Mutations in COL1A1 and COL27A1 Associated with a Pectus Excavatum Phenotype in 2 Siblings with Osteogenesis Imperfecta

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Case Reports:
We studied the Skeletal Disorders Genetic Panel of 2 siblings with osteogenesis imperfecta type I and severe pectus excavatum requiring surgical correction. Both had severe respiratory symptoms secondary to the chest wall deformity, and the male patient had evidence of mitral valve insufficiency on an echocardiogram. Results of the genetic panel were remarkable for a homozygous copy number gain in exons 2 to 51 in gene COL1A1. Additionally, both had a heterozygous pathogenic variant in exon 7 of gene COL27A1 (replacement of a glycine with arginine in codon 697 of the protein).

Conclusions:
Gene COL27A1 plays a role during the calcification of cartilage to bone and is associated with Steel syndrome, a skeletal disorder mainly found in the Puerto Rican population. Heterozygous carriers of the p.Gly697Arg variant in COL27A1 have not been described to have a phenotype with chest wall deformities. Additionally, a genotype-phenotype relationship regarding pectus excavatum in patients with osteogenesis imperfecta has not been described, suggesting that having COL1A1 gene mutations and simultaneous haploinsufficiency of COL27A1 can result in a phenotype of osteogenesis imperfecta with pectus excavatum and predispose these patients to additional phenotypic features.

Keywords: Collagen • Funnel Chest • Osteogenesis Imperfecta • Phenotype

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/935526
Background

Osteogenesis imperfecta (OI) is a genetic disease most commonly due to a mutation of collagen type I, which is encoded by genes COL1A1 and COL1A2 and has an essential role in bone tensile strength. Currently, there are multiple types of OI, which vary in severity and type of mutation. However, because of very broad variability, genotype-phenotype correlations are still being described [1]. OI type I, caused by a COL1A1 quantitative mutation, is the most predominant, and patients usually present with blue sclera, fractures during childhood, and dentinogenesis imperfecta [1]. These patients can also have chest wall deformities, such as scoliosis, pectus excavatum, or carinatum, but the number of reported cases is scarce [2]. Pectus excavatum, described as a depression of the sternum in the anterior chest wall, accounts for over 90% of all chest wall deformities. Severe cases of pectus excavatum are surgically corrected because patients are greatly affected in their physical and psychological development [3].

Steel syndrome, a rare genetic disorder previously known as the “Puerto Rican syndrome,” was first described by Steel et al [4] and is characterized by congenital hip and radial head dislocation, short stature, scoliosis, foot abnormalities, and wrist deformities. In 2015, Gonzaga-Jauregui et al [5] identified the Puerto Rican founder mutation, a homozygous missense variant c.2089G>C (p.Gly697Arg) of the COL27A1 gene. COL27A1 is a type C fibrillary collagen expressed by various tissues during early embryonic development and is exclusively expressed in cartilage throughout adulthood [5]. Although the variant is rare, patients with it have also been described to have chest wall deformities, such as pectus excavatum. Amilie-Wolf et al [6] reported on 2 patients of Puerto Rican descent with Steel syndrome who had pectus excavatum on physical examination. Nonetheless, the effect of this heterozygous variant of COL27A1 on the phenotype of an individual with OI has not been reported in the literature. This is a case report of 2 siblings of Puerto Rican descent with autosomal dominant OI and severe pectus excavatum requiring surgical correction. Both patients had genetic variants in COL1A1 and COL27A1 genes.

Case Reports

We report the cases of a 10-year-old boy and 12-year-old girl with autosomal dominant type I OI. The patients were siblings born to a mother who also had OI but no chest wall deformities. The girl started bisphosphonate therapy at approximately 1 year of age, while the boy began therapy at 6 months of age. They are currently receiving intravenous pamidronate therapy every 3 months for 3 consecutive days at a dose of 1 mg/kg.

Table 1. Patients’ phenotypic characteristics.

|                        | Female patient | Male patient |
|------------------------|----------------|--------------|
| Pectus excavatum       | Yes            | Yes          |
| Haller index           | 4              | 3.5          |
| Cardiac valvulopathy   | No             | Mitral valve insufficiency |
| Pulmonary function tests| Normal         | Normal       |
| Short stature          | Yes            | Yes          |
| Blue sclerae           | Yes            | Yes          |
| Non-traumatic bone fractures | Yes         | Yes          |
| Biconcave flattened vertebrae | Yes     | Yes          |

On physical examination, they had severe pectus excavatum, short stature, blue sclerae, history of multiple non-traumatic fractures, and biconcave flattened vertebrae (Table 1). A computed tomography scan of the chest showed a Haller index of 4.0 for the girl and 3.5 for the boy (Figure 1A, 1B). Pulmonary function tests were in the reference range for both patients. Echocardiogram of the boy revealed mitral valve insufficiency; the girl had no cardiac pathology. Both patients were symptomatic with shortness of breath, associated with physical exertion, and limited exercise tolerability. In view of the symptoms, cardiac valvopathy, and Haller index score, both patients met the criteria for surgical correction of the chest wall deformity. The boy underwent the Nuss procedure at 7 years of age and his sister at 8 years. After 3 years of bar placement, they underwent surgical bar removal. Both surgeries were successful, with noticeable improvement in physical activity capacity and correction of the chest wall deformity.

A Skeletal Disorders Panel was conducted to analyze blood samples from both patients (Table 2). Tests were performed following approval of the protocol by an institutional review committee. The results were remarkable for a homozygous copy number gain in exons 2 to 51 in gene COL1A1 and a concomitant heterozygous pathogenic variant in exon 7 of gene COL27A1 (replacement of a glycine with arginine in codon 697 of the protein). Both siblings had the same mutation in both genes.

Discussion

Past studies on OI have focused on describing different mutations to the COL1A1 and COL1A2 genes and their relationship...
to the multiple phenotypes of OI. This disease can also include chest wall abnormalities, such as pectus excavatum and pectus carinatum, variations which have yet to be linked to a specific genotype. These conditions have an impact on health due to the cardiac and pulmonary morbidity and mortality associated with these deformities. The purpose of this study was to explore and describe the genetic haploinsufficiency effect of the \textit{COL27A1} gene in patients with concomitant \textit{COL1A1} gene mutations.

The \textit{COL1A1} and \textit{COL1A2} genes produce collagen type I which has been established as the primary component of the organic matrix in skeletal tissue and the protein responsible for 90\% of OI cases \cite{1}. OI can be classified based on radiological, clinical, and hereditary findings as types I to IV \cite{1,7}. The most common is the mild type I, which tends to present with blue sclera, fractures during childhood, and sometimes dentinogenesis imperfecta. This type is often associated with synthesis of collagen molecules with structural anomalies or quantitative mutations that still contain functional protein but in decreased amounts \cite{7}.

There are several reported mutations in \textit{COL1A} genes, including splicing, deletion type, missense, and single-base substitutions. Augusciak-Duma \textit{et al} reported at least 8 gene variants in \textit{COL1A} genes that lead to OI. These include a single-base substitution in intron 13 of gene \textit{COL1A1} (c.904-9 G>T), which is associated with OI type I \cite{8}. A mutation in exon 22 of the \textit{COL1A2} gene (c.1207G>T) was also reported to be linked to OI type III \cite{8}. Gug \textit{et al} described a new heterozygous splicing mutation (c.1155+1G>C) that is located at the beginning of intron 17 of the \textit{COL1A1} gene and is characterized by replacement of guanine with cytosine at the 1155\textsuperscript{th} nucleotide of the gene sequence \cite{9}. The effects of any given mutation are thought to differ based on its location on the triple helical domain. N-terminal helical mutations in \textit{COL1A1} have been previously linked to blue sclerae and confirmed in the study on the Swedish population by Lindahl \textit{et al} \cite{1}. Similarly, C-terminal helical mutations were linked to dentinogenesis imperfecta in both \textit{COL1A1} and \textit{COL1A2} mutations \cite{1}.

The \textit{COL27A1} gene encodes a fibrillar collagen that is seen mostly in cartilage and is thought to be involved in the transition from cartilage to bone. Steel syndrome, which occurs usually in homozygous \textit{COL27A1} variants (c.2089G>C;p.Gly697Arg), is thought to have been derived from a founder mutation from Puerto Rico \cite{5}. Additional genetic variants consisting of a frameshift 5-nucleotide insertion and a large deletion encompassing 23 exons have also been reported in patients who are not from Puerto Rico \cite{10}.

Prior studies have been unable to determine significant relationships between heterozygous carriers of the \textit{COL27A1} (c.2089G>C;p.Gly697Arg) allele and skeletal abnormalities \cite{11}. The effect of heterozygosity of \textit{COL27A1} (c.2089G>C;p.Gly697Arg) on patients already affected with another bone disease, such as OI, has not been described in the literature. Based on the results from the genetic panel, we hypothesize that having OI and concomitant haploinsufficiency of \textit{COL27A1} can result in a phenotype of OI characterized by pectus excavatum.

![Figure 1. Chest computed tomography scan showing pectus excavatum deformity in (A) the female patient and (B) the male patient before surgical correction.](image-url)

| Gene     | Genetic variant                  | Zygosity         |
|----------|----------------------------------|------------------|
| \textit{COL1A1} | Gain (exons 2-51)                 | Copy number=3    |
| \textit{COL27A1} | c.2089G>C (p.Gly697Arg)          | Heterozygous     |

Table 2. Invitae skeletal disorders panel results.
It is important to describe this genotype-phenotype relationship because it can guide physicians to recognize genetically predisposed patients and to correct the pectus excavatum early in the clinical course. Pectus excavatum can lead to symptoms such as chest pain, fatigue, dyspnea, respiratory infections, palpitations, and heart murmurs. More serious cardiac concerns include mitral valve prolapse, mitral valve regurgitation, and ventricular compression [12,13]. In patients with skeletal diseases, such as OI, it is known that pectus excavatum increases mortality secondary to cardiac and respiratory problems [13].

Both of our patients had fatigue and intolerance to physical exertion, with a Haller Index >3.25, which is considered severe. The male patient also had evidence of mitral valve insufficiency on echocardiogram, meeting criteria for surgical correction. Identification of the chest wall deformity before puberty was crucial to allow for surgical correction and reversal of pulmonary and cardiac disease. Both patients were asymptomatic at the time of this report, with increased exercise tolerability and improved quality of life. Further genetic testing and molecular studies are in progress, including proteomic studies, to establish the relationship between variants in gene COL27A1 and this phenotype of OI.

Conclusions

COL1A gene mutations and simultaneous haploinsufficiency of COL27A1 can result in a phenotype of OI with pectus excavatum. Genotype-phenotype relationships for OI have been described in the literature, but genetic variants causing phenotype differences remain to be established. Genetic testing of patients with OI and chest wall deformities can help elucidate new genotype-phenotype relationships and confirm existing ones. We present the cases of 2 Puerto Rican patients with mutations in the COL27A1 and COL1A1 genes and a phenotype of pectus excavatum in OI.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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