The clinical features of *Osteogenesis Imperfecta* in Vietnam

Ho Duy Binh[1,2], Katre Maasalu[2,3], Vu Chi Dung[4], Can T. Bich Ngoc[4], Ton That Hung[5], Tran V. Nam[6], Le N. Thanh Nhan[1], Ele Prans[7], Ene Reimann[7], Lidiia Zhytnik[2], Sulev Kõks[7], Aare Märtson[2,3]

[1]Hue University of Medicine and Pharmacy, Hue University, Vietnam

[2]Clinic of Traumatology and Orthopaedics, University of Tartu, Estonia

[3] Clinic of Traumatology and Orthopaedics, Tartu University Hospital, Estonia

[4]National Hospital of Pediatrics, Hanoi, Vietnam

[5]OI Booming Diamond Center, Ho Chi Minh City, Vietnam

[6]Traditional Medicine Institute, Ho Chi Minh City, Vietnam

[7]Pathophysiology Department, University of Tartu, Estonia

Abstract

Aim

OI have not been studied in a Vietnamese population before. The aim of study was to systematically collect epidemiological information, investigate clinical features and create clinical database of Osteogenesis Imperfecta (OI) patients in Vietnam for future research and treatment strategy development

Methods

Participants underwent clinical and physical examinations, also medical records were reviewed. Genealogical information was collected and family members' phenotypical manifestations recorded. Cases were classified according to the Sillence classification.

Results

Totally 146 OI patients from 120 families studied, 46 with OI type I, 46 patients Type III and 54 Type IV. All patients had skeletal deformations. 142 history of fractures, 117 blue sclera, 89 dentinogenesis imperfecta and 26 hearing loss. Total number of fractures was 1932. 34 patients had intrauterine and 9 perinatal fractures. Surgery was performed in 163 times in 58 patients, 100 osteosynthesis and 63 osteotomies. Bisphosphonate treatment was used in 37 patients.

Discussion

The number of affected individuals and predominance of severe forms of OI indicate that disease is underdiagnosed in Vietnam, especially in cases without family history or with mild OI form. Deformities appeared in all patients with different severity and localization, affecting

mostly lower limbs. OI medical and surgical treatment rates are low and in most cases surgery was performed due to fractures.

Conclusion

Compared to previous studies, our results indicate a lower OI prevalence and greater severity of symptoms in the Vietnamese population comparing to other areas. Further investigation, improved diagnosis and treatment is needed to increase patients' quality of life.

***Key words*:** *Osteogenesis imperfecta* (OI), skeletal deformations and bone fractures, *Dentinogenesis imperfecta*, OI in Vietnam

Introduction

Osteogenesis imperfecta (OI) is a group of genetic disorders, also known as "brittle bone disease". OI is characterized by low bone mass, bone fragility and skeletal deformity [1]. Clinical severity varies widely, from nearly asymptomatic with a mild predisposition to fractures, normal stature and normal lifespan, to profound disability or even fatality [2]. The genetics of this disorder are extremely heterogeneous. An estimated 90% of individuals affected by OI are heterozygous for the causative variant in one of two genes (*COL1A1* or *COL1A2*) that code the main structural protein of bone - collagen Type I [3, 4]. Estimated OI prevalence rate in the United States is one case per 10,000 live births, but incidence worldwide varies [5]. Sillence *et al.* reported a prevalence of 3-4/100,000 and an incidence of 3.5/100,000 live births for OI Type I in Victoria, Australia [4, 6].

The major clinical characteristics of OI include bone fragility, osteopenia, varying degrees of short stature and progressive skeletal deformities. Additional clinical manifestations are blue sclera, *Dentinogenesis imperfecta* (DI), joint laxity and mature-onset deafness. Mobility, self-care and other functional activities are curtailed as a result [1, 3]. The Sillence (1979) Classification of OI, which is still in use today, is based on clinical symptoms, type of inheritance and radiographic findings [3, 6]; Type I is a mild form of the disorder; Type III is characterized by severe deformity and short stature; Type IV varies from mild to severe and represents an intermediate stage between Types I and III [2-4, 7]; OI Type II patients usually die in the prenatal age [1, 7].

Information regarding the clinical features and epidemiology of OI in Vietnam is lacking. In addition, there is no systematic reports of OI patients in Vietnam. With a population of almost 90 million, Vietnam is predicted to have a large number of OI patients. We started to systematically investigate OI in Vietnam during 2013. The main aim of this study was to describe

the clinical features of OI patients in Vietnam, systematize the phenotype manifestations of affected individuals, collect genealogical information from Vietnamese OI families, describe the epidemiology and create an OI database with the aim of improving assessment of and treatment quality for OI patients in Vietnam.

Methods

Lists of OI patients were collected from hospitals and OI centres from 34 of Vietnam's 63 provinces (populations of 60,927,100 and 90,728,900 respectively) [8]. Investigators contacted families directly to agree an interview and a clinical examination. The study was conducted in accordance with the Helsinki Declaration and received approval from the ethical review board of Hue University Hospital (approval No. 75/CN-BVYD). Informed written consent from patients or their legal representatives was obtained before they were included in the study. Consent was also obtained for the publishing of photographs and or pedigrees in medical journals. A total of 146 OI patients from 120 OI families agreed to participate in the study. To characterize OI patients' clinical features, all participants underwent clinical and physical examinations and their medical records were reviewed. Cases were described according to the Sillence classification (Types I–IV).

All genealogical and clinical information was registered. Interviews with OI families were conducted in order to obtain genealogical information for a minimum of three consecutive generations. Genealogical information included OI history and family consanguinity data. In addition to information regarding the healthy and OI affected members of each family, the history of miscarriages and full term pregnancies was obtained. Based on this information a pedigree was constructed for each family using satistical program R. Patient and their family clinical information, medical history, health problems and treatment associated with OI were recorded from patients medical records or as stated by patient. Each patient was examined for skeletal and extraskeletal sings of OI and radiology records, if available, reviewed. Diagnosis and type confirmed based on observed clinical features and radiologic findings. Phenotype description was based on patient information, *i.e.* birth data (height, weight, intrauterine and birth fractures), fracture history (time and location of the first fracture, total number of fractures and location of

fractures), skeletal deformations, non-skeletal OI features (hearing loss, presence of DI, sclera colour) and degree of physical mobility. Deformities of the skeleton were assessed by observation and palpation. Scoliosis, kyphosis and mobility of the spine were assessed in different positions, including with the patient bending forward. Hearing was not tested, but information regarding hearing problems was collected from patients and their relatives. Weight (kg) and height (cm) were measured during examinations. Birth-weight (kg) and height (cm) information were obtained from parents or clinical files.

Data analysis was performed with the statistical program R [9].

Results

Of the 120 Vietnamese OI families investigated, 30.8%, 44.2% and 25.0% were residents of North, Central and South Vietnam respectively. 61 of the OI patients were female and 85 male (Total=146). 70.55% of the OI patients were in the age group 0–15 years. The mean birthweight for males and females was 2.7kg±0.53 and 2.6kg±0.43 respectively. Low birthweight (<2.5kg) was identified in 39 of 146 cases. 46 patients had OI type I, 46 patients Type III and 54 patients Type IV, according to Sillence's classification (Table1).

All patients also had some non-skeletal OI features. 117 patients had blue sclera, 89 patients DI and 26 patients suffered from hearing loss. Musculoskeletal deformations were present in all patients. Lower limb deformations were found in 121 patients and upper limb deformities in 80 patients. Spine deformations were present in 91 patients and chest deformations in 74 patients. Most of the patients needed some mobility assistance. Only 58 patients were capable of ambulating independently. The frequency of signs and symptoms according to different OI types are presented in Table 2.

142 of the 146 patients studied had suffered fractures, totally 1932 fractures. The four individuals who had not suffered fractures were diagnosed with OI based on positive family history, typical long bone deformations and extraskeletal manifestations. 125 of the studied individuals suffered their first fracture during the first six years of life. 34 OI patients had a history of intrauterine fractures. Perinatal fractures had occurred in 9 patients. The first fractured bone for 92 of 142 patients was the femur. The femur was also the most common fractured bone and was fractured in 132 of the patients (Table 3). Among those with OI Type III and IV, a total of 18 patients had suffered more than 30 fractures during their lifespan. Patients with OI Types I, III and IV had mean fracture values of 6.04; 20.76 and 12.94 respectively (Figure 1).

Out of 146 patients only 37 were treated with bisphosphonates. Previously different bisphosphonates were used in treatment of OI, but during last years only i/v zoledronic acid treatment protocol is used. Surgical treatment was performed 163 times, including 100 osteosynthesis and 63 osteotomy surgeries, in 58 patients (Table 3b). Out of 163 surgeries, femur were operated 115 and and tibia 41 times. Most of the surgical devices used in Vietnam are self-designed due to expensiveness of the commercial implants (Figure 2).

The 146 OI patients were born to 133 mothers. A history of miscarriages was reported by 36 of these mothers. Twenty one of the patients were born preterm (less than 37 weeks gestation) and 129 of the patients were born to mothers under 35 years old (Table 4). Genealogical information revealed that 99 of the families had no known history of OI. Seventeen and four families respectively had two or more generation OI histories and pedigree of typical OI family is presented in Figure 3. Four families had twins with at least one twin OI affected.

Discussion

Incidence of OI worldwide varies, but is frequently estimated to be approximately 1 case per 100,000 people [5,10]. We do not believe that incidence of OI in Vietnam is disproportionately low, therefore our results suggest that OI is significantly underdiagnosed in Vietnam, especially in cases where there is no history of OI in the family and or symptoms are mild. Low OI incidence may also be explained by several cultural and economic barriers of diagnosis and health care system in Vietnam.

In our study we identified relatively equal numbers of patients with OI Types I (31.51%), III (31.51%) and IV (36.98%). Other studies have shown that the prevalence of Type I patients is usually higher compared to Types III and IV [5]. Lin *et al.* reported OI prevalence in Taiwan as 39.6% Type I, 20.8% Type III and 39.6% Type IV [11]. We were unable to find reports of OI Type II patients, as this form is typically lethal in utero. The predominance of severe forms of OI in Vietnam suggests underdiagnosis of mild types of OI.

There has been discussions about OI classifications. The original Sillence clinical OI classification was expanded with new OI types. According to a genetic cause of an OI, a new classification of OI was proposed in the last years, where every OI type corresponds to a mutated gene. About 90% of OI cases arise due to mutations in the *COL1A1* and *COL1A2* genes. The rest of the cases (estimated 10%) are represented by mostly recessive mutations in the genes (*CRTAP, LEPRE1, PPIB, SERPINH1, FKBP10, PLOD2, SP7, SERPINF1*), including the type: I-VI [3,4,6]. New classification of OI is type I-VIII, where type I- IV is based on classical Sillence classification. Type V is dominantly inherited and represents moderate-to-severe OI cases characterised with hypertrophic calluses and interosseous membrane calcification between the radius and ulna. Type VI is clinically similar to type IV however is identified by a characteristic mineralization defect revealed in bone biopsy. Type VI is extremely rare and mode

of inheritance is probably recessive, but it has not been identified yet. Type VII is based on recessive *CRTAP* mutations. Clinically white sclerae, small heads and short stature and *Coxa vara* is common. Type VIII is caused by mutations in the *LEPRE1* gene and characterized by severe growth deficiency and extreme under-mineralization of the skeleton [12]. However, so far we can not use the new genetic classification in our study, as we do not have data on genetic causes of all OI cases from the sample. In the future availability of the sequencing technologies might decrease the need of phenotyping in diagnosis, but to assess severity and classification, the phenotyping still remains important in combination with genetic evaluation and in clinical practice the phenotype classification is still essential [13].

There were a total of 61 females (41.78%) and 85 males (58.22%) with OI, resulting in a female to male with a ratio 1:1.39. In Taiwan there was a predominance of female patients with a female to male ratio of 2.2 to 1 [11]. Most studies have not shown the genders of affected individuals and OI worldwide usually occurs without gender differences [5, 6]. The difference in the gender ratio at birth of OI patients in Vietnam could be explained by insufficient diagnosis of OI cases, but could also be related to the slightly higher number of male births in Vietnam (male to female ratio of 112:100) [14].

In our study low birthweight (<2.5kg) [15] was identified in 39 OI patients. The mean birthweight was 2.7kg for boys and 2.6kg for girls with OI, which is significantly lower than for non-OI Vietnamese boys and girls (3.1kg and 3.0kg respectively) [16]. Decreased birth weight and short stature of OI sufferers are caused by abnormal intrauterine development of the foetus. The differences between the OI groups and controls appeared to be larger than might be expected from the overall smaller body frame in OI [17]. In a study by Sillence, similar data was presented and the majority of patients also had low birthweight [6].

117 patients (80.14%) were found to have blue sclera, including 41 patients with OI Type I, 34 patients with OI Type III and 42 patients with OI Type IV. The presence of blue sclera was slightly higher than in previous studies, especially for patients with Type IV. Other OI research studies have noted: a 75% incidence of blue sclera, including 89%, 80% and 58% for OI Types I, III and IV respectively [11]; a 78.1% (425/544) incidence of blue sclera [18].

In our research DI was identified in 89 patients (60.96%), including 21 OI Type I patients, 34 OI Type III patients and 34 OI Type IV patients. Reported prevalence of DI in OI sufferers has been highly variable. In a study by Majorana, DI prevalence was shown to be 62.5% (10/16), with 30% of Type III patients affected [19]. Other authors have reported the prevalence of DI to be as low as 19% [20] and as high as 80% for OI Type III patients [11]. In our study, 26 patients (17.81%) were diagnosed with hearing loss of varying levels, however the incidence worldwide is variable, *e.g.* 6.7% [21] or 13.4% (73/544) of cases [18].

Deformities appeared in all patients with differing severity and localization, and were most frequently observed in long bones. Spinal deformities and scoliosis were also common (Figure 4). Deformities in the lower limbs were found in 121 patients (82.88%), in upper limbs in 80 patients (54.80%), in the spine in 91 patients (62.33%) and the chest in 74 patients (50.68%). Bowing and angulation deformities exist to varying degrees in OI sufferers, with frequent over-modelling of the shafts of long bones [3]. In addition to long bone deformities occurring due to imperfect bone development or fracture healing problems, weight bearing alone can cause leg bowing [22]. In the Taiwan study, bone deformities were observed in 54% of patients [11]. Scoliosis, kyphosis, flattened vertebra and compression fractures are common in OI sufferers. Severe vertebral deformity may cause respiratory problems in some patients [22]. Previous studies reported scoliosis in 74.5% (76/102) [23] and 50% (157/316) of cases [24].

The mean number of lifetime fractures for each OI patient in our study was 13.23. The mean number of lifetime fractures in Type I patients was 6.043, in Type III patients 20.76 and in Type IV patients 12.94. There were statistically signficant differences between the number of total fractures between the Type I and III groups (p=3.028×10^{-12}), Type I and IV groups (p=2.81×10^{-6}) and Type III and IV groups (p= 0.0001254) (Figure 1). Among those with Type III and Type IV OI, 18 patients (12.33%) had suffered more than 30 fractures each. We found 125 of the 146 patients (85.62%) suffered their first fracture in the first six years of life. Sillence also found that fractures usually first appear during the preschool period [6]. In both genders and for all OI Types fracture rates diminish during the teenage years, however the reason is not known [25].

Bisphosphonate therapy has been used in worldwide practice for OI treatment during three decades. In the beginning mostly pamidronate was used, there are also some studies about alendronate, but during last decade the most widely used medication is zoledronate [2, 26,27,28,29]. Bisphosphonate therapy has demonstrated good results by increase of the BMD and reduction of the fracture rate in the long and vertebral bones of the patients. In our research only 37 patients (10 type I, 12 type III, 15 type IV) were treated with bisphosphonates. Most of the OI Vietnamese patients could not follow bisphosphonate therapy due to inaccessability of adequate medical care, sustainment or counseling from the medical professionals.

Totally surgery was performed in 163 times, including 100 osteosynthesis and 63 osteotomy, with shows that in 2/3 cases surgery is performed due to fractures. The Fassier – Duval telescopic rod is the best way to promote osteosynthesis and is broadly used in OI patients. Advantages of this new method is that implementation of telescope requires one proximal epiphyseal entry point to reach the distal eiphysis, without requiring arthrotomy and with minimal damage of the growth plate. Following the patients, this method showed a reduction in secondary

fractures and a long lasting osteosynthesis or osteotomy during growing bone [30,31]. Over an 18 month period observation showed an average reoperation rate of 13% in OI patients treated by femoral and tibia Fassier-Duval telescopic IM [32]. Additional research showed Fassier-Duval telescopic rod was most effectively applied in the case of multiple fractured long bone as well as severe deformities [33]. However in Vietnam conditions for the application of Fassier-Duval telescopic nails are absent. Intra-medular rod and sliding rod were currently the choice for many surgeons (55/58 patients), but implants are locally produced, also carry the sliding principle (figure 2) and have shown good clinical outcome. But the surgical activity for deformation correction was low, comparing to deformity rate in the lower limbs (82.88%), upper limbs (54.80%) or number of patients who needs assistance (39.73%). Correction of deformities will help improve quality of life in OI patients.

Most of the patients in our study required assistance with ambulation: 58 (39.73%) moved independently; 22 (15.07%) were wheelchair-bound; 49 (33.56%) were only able to sit; 17 (11.64%) were only able to lie down in bed. Lin *et al.* performed a retrospective study and documented the ability to walk without aids or devices in 100% of OI Type I, 63% of Type IV and 0% of Type III patients. Reliance on a wheelchair was reported in 100% of OI Type III and 21% of OI Type IV sufferers in the same study [11]. Wekre reported ambulation using a wheelchair in 20% (19/97) of patients of all OI types and 100% of patients with OI Type III [34].

Conclusion

In this study we systematically detected OI patients in Vietnam, assessed their health, treatment and genealogical information. The number of affected individuals and amount of severe phenotypes found indicates that the disease is underdiagnosed in Vietnam, especially in cases where there is no family history and or mild cases. Our database is the foundation for improving OI investigation and treatment in Vietnam, and future phenotype-genotype studies. The results of this study will also be used to educate physicians and other medical professionals throughout the country on the signs and symptoms of OI in order to increase diagnosis and treatment levels and improve the quality of life of OI patients and their families.

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Conflict of interests

The authors declare no conflict of interest.

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Ethics Approval and Consent to Participate

The study was conducted in accordance with the Helsinki Declaration and received approval from the ethical review board of Hue University Hospital (approval No. 75/CN-BVYD) and the Ethical Review Committee on Human Research of the University of Tartu (permit № 221/M-34).

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent from the patients or their legal representatives was obtained prior to inclusion to the study.

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Figure 1. Association between OI Type and number of fractures

Mean number of total fractures by OI Type:
OI type I = 6.043; OI type III = 20.76; OI type IV = 12.94
(*p*-value OI type I and OI type III = 3.028e-12 , *p*-value OI type I and OI type IV = 2.81e-06
p-value OI type III and OI type IV= 0.0001254)

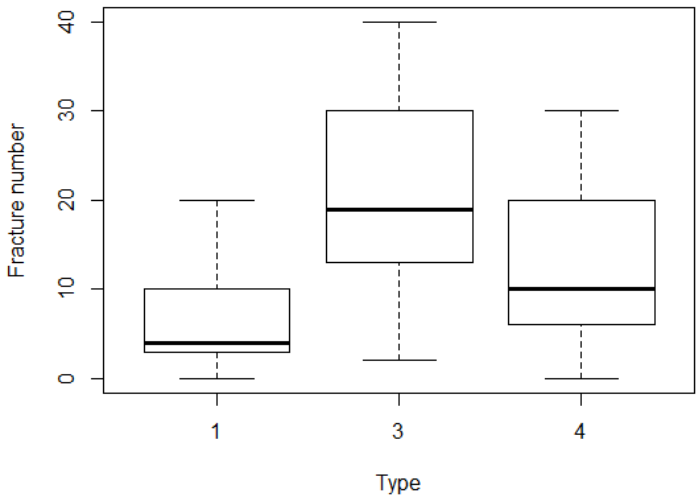


Figure 2. Osteotomy in OI patient with sliding rod method

(a) Type III OI patient before operation; (b) X-ray of the patient before operation; (c) The patient 12 months after osteotomy; (d) X-ray 12 months after osteotomy.

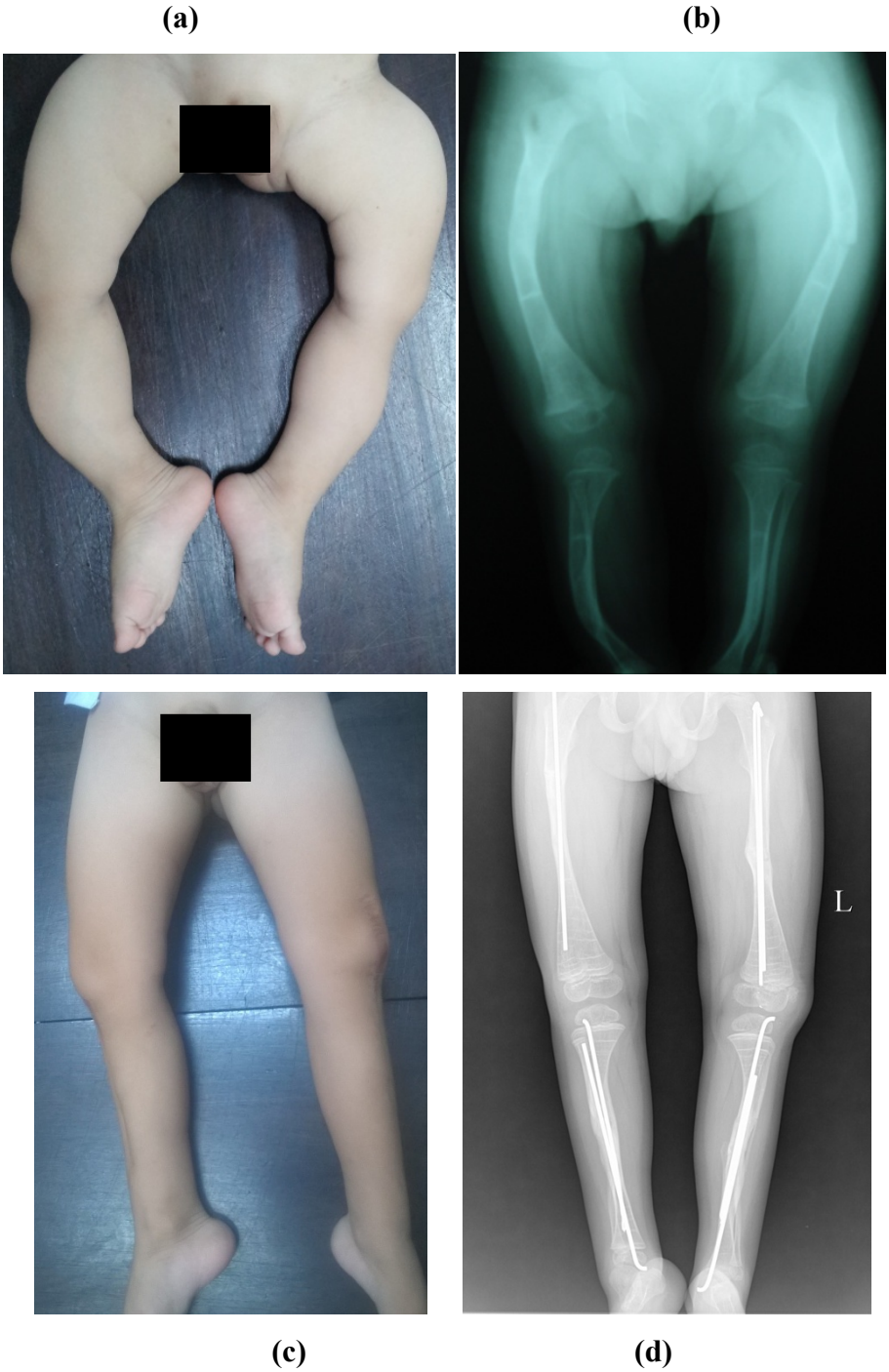


Figure 3. Pedigree tree of the family with an OI history in two generations

OI affected family members (circle – female; square – male) are highlighted in solid red. All family members marked with red colour (906, 911, 916, 917, 918) were subjected to genetic analysis and included into the biobank.

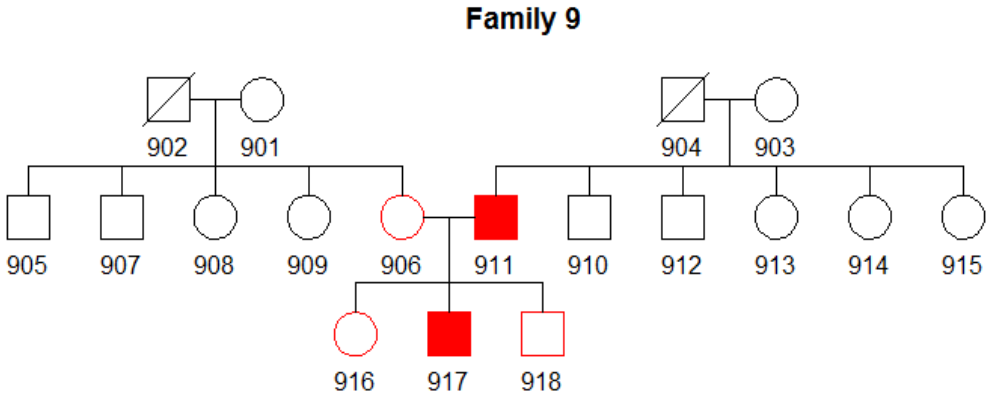
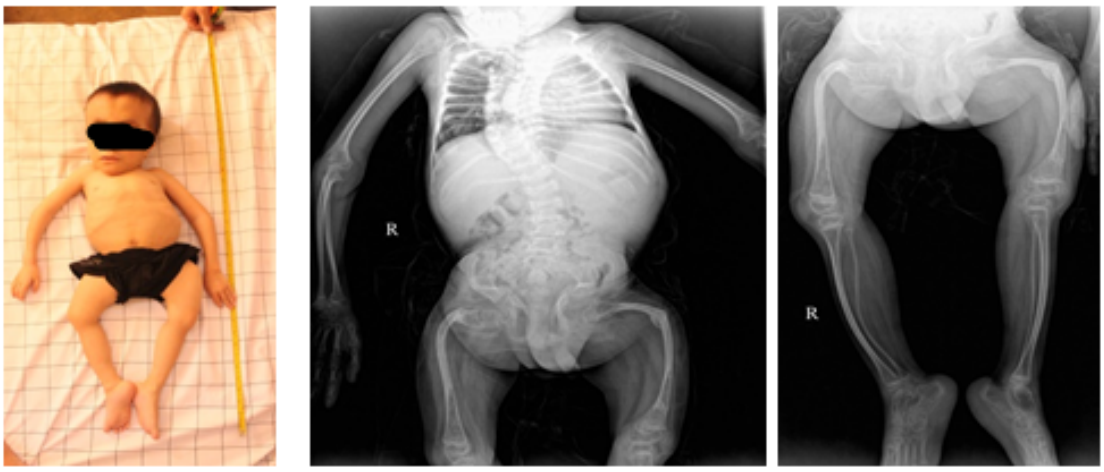


Figure 4. Typical patient with OI type III (severe deforming OI)

(a) Type III OI patient aged 10 with short stature; (b) X-ray showing scoliosis;

(c) X-ray showing lower limb deformities



(a) (b) (c)

Table 1. Characteristics of 146 Vietnamese OI patients

Characteristic	Number of patients	%
Gender		
Male	85	58.22
Female	61	41.78
Age		
0-5	32	21.92%
6-10	40	27.40%
11-15	31	21.23%
16-20	16	10.96%
21-25	9	6.16%
26-30	1	0.68%
31-35	5	3.42%
36-40	5	3.42%
41-45	3	2.05%
46-50	3	2.05%
>50	1	0.68%
Low birthweight		
Male <2.5kg	21	14.38
Female <2.5kg	18	12.33
No information	7	4.79
OI Type by Sillence		
I	46	31.51
II	0	0.00
III	46	31.51
IV	54	36.98

Table 2. Frequency of signs and clinical symptoms of 146 Vietnamese OI patients

	Total number of patients	%	Number of patients according to OI type		
			OI Type I	OI Type III	OI Type IV
Blue sclera					
Yes	117	80.14%	41	34	42
No	29	19.86%	5	12	12
Hearing					
Hearing loss	26	17.81%	5	11	10
Normal	120	82.19%	41	35	44
Teeth					
DI	89	60.96%	21	34	34
Normal	57	39.04%	25	12	20
Mobility					
Lying	17	11.64%	0	14	3
Sitting	49	33.56%	0	26	23
Wheelchair bound	22	15.07%	3	6	13
Normal	58	39.73%	43	0	15
Deformity					
Upper limb	80	54.80%	11	43	26
Lower limb	121	82.88%	27	45	49
Spine (scoliosis, kyphosis)	91	62.33%	13	44	34
Chest	74	50.68%	7	42	25

Table 3. a)Fracture characteristics of 146 Vietnamese OI patients

	Number of patients	%
Time of the first fracture		
Intrauterine	34	23.29%
Perinatal	9	6.16%
Before 6 years old	82	56.17%
≥7 years old	14	9.59%
*No information and no fracture**	7	4.79%
First fractured bone		
Upper arm	15	10.29%
Forearm	9	6.16%
Femur	92	63.01%
Lower leg	14	9.59%
Mixed (≥2 different bones)	9	6.16%
*No information and no fracture**	7	4.79%

*There were 4 patients without any fractures, and 3 patients could not report the time of the first fracture and first fractured bone

b) The types of fractures and the surgical treatment

	Femur	Lower leg	Humerus	Forearm	Other	Total
Number of all fractures	764	575	306	196	91	1932
Number of patients with fractures	132	102	87	72	41	142
Number of surgeries	115	41	1	6	0	163
- *Osteosynthesis*	75	18	1	6	0	100
- *Osteotomy*	40	23	0	0	0	63

Table 4. Characteristics of 133 mothers of 146 Vietnamese OI patients

	Number of mothers	%
Miscarriage		
Yes	36	27.07%
No	88	66.17%
No information	9	6.76%
Full term pregnancy		
Yes	111	76.03%
No (≤37weeks)	21	14.38%
No information	14	9.59%
Mother's age at OI patient's birth		
≤35 years old	129	88.36%
>35 years old	17	11.64%