We contributed to the genomic discovery of the pathogenesis of Bruck syndrome type 2, *PLOD2*-related and spondylo-ocular dysplasia, *XYLT2*-related.[18]

The International Skeletal Dysplasia Society (ISDS) was formed in 1993 and assumed responsibility for reviewing and revising the nosology (naming) and classification of skeletal dysplasias, including syndromes of OI and bone fragility. Nosology revisions have been published approximately every 4 years since. The Nosology Working Group acknowledged the utility of the Sillence phenotypic groupings early in its reports.

The 2010 Nosology aimed to return to a more descriptive grouping of syndromes. One of the concerns expressed from time to time was that the numerical nomenclature (types 1–5) was often misinterpreted as a severity scale. An unfortunate trend had emerged in some settings, where OI type 1 was equated with mild disease, type 4 with moderate and type 3 with severe OI. In reality, the numerical nomenclature was intended only to reflect the order in which the syndromes were first described, and not their clinical severity. Thus, the Nosology Committee proposed that, where numerical shorthand was used, each disorder group should be designated with Arabic numerals—OI types 1–5.

Dr Fleur van Dijk and I prepared a paper explaining the approach and published a scale for the assessment of severity (figure 3 in Van Dijk and Sillence 2024).[19] This classification was based on a comprehensive analysis of baseline fracture data, radiographic findings, bone densitometry and the natural history of research cohorts we had followed over a 30-year period. Family studies revealed that the severity descriptor *mild* could apply equally to individuals with OI types 1, type 4 and type 5—just as the term *moderately severe* could also apply equally to the same three phenotypes. Consequently, beginning in 2014, we renamed OI type 4, *common variable OI with normal sclerae*.

A DYADIC NOSOLOGY FOR OI

In 2023, after lengthy deliberation, the Nosology Committee of the ISDS recommended that health professionals, scientists and patients use a dyadic nosology for OI and bone fragility disorders.[20 21] They proposed that the time-honoured descriptive form, or a numerical shorthand, should be combined with the name of the related gene in which a genomic variant causes bone fragility. The committee noted that the Sillence groupings had been adopted as the universally agreed clinical designations for over 40 years. The online database OMIM has continued to use Roman numerals for each new gene and gene product proposed as a cause for a type of OI (see online supplemental table 1).

In 2024, at the request of the journal *Calcified Tissue International (CTI)*, I published *A Dyadic Nosology of Osteogenesis Imperfecta and Bone Fragility Syndromes 2024*.[21] The 23 loci identified by the committee as having genomic variants associated with an OI pattern of bone fragility are listed in online supplemental table 1. The dyad consists of the clinical grouping in column 1, paired with the specific gene identified in column 2. In addition, a further 16 gene loci have been identified in which genomic variants result in either a pattern of familial osteoporosis or a syndromic disorder featuring osteoporosis, such as Bruck syndrome. This extensive review—which, in retrospect, should have been titled *A Dyadic Nosology and Genetics of Osteogenesis Imperfecta and Bone Fragility Syndromes*—encompasses the dyadic nosology and provides an extensive discussion of the contemporary clinical genetics of OI. The factors contributing to genetic heterogeneity, somatic and germ cell mosaicism, variable expressivity and digenic inheritance were discussed. The specific case of digenic inheritance, for which there are now multiple reported examples, was also reviewed. X-linked OI and bone fragility resulting from pathogenic genomic variants in *PLS3, MBTPS2* and *SMS* were also discussed as a special counselling challenge. In counselling, all the daughters of an affected male inherit the pathogenic genomic variant and may present with one of the various patterns of osteoporosis/osteopenic bone disorder, which includes young adult osteoporosis, intrapartum or postpartum osteoporosis or exaggerated postmenopausal osteoporosis.[22] Moderate-severity X- linked osteoporosis, *PLS3*-related, has been reported in a prepubertal girl who presented at 6 years of age.[23]

A companion paper, published in the November 2024 issue of *CTI* and entitled *Update on the Genetics of Osteogenesis Imperfecta*, provides an extensive overview of current biochemical and genomic discoveries. However, it does not address the complex

genetic diagnostic and counselling challenges faced by clinicians and genetic counsellors.[24]

GENETIC HETEROGENEITY IN OSTEOGENESIS IMPERFECTA AND BONE FRAGILITY SYNDROMES

Our conclusion, made 50 years ago, that OI and a continuum of familial bone fragility syndromes would ultimately be shown to demonstrate genetic heterogeneity was, at the time, an act of faith. The methodologies of formal clinical genetics involved clinical histories, phenotypic evaluations, skeletal radiology and tissue pathology of probands and their family members. We observed and reported variable expressivity both within and between families, along with allelic and locus heterogeneity, encompassing three patterns of inheritance—autosomal dominant, autosomal recessive and even X-linked—well before discoveries in matrix biochemistry or genomics confirmed our conclusions. From the outset—and even recently—many investigators have preferred to rely on phenotypic classifications of OI as mild, moderate, severe or extremely severe. However, over a decade ago, the need for a dyadic nosology was proposed. Only this approach allows for accurate interpretation of state-of-the-art research and clinical investigations. A dyadic nosology is essential for enabling the precise evaluation and tailoring of therapies.

POSTDYADIC NOSOLOGY DIAGNOSIS—WHERE TO NOW

Studies of OI must continue, with a focus on integrating clinical genetics and counselling with lived experience, adult complications, underlying matrix biology and structure, matrix biochemistry and genomics. A recent editorial in *CTI* is commendable for highlighting a series of important current reviews.[25] There is no doubt that the quality of life for many individuals with OI has been transformed, and our understanding of the factors that contribute to optimal care has advanced significantly. From the early days of patient and family support groups, it has been widely recognised that the best outcomes—for patients, parents and siblings alike—are achieved through integrated, multidisciplinary care.[26] The programme for children with OI in the Sydney Children's Hospital Network—including the trialling and adoption of bisphosphonate therapies and intermittent orthopaedic surgical interventions—has been centred around physiotherapy, occupational therapy and physical rehabilitation programmes provided throughout childhood and adolescence.[27] Arundel and Bishop have provided a comprehensive review of current medical therapies.[28] The transition to adult care has been featured and reviewed in an excellent recent review.[29]

More than ever, young adults need to begin their lifelong care with a precise dyadic diagnosis and the assurance that a regional centre of expertise is available to provide multidisciplinary management, therapeutic support and ongoing updates. In their excellent update on the management of OI, Maron *et al* highlight that therapy with parathyroid hormone analogues such as teriparatide (Forteo) may be effective in promoting bone repair and augmentation in adults with OI type 1, *COL1A1-related*, whereas it is usually ineffective in OI type 3 or type 4, when *COL1A1*-related.[30]

IS THERE STILL MORE TO LEARN ABOUT BONE FRAGILITY AND GENOMIC PREDISPOSITION?

In our original report in 1979, we noted that 7% of individuals affected with OI type 1 had no history of fracture. Similarly, studies across multiple pedigrees with OI type 4 have confirmed that several family members who transmitted a pathogenic genomic variant in *COL1A1* or *COL1A2* had not experienced a fracture at the time of ascertainment—demonstrating transmission of an allele with reduced penetrance.

A more challenging—though hopefully now less common—clinical scenario involves the presentation of a patient with OI-like low-impact bone fragility who does not have a pathogenic variant in any of the known bone fragility gene panels. Clinicians need to be aware that:

1. there remain monogenic or digenic bone fragility disorders yet to be delineated and/or reported;
2. most commercial bone fragility panels include only a limited number of the many known genes in which pathogenic variants causing bone fragility have been identified;
3. in my *CTI* review, I provide four tables listing some of the many rare disorders in which unexplained bone fragility is a feature of the syndrome. These include premature ageing disorders, connective tissue dysplasias, special syndromes with bone fragility and disorders predisposing to transient infantile hyperparathyroidism.[21] The diagnostic challenges are thoroughly reviewed in a comprehensive discussion, including an overview of bone biopsy and the investigation of bone material properties, which contribute to a deeper understanding of the pathogenesis of bone fragility disorders.[31] There is still much to be discovered by investigating each one of these rare syndromes, particularly when selected based on dyadic diagnosis within research cohorts. A recent investigation of the musculoskeletal impairments in adults with OI type 1—which correlated functional impairments with assessments of bone and muscle using DXA and peripheral quantitative CT—reinforces the importance of studying cohorts with a precision diagnosis.[32]

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