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Impact of genomics on the identification and family characterization of genetic diseases collagen

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Abstract

Introduction: Osteogenesis Imperfecta (OI) is a genetic disorder primarily resulting from pathogenic variants in the COL1A1 or COL1A2 genes, responsible for collagen synthesis. This autosomal dominant condition is characterized by high morbidity and mortality due to its disabling symptoms, including pain and skeletal deformities. OI is a rare disease and part of the group of orphan diseases.

Case Report: We describe a 35-year-old female patient with a history of osteoarticular symptoms, including multiple fractures and dislocations. Her maternal lineage includes relatives with similar symptoms, and she is the parent of an 8-year-old diagnosed with OI. Genetic testing revealed the same heterozygous pathogenic variant in the COL1A1 gene in both the patient and her child.

Methodology: The diagnosis was confirmed through targeted genetic studies following the identification of an index case. This approach helped identify asymptomatic carriers and confirmed the condition in other family members.

Results: The targeted genetic study revealed a pathogenic variant in the COL1A1 gene in a heterozygous state, confirming the diagnosis of OI in the patient and her child. This case underscores the phenotypic variability and genetic heterogeneity of OI.

Discussion: Early detection and diagnosis of heritable genetic diseases through index case studies can identify asymptomatic carriers and confirm the condition in relatives. This approach facilitates personalized treatment, preventive measures, and anticipatory care. It also underscores the importance of public health policies and the need for healthcare professionals to be aware of the benefits of screening for rare genetic disorders, advancing precision, predictive, personalized, and preventive medicine.

Introduction

Osteogenesis Imperfecta (OI), also called "brittle bone disease", was made known in 1788 by the swedish surgeon Olaus Jakob Ekman, when describing in his doctoral thesis a family with cases of bone fragility, which he called "congenital osteomalacia", in which it occurred for three generations [1].

OI encompasses a series of syndromes that have alterations in the connective tissue, all secondary to pathogenic variants that are involved in collagen production [2]. The clinical presentation of these patients is variable, they can be asymptomatic until they have a severe and lethal manifestation. This disease is characterized by its great involvement at the bone level, where we can find short stature, fractures that occur recurrently in uncommon anatomical areas, secondary to the presence of thin bone trabeculae and collagen matrix, narrow cortices, wide and irregular physis. Within these bone manifestations, we can find arching of the femur in an anterolateral direction and of the tibia in an anterior direction (sable tibia), and scoliosis. They can also frequently present joint sprains and dislocations, this secondary to joint hypermobility [3]. As extra skeletal symptoms we can find dentinogenesis imperfecta, blue sclera, hearing loss, valve insufficiency and muscle weakness [4-6].

Regarding its etiology, in 90% of cases, pathogenic variants of genes that encode proteins for the construction of collagen have been found, such as the COL1A1 or COL1A2 gene, which has an autosomal dominant inheritance, and in a lower percentage its etiology is related to variants that encode factors or signaling molecules determining the mineralization of bone cells, which are autosomal recessive or linked to the X chromosome. Currently it has been possible to identify new genes that cause this disease [4,7,8].

This disease was classified in 1979 for the first time by the Australian Sillence, taking into account both, its clinical manifestations and its inheritance, into four subgroups (I-IV), I and IV with autosomal dominant inheritance and types II and III with autosomal recessive inheritance. Type I has mild deformities with blue sclerae, type II is associated with perinatal lethality and femur deformity, type III with non-lethal progressive deformities and type IV with a moderate severity of the disease with normal sclerae [3,9,10].

Currently, the classification of the International Society of Skeletal Dysplasias classified this disease into 5 subgroups (IV), according to their inheritance and affected genes. Non-deforming osteogenesis imperfecta with blue sclerae (type I), which has autosomal dominant inheritance (*COL1A1, COL1A2) or* X-linked (*PLS3); Perinatal lethal* (type II), with autosomal dominant or autosomal recessive inheritance (*COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, BMP1); Progressive deformans* (type III), with autosomal dominant or autosomal recessive inheritance (*COL1A1 , COL1A2, CRTAP, LEPRE1, PPIB, FKBP10, SERPINH1, SERINF1, WNT1); Common variable with normal sclerae* (type IV), with autosomal dominant or autosomal recessive inheritance (*COL1A1, COL1A2, CRTAP, FKBP10, SP7, SERPINF1, WNT1, TMEM38B); and,* Interosseous membrane calcification or hypertrophic callus (type V), with autosomal dominant inheritance (*IFITM5).* There are other types of variants that represent less than 5% of OI cases with autosomal recessive inheritance, which are types VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII), these variants encode certain proteins that are part of the collagen production and stabilization process. It has been found that transforming growth factor beta (TGFb) is also affected in this pathology [4,5,11].

Osteogenesis imperfecta is a rare disease, it has a worldwide incidence of 1:10,000 to 20,000 live births. The reported population frequency of OI type I ranges between 2.35 and 4.7 per 100,000 inhabitants worldwide. The incidence of type II OI is 1 in 40,000 and 1.4 in 100,000 live births; the incidence of the other subgroups is unknown since they are less common [5,7].

The pathophysiology of this disease has a lot to do with the extracellular matrix of the connective tissue, because it is composed mostly of type I collagen and this gives elasticity and flexibility to the bone to prevent fractures, due to the presence of pathogenic variants in the COL1A1 or COL1A2 gene, which affects collagen production and triggers its symptoms. The COL1A1 gene encodes two alpha-1 chains and the COL1A2 gene encodes an alpha-2 chain. The conformation of these three chains or triple helix is part of the collagen precursor molecule called procollagen I. The stabilization of these chains occurs thanks to enzymatic processes and proteins by carrying out the hydroxylation of the amino acid proline in collagen molecules. Subsequently procollagen I is transported to the outside of the cell to be transformed into type I collagen and grouping together, pathogenic variants in CRTAP, P3H1 and PPIB genes that encode this prolyl hydroxylase complex, will generate a decrease in the amount of normal collagen with a moderate to severe phenotype of the disease [3].

Patients with mild symptoms have nonsense type variants, generating as a result a lower amount of type I collagen, but without alteration in its structure. For example, patients with a heterozygous trait for this type of variants will secrete 50% of their collagen in a normal way, and patients with severe symptoms have frameshift or splicing type variants that involve the glycine peptide (Gly) in the polypeptide chains at the carboxy end or at the amino end that generates altered chains of procollagen I and will lead to the production of a defective collagen. The triple helix that are the precursor chains of collagen are found at the carboxy end of the polypeptide chain and when the affected peptide is found at this end of the polypeptide chain, its symptoms are more severe, and this is secondary to the defective cross-linking that it is generated in the three chains or also called the triple helix [3,7,12].

Achieving the phenotypic classification of patients with OI among the 5 subgroups of this entity can give us guidance on its genetic defect and heritability. It is important to recognize that patients with OI type I as a characteristic may have fractures with little or no impact from the birth. Patients with OI type II can be diagnosed from their prenatal stage with ultrasound findings. Regarding OI type III it will be detected more easily in the growth stage, highlighting findings such as low height in the anthropometric assessment, being below the percentiles corresponding to height/age and arrest in the growth curve since the height compromise is the most striking. For subgroups IV and V their clinical presentation may appear later. It is important to inquire about the presence of these symptoms in the family group, since there may be an ascending or descending affectation, and this disease should be suspected if other affected individuals are found. Corresponding studies are carried out to achieve sequencing of genes related to collagenopathies allowing timely diagnosis, early treatment, genetic counseling, risk of heritability, search for others affected through the index case, implementing anticipatory and preventive measures, for the sake of precision medicine, prediction, prevention, proactive, personalized, participatory [13].

Materials and methods

35-year-old female patient, with a personal history of 6 fractures at the level of the right elbow, right wrist, right hallux, right knee, right ankle, and left foot, in addition to 5 dislocations in the right foot. At the ocular level, there was no involvement of the scleras, with diagnoses of astigmatism, myopia. Had spondyloarthritis with pharmacological treatment sulfasalazine, methotrexate and folic acid. The only surgical history was uncomplicated umbilical herniorrhaphy in childhood.

On the physical examination, the patient had a height of 152 cm, blue scleras, lumbar scoliosis, hip asymmetry with symmetrical, non-deformed extremities, no dental alterations or other musculoskeletal compromises, no cognitive compromise.

Family history: Product of non-consanguineous parents, mother and maternal uncles with suspected collagen disease due to repeated fractures without confirmatory genetic diagnoses, 8-year-old daughter with a molecular diagnosis of osteogenesis imperfecta type I, as a result of a molecular study panel of associated genes to collagenopathies, Next Generation Sequencing (NGS) + Copy Number Variations (CNVs) methodology, technology that is designed to sequence large quantities of DNA segments massively and in parallel, in a shorter amount of time, also identifying variants of specific segments of DNA. As a result of this study, a heterozygous pathogenic variant was found in the COL1A1 gene, which allows supporting the clinical suspicion of hereditary collagenopathy, osteogenesis imperfecta type and other pathologies related to bone and connective tissue involvement. COL1A1 GENE (NM_000088.4), variant c.3652G>A (p. Ala1218Thr), missense variant type, reference rs72656337.

Taking the above into account, with the result of a genetic study in the index case (the patient's daughter), a study targeting the COL1A1 gene variant c.3652G>A (p. Ala1218Thr), related to osteogenesis imperfecta type I, was requested.

A whole exome sequencing (the entire coding region of the genome) was performed on a next-generation massive sequencer DNB-SEQ400. From these data, the gene sequence was analyzed, with an average coverage greater than 98% and a minimum depth of 20x. The sequencing results were analyzed bioinformatically in a secondary analysis to evaluate the quality of the data obtained from sequencing and in a tertiary analysis to align the sequences, perform variant calling and filtering. The variants were analyzed with respect to the hg19 reference genome, for annotation and variant calling.

The identified variants were evaluated taking into account the parameters recommended by the American College of Medical Genetics (ACMG) guidelines for the classification of variants (Richards et al, 2015) and their updates according to ClinGen (clinicalgenome.org), including the information of databases such as ClinVar, HGMD, LOVD, dbSNP and gnomAD, and the association of the identified variants with the syndromes described in Online Mendelian Inheritance in Man (OMIM) and in the scientific literature, and the clinical association with the phenotype described in the patient were evaluated.

Results

A pathogenic heterozygous variant was identified in the COL1A1 gene Table number 2 that generates the change of a guanine for an adenine in position 3,652 of the cDNA, in exon 48 of the gene (c.3652G>A) and that at the protein level produces the change missense of an alanine to threonine at amino acid 1,218 (p.Ala1218Thr), a moderately evolutionarily conserved amino acid. This variant has a functional study that indicates that type I collagen is a heterotrimer composed of two alpha-1 chains and one alpha-2. The chains are synthesized as promolecules, with globular extensions at the amino (N-) and carboxyl (C-) ends necessary for the assembly of the chains into the triple helix characteristic of type I collagen. Once the chains are assembled, the N propeptides and C are cleaved by specific proteinases N and C. The main proteinase for propeptide C removal is bone morphogenic protein 1 (BMP1). The cleavage reaction occurs at the Ala-Asp bond at position 1218-1219 of the alpha-1 chain and at the Ala-Asp bond at position 1119-1120 of the alpha-2 chain. The Ala1218Thr variant replaces alanine with threonine at position 1218 of the alpha-1 chain, thus altering the BMP1 cleavage site (PMID: 24891183) and another indicating a deleterious effect on the protein (PMID: 29669177). This variant is reported in the ClinVar databases (ID:853496) classified as pathogenic in 2 entries, in The Human Gene Mutation Database (HGMD) (CM114195) and in the Leiden Open Variation Database (LOVD) classified as pathogenic in 4 entries, and as VUS in 1 entry; and in the scientific literature consulted associated with osteogenesis imperfecta (PMID: 21344539, 28173822, 31447884, 32166892). Its allelic frequency is unknown in the general population (gnomADv.4).

Discussion

OI is part of the group of genetic skeletal disorders, the incidence rate of Osteogenesis Imperfecta (OI), being one of the most common diseases of this group, is 1 in 15,000 live births worldwide [14]. In 2023, the latest classification and update of this type of pathologies was published in the American Journal of Medical Genetics, which were cataloged into 41 groups, according to their genetic and clinical characteristics. OI belongs to group number 26, called Osteogenesis imperfecta and bone fragility group, day by day it has been possible to obtain extensive knowledge about the etiology of these clinical entities, thanks to massively parallel sequencing technology, which has made it possible to sequence a large number of DNA segments massively and in parallel, in less time and at a lower cost, achieving the diagnosis of rare and ultra-rare disorders [15].

Collagen chains have repeated glycine (Gly) sequences and are part of the characteristic in their structure, most patients with OI will have pathogenic variants for the coding of these chains, this results in a change in the coding of Glycine (Gly), amino acid that belongs to the conformation of these chains, which is replaced by another amino acid, generating a conformational change in the procollagen I chains. The phenotype or clinical characteristics will depend on the amino acid that is generated with the codon changes or the place where the alteration is generated, we can find a serious spectrum of the disease when we have greater substitutions of the amino acid glycine (Gly) especially in the COL1A1 gene generating alteration in the two alpha-1 chains. The types of variants that can occur are, frameshift type, variant that inserts or deletes a nucleotide in the DNA sequence, splicing type genetic variant that inserts, deletes or changes a nucleotide in the splicing site of the messenger RNA (mRNA). Finally, the nonsense type genetic variant that results in the formation of a stop or premature termination codon, depending on the genetic defects we have, will be the clinical manifestations [3,4,7].

The patient described presents a pathogenic heterozygous variant in the COL1A1 gene, which agrees with what has been mentioned in the literature, because the majority of patients with OI, between 80-90%, have involvement of the COL1A1 genes located on chromosome 17 and the COL1A2 gene located on chromosome 7, which codes for the formation of collagen, has *an* autosomal dominant inheritance, as described in the work by Maioli M et al. in which 89% of patients with OI in their molecular screening presented a pathogenic variant of collagen in which 66% with variants in the COL1A1 gene [16]. Other genes that are part of collagen formation, have X-linked or recessive inheritance, these represent 15 to 25%, such as variants in genes CRTAP, P3H1, PPIB, SERPINH1, FKBP10, PLOD2 and SP7, in addition to having the association of different pathogenic variants are related to a more severe expression of the disease, as found by Caudevilla et al. in a case with severe spectrum with two pathogenic variants in the COL1A1 and CRTAP gene [17]. The patient described had an evident commitment of skeletal symptoms in her family group on the part of the maternal lineage, hence the importance of knowing the family history in this type of entities with autosomal dominant inheritance, should make us suspect a genetic commitment and thus it also motivates carrying out studies to identify different variants related to this disease. Bioinformatics study is carried out with in silico predictors.

According to Human Phenotype Ontology (HPO), this gene encodes the pro-alpha1 chains of type I collagen whose triple helix comprises two alpha1 chains and one alpha2 chain. Type I is a fibril-forming collagen found in most connective tissues and is abundant in bone, cornea, dermis, and tendon. Variations in this gene are associated with osteogenesis imperfecta types I-IV, Ehlers-Danlos syndrome type VIIA, Ehlers-Danlos syndrome Classical type, Caffey Disease, and idiopathic osteoporosis. Reciprocal translocations between chromosomes 17 and 22, where this gene and the gene for platelet-derived growth factor beta are located, are associated with a particular type of skin tumor called dermatofibrosarcoma protuberans, resulting from unregulated expression of the growth factor. Two transcripts, resulting from the use of alternate polyadenylation signals, have been identified for this gene, it has 177 term associations [19].

Patients with OI are phenotypically affected by various systems, the most notable of which is skeletal alterations, symptoms that appear in childhood, with compromised height, and presence of fractures. These fractures are rare in the neonatal stage. In the study carried out by Caudevilla et al [17]. They found that the patients presented 3.4 fractures as an average number of fractures at diagnosis and a maximum of 18 fractures in the case of our patient there were 6 fractures prior to diagnosis. Other symptoms that we can find in these patients are osteopenia, joint hypermobility, vertebral flattening, involvement of the sense organs, loss of sensorineural or conductive hearing in 28% of patients, at the ocular level the presence of blue sclera is pathognomonic, less frequently: dentinogenesis imperfecta, cardiac alterations specifically with valvular involvement. In the study by Maioli M et al [16]. The presence of valvular disease occurred in 23% of patients, with mitral insufficiency being the most common valvular disease, representing 40% in their study, in the case of our patient she did not present symptoms since childhood, her presentation was late, she had no systemic involvement, no heart condition, normal scleras, symptoms were specifically at the skeletal level and did not cause deformity, therefore which refers to the subgroup of OI type IV as described above, no study was carried out to evaluate hearing impairment, which is also characteristic in the clinical presentation of this subgroup [20-22].

The diagnostic approach of patients with Osteogenesis Imperfecta is based mainly on the clinical and family history. From the intrauterine stage, we can find in the prenatal ultrasound the presence of fractures or short limbs suggestive of this entity. As a typical characteristic of pathological fractures we find that 70% of patients will present fractures at the vertebral level, which as we well known in the general population are extremely rare, during the normal growth period there is a compromise in the speed of growth, which should also alert us to this disease, patients with OI type I presents with short stature and some mild bone deformities, OI type II with decreased mineralization of the skull, deformation in the ribs and long bones, OI type III severe symptoms and progressive bone deformation, OI type IV short stature, symptoms moderate, OI type V variable severity of the disease, associating this symptomatology with the ocular, cardiovascular and dental compromise that the majority of patients have, we must perform genetic studies for OI, with respect to laboratory studies there are really none that suggest me the presence of this disease, in some cases elevated alkaline phosphatase can be found, so the support of radiological imaging studies is important when finding in the skull and vertebrae the umbilicate sutural bones, which are abnormal ossicles that develop from centers of additional ossification within the skull, kyphoscoliosis, platyspondyly, in thorax pectus excavactum or carinatum, pelvis coxa vara, osteoporosis, cortical thinning, hypertrophic callus formation, “popcorn” calcifications are large, dense calcifications that affect the metaphysis and epiphysis, pseudoarthrosis at the site of the fractures [4,5].

Currently, multidisciplinary management and orthopedic interventions are the pillars to treat this disease. This will depend on the severity of the symptoms and their phenotypic classification. In our case described, multidisciplinary management was initiated with orthopedics, endocrinology, cardiology, physiatry, nutrition, psychology, social work and received genetic counseling on the importance of achieving genetic assessment within their family group, education was conducted on the medical condition, possible complications and systemic compromise, in addition to the potent ongoing risk of developing low-impact fractures, it is It is important to treat pain, avoid fractures, which is the most frequent symptom, so that the patient achieves better functionality in their daily life; For mild cases, as is the case of our patient, it is suggested to avoid high-impact movements such as contact sports and treat fractures if they occur. In moderate or severe cases, management involves physiotherapy, rehabilitation, and orthopedic interventions such as splints, intramedullary nails to correct the deformity of the long bones, due to generalized bone involvement.

Nutritional support seeks to maintain normal calcium and vitamin D levels, thus helping the bone recovery process. Management with bisphosphonates is most common, specifically with intravenous pamidronate and oral alendronate. These medications have shown benefits by helping to improve bone density and reduce resorption capacity by inhibiting osteoclasts. In the study carried out by Caudevilla et al [17]. 19 patients who received treatment with bisphosphonates had a decrease in fractures, improvement in chronic pain, and functional capacity. Currently, gene therapy is one of the advances in this type of pathology, since we have extensive knowledge of its genetic etiology, this helps us to have a targeted and individualized treatment, studies have been carried out in animals to correct the genes affected COL1A1 and COL1A2, with the use of antisense Oligodeoxyribonucleotides (ODN), short interfering RNA (siRNA) and ribozymes, trying to silence or inactivate these altered genes and good results have been obtained, changing the entire spectrum of the disease. Fresolimumab is an antibody against transforming growth factor beta (TGF- β) and has currently been studied in the pathogenesis of OI. Thanks to Gene Set Enrichment Analysis (GSEA), it was identified that the signaling by TGF- β, when activated, is responsible for bone changes in OI, hence the importance of treatment to inhibit TGF-β [4,5,9,23-26]. As mentioned in the clinical trial by I-Wen Song et al [27]. found a decrease in the levels of Serum osteocalcin at a dose of Fresolimumab 4 mg/kg single dose without presenting serious adverse events related to the medication, measured bone density with improvement in patients with OI type IV.

Treatment with stem cell transplantation has attracted attention in OI due to the ability of these cells to differentiate into osteoblasts, osteocytes and chondrocytes; an increase in growth and bone mineral content has been found with a decrease in the presence of fractures in patients with OI, said bone marrow transplants have been performed from siblings with HLA compatible, it has been postulated to perform these procedures from the prenatal stage in order to foresee the complications of the disease from the early stage, however this treatment is not widely used due to low evidence from few studies in this population [9].

Gene therapy is part of the latest promising research for the treatment of this entity; it is widely known that most of cases of patients with OI have variants in the gene. COL1A1 or COL1A2, so strategies have been designed to suppress these affected alleles with antisense oligonucleotides, ribozymes and interfering RNA (siRNA), through non-viral vectors such as nanoparticles, liposomes and lipid nanoparticles, however until now this therapy has not achieved long-term effectiveness in bone cells, due to rapid degradation in vivo [28].

Conclusions

The availability of advanced genetic testing methods enables high-throughput, parallel DNA sequencing, accurate diagnoses, and individualized therapeutic approaches. Additionally, genetic testing facilitates cascade screening, allowing the identification of other affected oligosymptomatic carriers and other at-risk family members through cascade screening.

The search for the significance of variants in the different databases, use of high-performance bioinformatic algorithms, individual predictors, and MetaScore, combined with knowledge about functionality, biological bases, data from genomic and molecular annotations, protein structure and function, population frequencies for which this variant did not report, neither exomic – genomic, and no publications for rs72656337, with 2.9k total variants in COL1A1, allow knowledge about the genes and variants explaining the great phenotypic - genotypic heterogeneity for this specific variant, according to Standards and guidelines for the interpretation of sequence variants, American College of Medical Genetics and Genomics, Association for Molecular Pathology, ClinGen: PP1M Segregates - Multiple Families, PS4M Multiple Cases, PM1 Located in the Nonhelical Region (C-terminal) Domain, PM2 Rare Allele frequencies are below 0.0005 in gnomAD v.4, PP1M2, PP2 is typically missense. This is a missense variant in a gene that has a low rate of benign missense variation and in which missense is a common mechanism of disease, which is why it is classified as probably pathogenic (25) and is established by phenotype/endotype/genotype correlation.

This precision medicine approach in osteogenesis imperfecta improves treatment outcomes, quality of life, and functional capacity of affected individuals by applying proactive management strategies of prevention, prediction, monitoring, and prognosis, as well as establishing guidelines for early detection in other family members, bringing us closer to a comprehensive and multimodal solution. This underscores the transformative potential of genetic testing to shape the future of personalized medicine.

Declarations

Ethics approval and consent to participate: Not applicable to this case report.

Consent for publication: Written and oral informed consent was obtained from patient and/or their legally authorized representative (LAR).

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests. This manuscript is not being considered by any other journal.

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Authors' contributions: Each author contributed to the redaction, proofreading, and correction of the manuscript. SPR contributed to the research, writing, and proofreading, while LJNM contributed in corrected and adding relevant medical changes to the case. All authors read and approved the final manuscript. All authors participated in the acquisition, analysis, and interpretation of the data. Each author has agreed both to be personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, (even ones in which the author was not personally involved), are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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