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Clinical and molecular analysis of 40 Lithuanian families with *osteogenesis imperfecta*

Eglė Benušienė, Vaidutis Kučinskas

Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Osteogenesis imperfecta (OI) is a generalised disorder of connective tissue, characterised by an increased fragility of bones and manifested also in other tissues containing collagen type I, by blue sclera, hearing loss, dentinogenesis imperfecta, hyperextensible joints, hernias and easy bruising. OI is dominantly inherited. More than >90% of OI cases are caused by mutations in one of the two genes, COL1A1 or COL1A2, coding for the type I procollagen. The Lithuanian OI database comprises 137 case records covering the period 1980–2001. Clinical and genealogical analysis of OI cases/families from Lithuania, available for examination, revealed 17 familial cases of OI (16 cases of OI type I and 1 case of OI type IV) and 23 sporadic cases of OI type II (2 cases), type III (13 cases) and type I (8 cases). As a result of molecular genetic investigation, 13 mutations were identified in the COL1A1 gene: missense (4), nonsense (2), frameshift (4), and splice site mutations (3). Nine mutations identified in the present study (E500X, G481A, c.2046insCTCTCTAG, c.1668delT, c.1667insC, c.4337insC, IVS19+1G>A, IVS20-2A>G, IVS22-1G>T) were registered in the Human Type I and Type III Collagen Mutations Database as novel mutations, *i.e*. not yet published by other researches. Nine COL1A1 gene mutations (E500X, R183X, c.2046insCTCTCTAG, c.1668delT, c. 1667insC, c.4337insC, IVS19+1G>A, IVS20-2A>G, IVS22-1G>T) lead to a mild OI phenotype. OI was differently manifested in related and unrelated patients with the identical COL1A1 genotype. These findings suggest that the phenotypic expression of the disease may be influenced by other factors, genetic or epigenetic, which may play a role in the process of bone formation.

Key words: osteogenesis imperfecta, COL1A1, mutations, molecular diagnosis

INTRODUCTION

Osteogenesis imperfecta (OI) is a heritable connective tissue disorder caused in >90% cases by dominant mutations in two genes, COL1A1 (17q21.31–22) and COL1A2 (7q22.1), which encode the proα1(I) and proα2(I) chains of type I procollagen, respectively (1).

Mutation-induced structural changes in procollagen molecules perturb normal collagen assembly in the cell, secretion from the cell, and fibril assembly in the extracellular spaces, which – collectively – result in the OI phenotypes (2). The spectrum of clinical OI severity ranges from lethality in the perinatal period to a mild increase in the propensity for adult onset fractures. The varying clinical characteristics of OI reflect different classes of mutations in different regions of type I collagen genes. More than 300 different mutations in COL1A1 and COL1A2 genes were characterised in the Database of Human Type I and Type III Collagen Mutations (3) by year 2004. The mutations vary in type and location, and result in disrupted collagen type I architecture by either undersynthesis of non-mutated collagen or by producing abnormal collagen in the amount corresponding to that of normal alleles. The most common mutations in COL1 loci are single base substitutions in the part of the gene coding for the triple helical domain, which change a codon for glycine (Gly) to a codon for another amino acid with a bulkier side chain. The severity of the OI phenotype is strongly associated with the polypeptide chain type, mutation site, flanking sequences, and amino acid substituting Gly (4). Mutations are less common in conserved RNA splice consensus sequences, which lead to partial or complete exon exclusion or intron inclusion with va-

Correspondence to: Prof. Dr. Habil. Vaidutis Kučinskas, Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University, Santariškių 2, LT-08661 Vilnius, Lithuania. Fax: +370-5 2365199. E-mail: vaidutis.kucinskas@santa.lt

riations in the effect on both the RNA and protein level and subsequently in phenotype. Mutations are still less prevalent in-frame deletions or duplications that involve fewer than 18 amino acids (2). Mutations in the C-propeptide coding region are rare if compared to other types of COL1 loci mutations.

Genes coding for collagen type I are regions of increased mutation rate, therefore the majority of their mutations identified are private, *i. e*. found in a single individual or a single family (5).

The type and severity of OI depends on the nature and localisation of the mutation in either of the two genes, but the correlation between the COL1 locus genotype and clinical OI phenotype has not yet been investigated adequately. Molecular genetic investigation is in progress in a number of countries with the aim to identify OI-causing mutations, to reveal their nature and the genotype/phenotype correlation and to develop diagnostic molecular genetic tests, which are essential in the prophylaxis of OI.

The aim of the present study was to identify COL1A1 gene mutations related to OI in patients/families residing in Lithuania and to evaluate the phenotypic manifestation of the mutations.

PATIENTS, MATERIALS AND METHODS

The Lithuanian OI database comprises 137 case records covering the period 1975–2001. Of them, 17 familial and 23 sporadic OI cases were available for detailed clinical examination and molecular genetic testing. Written consent of the patients and their family members to the participation in the study was obtained.

Blood samples were collected and genomic DNA was extracted from the OI patients and their families (in total, 180 DNA samples were collected in 1998–2001, of them 79 samples from OI patients) for subsequent molecular genetic testing:

a) linkage testing; DNA from 102 individuals (41 OI patients and 61 family members);

b) DNA heteroduplex analysis; DNA from 35 unrelated OI patients (probands) and 120 family members;

c) sequencing of COL1A1 gene exons; DNA from 13 individuals.

Clinical and genealogical analysis

Osteogenesis imperfecta diagnosis and clinical classification were based on the Sillence OI classification (6) and International Classification of Constitutional Disorders of Bones (7). The OI cases were classified as familial or sporadic on the basis of genealogical data.

Genealogies of OI families were created using computer Progeny2000 Navigator, v. 3 software (licence No. 120000032).

Clinical phenotype was analysed and evaluated for 79 OI patients (40 probands and 39 affected family members).

Molecular genetic testing

Total genomic DNA was isolated from peripheral blood by salting out or phenol-chloroform extraction (8).

Linkage analysis. Three dimorphic restriction site marker systems were used for each gene analysed to distinguish OI-linked alleles. Relevant DNA fragments within or close to the COL1A1 and COL1A2 genes were PCR-amplified and then digested with the restriction enzymes *Mnl*I, *Msp*I, *Rsa*I and *EcoR*I (9, 10) and separated electrophoretically on 1.5% agarose or 8% polyacrylamide gel. Haplotypes were constructed on the basis of the segregation of the presence/absence of a restriction site.

DNA heteroduplex analysis. COL1A1 gene exons and flanking sequences were screened for the presence of changes in the nucleotide sequence, using PCR amplification followed by conformation sensitive gel electrophoresis (1, 11). DNA heteroduplex formation was identified by the presence of a characteristic electrophoretic pattern visualised by UV-image analyser (Gel Doc 1000 Gel Documentation System, BIO-RAD, USA).

Direct DNA sequencing. PCR-amplified COL1A1 gene fragments were sequenced using ABI PRISM™ 310 Sequencer and Big Dye Terminator Sequencing protocol (Perkin Elmer Applied Biosystems, USA). Mutations were identified by comparing the obtained DNA sequence with the reference cDNA sequence of the COL1A1 gene (GeneBank, cDNA accession number Z74615). Mutations were designated on DNA and protein levels according to the standard guidelines (12) and nucleotides were numbered from the first base of the start codon.

RESULTS

Clinical and genealogical analysis. Clinical and genealogical analysis of OI cases/families from Lithuania, available for examination, revealed 17 familial cases of OI (16 cases of OI type I and 1 case of OI type IV) and 23 sporadic cases of OI type II (2 cases), type III (13 cases) and type I (8 cases).

Linkage analysis. RFLP-based linkage analysis in 12 OI families (a total of 102 individuals) allowed discrimination between the OI-linked COL1A1 and COL1A2 loci in five families. In three families OI type I phenotypes segregated with COL1A1 locus mar-

kers and in two families OI type I and type IV phenotypes segregated with COL1A2 locus markers. In the remaining seven families, the available data appeared to be insufficient to identify a definite OI-linked COL1 locus (13).

DNA heteroduplex analysis. As COL1A1 gene mutations had been shown to cause the majority of mild OI (type I) cases, this gene was tested for the presence of OI-related nucleotide sequence changes in 36 probands (of them, 23 cases of OI type I, 13 cases of OI type III):

a) with OI linked to the COL1A1 locus (3),

b) from the genealogies with the uncertain COL1A locus (10),

c) with sporadic OI (23).

DNA heteroduplex analysis revealed the presence of changes in the COL1A1 gene nucleotide sequence in 13 probands.

DNA sequencing. Subsequent sequencing of the relevant COL1A1 gene exons resulted in identification of 13 mutations: missense (4), nonsense (2), frameshift (4), and splice site mutations (3) (molecular genetic and clinical data are summarised in Table 1; positions of the mutations are shown in Figure).

Three of the mutations were single-base deletions or insertions (Table 1, families OI-8, OI-9, OI-11), one mutation was an 8-bp insertion (family OI-14), and two of the mutations were single-base substitutions that converted the codon for arginine (family OI-30) and glutamic acid (family OI-2) to a premature-termination codon.

Three mutations altered the consensus sites of RNA splicing in the first two or last two bases of an intron (families OI-1, OI-15, OI-37). Two point mutations led to substitution of Gly for another amino acid (arginine or alanine). Of them, mutation c.769G>A (G79R) was found in three unrelated probands (families OI-3, OI-23, OI-36). The data on these mutations and their clinical manifestation are summarised in Table 1.

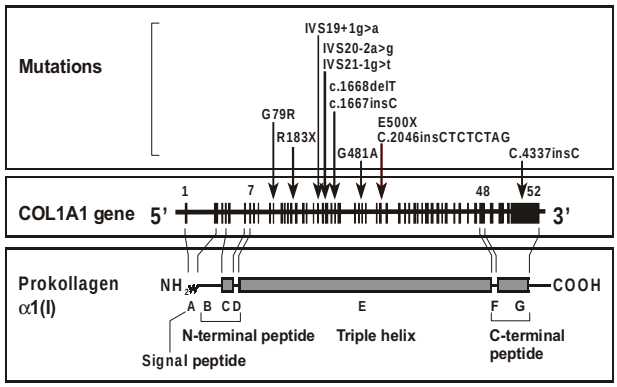

Figure. COL1A1 gene mutations identified in Lithuania

In the present study, COL1A1 gene mutations were identified in DNA only (neither mRNA nor protein were tested). Therefore, their designation on the protein level was theoretical and based on nucleotide sequence. Assumptions regarding their possible impact on the phenotype (structural or null mutation) were made referring to the clinical phenotype of OI patients harbouring the mutation and reports of other researchers.

Of 13 COL1A1 gene mutations identified in Lithuania, nine have been published as novel mutations (14) and registered in the Database of Hu-

Table 1. **Clinical manifestation of identified COL1A1 gene mutations in OI families**

Family	Mutations		OI Sillence type	Scleral color	DI	Hearing loss	Fractures at birth	Number of fractures	Deformity	References
	DNA level	Protein level*								
OI-36	c.769G>A	G79R	III	dark blue	–	+	–	>50	+	(16, 17, 18)
OI-3	c.769G>A	G79R	IA	mid blue	–	–	–	< 10	–	(16, 17, 18)
OI-23	c.769G>A	G79R	IA	dark blue	–	–	–	10–20	+	(16, 17, 18)
OI-26	c.1976G>C	G481A	III	dark blue	+	–	+	5	+	np
OI-30	c.1081C>T	R183X	IB	dark blue	+	+	–	<5	–	(1, 18)
OI-2	c.2032G>T	E500X	IB	mid blue	+	+	–	<10	–	np
OI-14	c.2046ins CTCTCTAG	G505fsX590	IB	dark blue	–	+	+	> 80	–	np
OI-11	c.1667insC	P378fsX455	IB	dark blue	+	+	–	< 10	–	np
OI-9	c.4337insC	D1268fs	IB	dark blue	+	+	–	>80	–	np
OI-8	c.1668delT	P378fsX401	IB	dark blue	+	+	–	> 50	–	np
OI-1	IVS20–2A>G	sp	IA	dark blue	–	+	–	10	–	np
OI-15	IVS19+1G>A	sp	I	dark blue	–	–	–	< 10	–	np
OI-37	IVS22-1G>T	sp	IB	dark blue	+	–	–	10–20	–	np

Notes: –, feature absent;*, theoretically deduced mutation; np, mutation has not been published by other researchers; +, feature present; fs, frame shift mutation; DI, dentinogenesis imperfecta; sp, splicing mutation

man Type I and Type III Collagen Mutations (3): E500X, G481A, c.2046insCTCTCTAG, c.1668delT, c. 1667insC, c.4337insC, IVS19+1G>A, IVS20-2A>G, IVS22-1G>T (Figure).

DISCUSSION

The great majority (about 85%) of COL1A1 and COL1A2 mutations causing OI (types II, III, and IV) are substitutions of a Gly (G) residue by an amino acid with a bulky, polar, or charged side chain (15). Two single nucleotide substitutions (G79R, G481A) of this kind in the COL1A1 gene were found in the present study in probands from the families OI-3, OI-23, OI-36 and OI-26 (Table 1). We reported a novel mutation: a single nucleotide substitution G>A within the Gly codon, resulting in the Ala codon (see Table 1, OI-26). This mutation lead to a severe OI phenotype (OI type III). G79R mutation was identified in three unrelated patients, but its clinical manifestation appeared to be different (Table 1): two patients (OI-3, OI-23) had a mild OI (type I), while the third one (OI-36) had a severe form of the disease (OI type III). Two cases of this mutation were reported in other populations (16–18). Mild OI phenotype was reported for two probands (17, 18), however, no information (familial background or phenotypic features) was provided on the third patient. Phenotypic variability has also been reported for a number of other COL1A1 and COL1A2 gene mutations in both related and unrelated patients harbouring the same collagen I mutation (15).

The majority of mutations leading to OI are "private", underscoring a high mutability of the COL1A genes, however, there are some sites suggestive of mutational hot spots rather than coincidental occurrence. One such point is codon 238 in the COL1A2 gene, where Gly to Ser substitution has been reported five times and Gly to Cys substitution once (19). Several above-stated cases of the mutation G79R (c.769G>A) in unrelated OI patients suggest the presence of a mutational hot spot in the codon 79 of the COL1A1 gene. These two putative mutational hot spots are in a CpG dinucleotide.

While structural mutations in the COL1A1 and COL1A2 genes most often lead to severe OI types, null alleles resulting from a premature translation termination codon or aberrant RNA splicing merely decrease production of normal type I collagen, thus leading to OI type I (20, 21). Mutations in the COL1A2 gene appear to be a rare cause of OI type I (21).

Six COL1A1 gene mutations (E500X, R183X, c.2046insCTCTCTAG, c.1668delT, c.1667insC, c.4337insC) identified in mild OI type I patients from Lithuania were considered as null mutations due to a premature stop codon arising either directly from a point mutation or indirectly from a frameshift mutation.

Three mutations (IVS19+1G>A, IVS20-2A>G, IVS22-1G>T) causing an abnormality in mRNA splicing in the corresponding families (Table 1, OI-15, OI-1, OI-37) also lead to a mild OI phenotype, supposing that cryptic intronic splicing sites were used, although neither mRNA nor protein were tested to prove that supposition.

OI was differently manifested in related patients with an identical genotype and ranged from a mild to severe phenotype in two families (OI-8 and OI-14, Table 2). The severity of OI was increasing in subsequent generations. This finding suggests that the phenotypic expression of the disease may be influenced by other factors (genetic or epigenetic), which may play a role in the process of bone formation.

As noted in previous reports (1), mutations tend to occur in common sequence contexts. Of a total of 11 mutations that converted the arginine codon CGA to the premature-termination codon TGA, ten were found in the sequence context of G/CCC CGA GG/T of the COL1A1 gene (16, 22, 23). The COL1A1 gene contains six sequences of this type. Only one mutation of this type was found in another sequence context of COL1A1 gene (24). In the present study two nonsense mutations were detected, one of them (R183X) being in this type of context (CCC CGA GG).

Single-base insertions or deletions in collagen genes are frequent in the context of CCC CCT. As noted by previous reports (25), such mutations are likely to occur in duplicated sequences. In the case of collagens, the sequence CCC CCT, coding for Pro-Pro or Pro-Hyp, is a common sequence in the COL1A1 gene, and 9 of the 19 reported single-base insertions or deletions in the COL1A1 gene are found in a sequence of this type (1, 5, 26). The single-nucleotide insertion and deletion (c.1668delT, c.1667insC) identified in the current study appeared to be in the nucleotide sequence CCC CTT.

On the other hand, most COL1A1 mutations that lead to OI fall within the triple-helical domain. Mutations affecting the carboxyl-terminal extensions have also been identified in OI, although with a much lower prevalence (20). Some of these mutations result in premature termination codons and the mRNA is unstable or, if stable, the peptide chain is either unstable and rapidly degraded or fails to associate in trimers (2). Only one mutation of this type (c.4337insC) was identified in the present study. The frameshift mutation in the corresponding family (Table 1, OI-9) lead to a mild form of OI. The rest twelve mutations were found in the triple-helical domain of the COL1A1 gene.

Table 2. **Varying clinical manifestation of OI in the families OI-8 and OI-14**

Generation	OI Sillence type	Scleral color	DI	Hearing loss	Fractures at birth	Number of fractures	Deformity
OI-14							
I	IB	dark blue	+	+	–	5	–
II	III	dark blue	+	–	+ (during delivery)	80	+
III	I/III	dark blue	–	–	+ (in uterus)	10 (until 1.5 years of age)	+
OI-8							
I	IB	dark blue	+	+	–	0	–
II	IB	dark blue	+	+	–	1	–
III	IB	dark blue	+	+	–	7	–
IV	I	dark blue	–	–	–	10	–
IV (Pr)	III	dark blue	–	–	–	50	+

+, feature is present. Pr, proband.
–, feature is absent. DI, dentinogenesis imperfecta.

Nine COL1A1 gene mutations identified in the present study appeared to be novel, *i.e*. not yet published by other researches. Such a high rate (82%) of novel mutations in OI patients from Lithuania is in consistence with the data of other researchers showing that in most of OI families the disease is caused by a "private" mutation (18). The high rate of new mutations presumably results from the vulnerability of the collagen gene/protein system to mutations (27).

Four COL1A1 gene mutations identified in four sporadic OI cases (Table 1, families OI-15, OI-23, OI-26, OI-36) are apparently *de novo* mutations, as are the majority of OI causing mutations, although paternal germline or somatic mosaicism (occurring in up to 6% OI cases) cannot be conclusively ruled out (20).

The findings of the present study confirm the clinical OI diagnosis in 13 cases and enable prenatal OI diagnosis based on direct identification of a COL1A1 gene mutation in corresponding families. COL1A1 gene mutations identified in OI patients from Lithuania contribute to the general knowledge on the molecular basis of OI.

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Eglė Benušienė, Vaidutis Kučinskas

KLINIKINĖ IR MOLEKULINĖ GENETINĖ 40-IES LIETUVOS ŠEIMŲ, KURIOSE YRA SERGANČIŲJŲ *OSTEOGENESIS IMPERFECTA,* ANALIZĖ

S a n t r a u k a

Osteogenesis imperfecta (OI) – paveldima jungiamojo audinio liga, daugiau nei 90% atvejų nulemta dominantinių mutacijų viename iš genų (COL1A1 (17q21.31–22) ar COL1A2 (7q22.1)), reguliuojančių kolageno I sintezę. Klinikinė OI išraiška varijuoja nuo perinatalinės letalios (II tipas), skeletą deformuojančios (III, IV, V, VI tipai), iki santykinai lengvos (I tipas).

Lietuvoje 1975–2001 metais užregistruoti 137 OI atvejai. Klinikinė ir genealoginė OI atvejų (šeimų) iš Lietuvos analizė išaiškino 17 šeiminių (OI I tipas (16), OI IV tipas (1)) ir 23 sporadinius (OI II tipas (2), OI III tipas (13), OI I tipas (8)) ligos atvejų.

Šiuolaikiniais molekuliniais genetiniais metodais nustatyta 11 ligą lemiančių COL1A1 geno mutacijų 13-ai negiminingų asmenų. Devynios tyrimo metu nustatytos OI lemiančios mutacijos (E500X, G481A, c.2046ins CTCTCTAG, c.1668delT, c.1667insC, c.4337insC, IVS19+1G>A, IVS20-2A>G, IVS22-1G>T) buvo užregistruotos Žmogaus I ir III tipo kolageno mutacijų duomenų banke (*Database of Human Type I and Type III Collagen Mutations*) kaip naujos (t. y. kitų tyrinėtojų neaprašytos) mutacijos.

Devynios mutacijos (E500X, R183X, c.2046ins CTCTCTAG, c.1668delT, c. 1667insC, c.4337insC, IVS19+1G>A, IVS20-2A>G, IVS22-1G>T) nulėmė lengvą OI klinikinę raišką (OI I tipas). Ryšys tarp mutacijos pobūdžio ir lokalizacijos bei ligos sunkumo stebėtas ekspresuotų taškinių mutacijų atveju (G79R, G481A). OI klinikinis pasireiškimas įvairavo (nuo lengvos iki sunkios ligos formos) dviejose šeimose tarp gimininių asmenų su identišku genotipu. Tai leidžia manyti, jog fenotipiniam ligos pasireiškimui svarbūs ir kiti veiksniai – genetiniai ar epigenetiniai, kurie dalyvauja formuojantis kaulams.

Atliktų tyrimų rezultatų pagrindu Lietuvoje 16-ai šeimų, kuriose diagnozuota OI, galima prenatalinė diagnostika molekuliniais genetiniais metodais: trims – netiesiogiai nustatant ligą lemiančias mutacijas (taikant COL1A1 ir COL1A2 genetinių sričių RFIP analizę) ir trylikai – tiesiogiai nustatant COL1A1 geno mutacijas.