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Short Communication

Prenatal diagnosis of recurrent autosomal dominant osteogenesis imperfecta associated with unaffected parents and paternal gonadal mosaicism

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Abstract

Objective: To present the prenatal diagnosis of recurrent autosomal dominant osteogenesis imperfecta (OI) associated with unaffected parents and paternal gonadal mosaicism.
Materials and Methods: A 37-year-old woman was referred for genetic counseling at 18 weeks of gestation because of advanced maternal age and a family history of OI. The woman had a daughter who was affected with OI type III and carried an insertion frameshift mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene. The woman and her husband were non-consanguineous and healthy. Amniocentesis was performed at 18 weeks of gestation.
Results: Cytogenetic analysis revealed a karyotype of 46,XX. Molecular analysis of the amniocytes revealed a recurrent mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene. Mutational analysis of the family revealed no mutation of the *COL1A1* gene in the parental bloods. However, mosaicism for the *COL1A1* mutation was found in the paternal sperms. Level II ultrasound examination showed a curved right tibia, a narrow chest with irregular ribs and mild frontal bossing in the fetus. The parents decided to terminate the pregnancy, and a female fetus was delivered at 23 weeks of gestation with curved long bones.
Conclusion: Recurrent autosomal dominant OI may occur in the offspring of unaffected parents with parental gonadal mosaicism. Genetic counseling of recurrent autosomal dominant OI should include a thorough mutational analysis of the family members, and mutational analysis of the sperm may detect paternal gonadal mosaicism for the mutation.

Keywords: COL1A1; osteogenesis imperfecta; prenatal diagnosis; recurrence

Introduction

Osteogenesis imperfecta (OI) is a heterogeneous heritable disorder that involves connective tissues and is characterized

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by bone fragility, decreased bone mass and other connective-tissue manifestations such as blue sclerae, hyperlaxity of skin and ligaments, dentinogenesis imperfecta (DI), and hearing loss [1,2]. OI occurs in approximately 1:20,000–1:60,000 births [3,4]. Here, we report the identification of an insertion frameshift mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene in an 18-month-old girl with OI type III and in a fetus with recurrent autosomal dominant OI in a family with unaffected parents and paternal gonadal mosaicism.

Materials and methods

A 37-year-old, gravida 4, para 3, woman was referred for genetic counseling at 18 weeks of gestation because of advanced maternal age and a family history of having a daughter affected with OI type III. The 18-month-old daughter was the woman's second child of her second marriage with a 44-year-old husband. The woman and her husband were nonconsanguineous and healthy. The couple's eldest 3-year-old son was healthy. The mother's other two children of the previous marriage were all healthy. Their affected daughter was delivered vaginally at 38 weeks of gestation after an uncomplicated pregnancy, with a body weight of 2800 g (15th centile) and a length of 48.5 cm (15th centile). Prenatal ultrasound findings were unremarkable. Immediately after birth, she was noted to have paralysis of the upper limbs. Shoulder dislocation or subluxation, birth trauma of the bones, brachial plexus injury and clavicle fractures were all suspected. During admission, X-rays showed healed fractures in the right humerus, left ulna and radius, bilateral femurs and bilateral ribs, and a new fracture in the left humerus. Her condition stabilized after parenteral bisphosphonate therapy. Over the next 18 months, she suffered from repeated fractures of the extremities after minimal traumas. The clinical findings were consistent with the diagnosis of OI type III.

Results

On examination, she had mild scoliosis, blue sclerae and DI, but no hearing loss. Molecular analysis of type I collagen genes revealed an insertion frameshift mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene (Fig. 1). During this pregnancy, amniocentesis was performed at 18 weeks of gestation. Cytogenetic analysis of the amniocytes revealed a karyotype of 46,XX. Molecular analysis of the amniocytes revealed a recurrent mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene (Fig. 2). Mutational analysis of the parental bloods did not find such a mutation (Fig. 2). However, molecular analysis of the sperm DNA derived from the father revealed mosaicism for a mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene (Fig. 2). Level II ultrasound examination of the fetus showed a curved right tibia, a narrow chest with irregular ribs and mild frontal bossing. The parents decided to terminate the pregnancy, and a 624 g female fetus was delivered, at 23 weeks of gestation, with curved long bones.

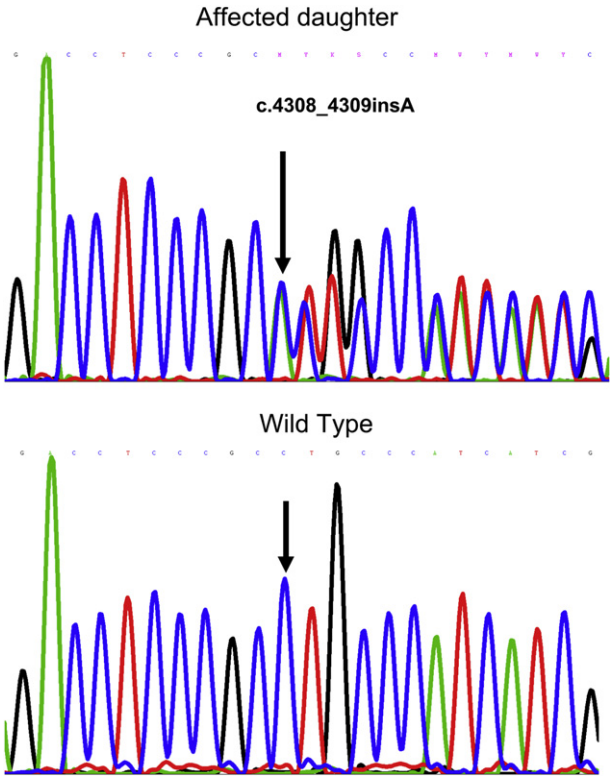

Fig. 1. Molecular analysis of the affected daughter shows an insertion frameshift mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene.

Discussion

To date, at least 12 types of OI have been identified, and approximately 90% of the patients of OI have dominant mutations in the *COL1A1* gene (OMIM 120150) encoding α1 type I collagen chain and in the *COL1A2* gene (OMIM 120160) encoding α2 type I collagen chain [5]. OI type I is associated with mutations in *COL1A1*, mostly because of a null allele caused by a premature stop codon due to deletions, duplications, nonsense mutations and frameshift mutations [6,7]. OI type II ~ type IV are associated with mutations in *COL1A1* or *COL1A2*, most commonly due to glycine substitutions and less frequently due to splicing defects, deletions, insertions or duplications [8–11]. OI type I ~ type V are inherited in an autosomal dominant pattern. OI type VI ~ type XII are inherited in an autosomal recessive pattern and can be caused by homozygous or compound heterozygous mutations in the genes of *FKBP10*, *CRTAP*, *LEPRE1*, *PPIB*, *SERPINH2*, *SP7*, and *SERPINF1*, respectively.

The present case provides evidence that an insertion mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene can result in OI, but not a lethal outcome. This insertion mutation causes a frameshift and predicts p.Leu1437Thrfs*114, with a substitution of leucine to threonine at 1437, an additional 85 amino acids, and a stop at the frameshift 114th codon. Such a mutation is novel and has not previously been described. OI cases with mutations in exon 52 near the carboxyl-terminal propeptide region of *COL1A1* have been

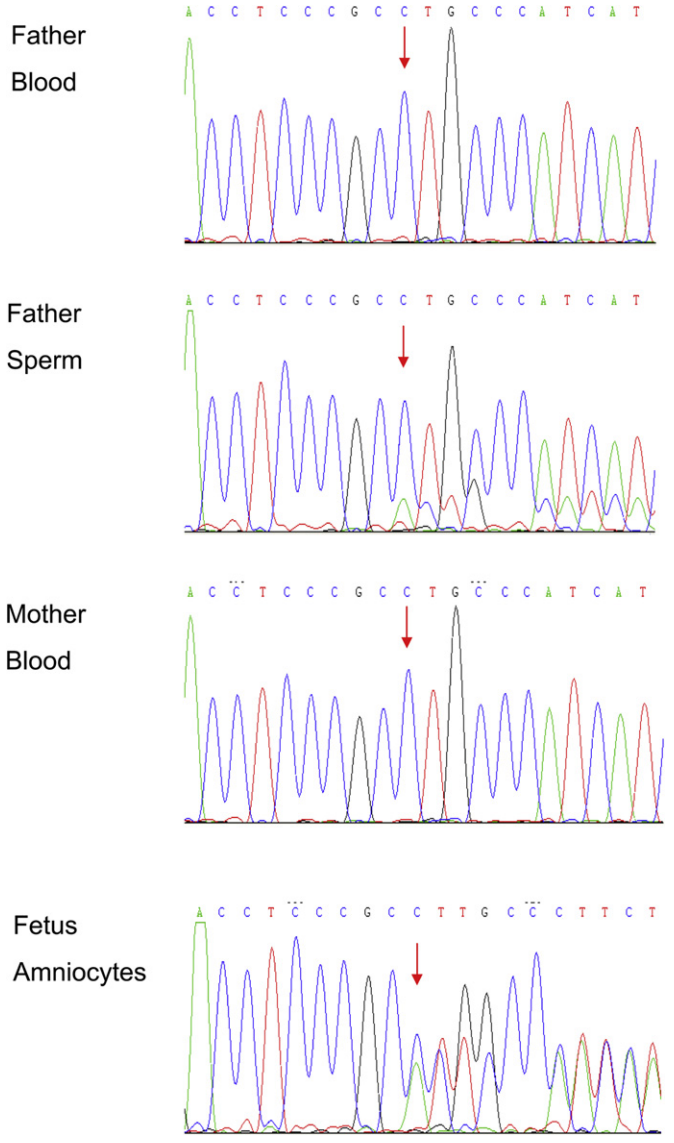

Fig. 2. Molecular analysis of the parental bloods, paternal sperms and amniocytes. The amniocytes have an insertion frameshift mutation of c.4308_4309insA in exon 52 of the *COL1A1* gene. The sperms have mosaicism for the mutation. The parental bloods do not have such a mutation.

described. Currently, 10 mutations in exon 52 of *COL1A1* have been reported according to the OI variant database [12]. These mutations include: (1) c.4257C>T, substitution, silent mutation; (2) c.4292C>T, substitution, missense mutation, p.Thr1431Ile, OI type IV; (3) c.4310T>A, substitution, missense mutation, p.Leu1437Gln, OI type II; (4) c.4321G>C, substitution, missense mutation, p.Asp1441His, OI type I; (5) c.4321G>T, substitution, missense mutation, p.Asp1441Tyr, OI type II; (6) c.4329_4340delinsAGACCAGGTC, insertion/deletion, frameshift mutation, p.Pro1444Aspfs*106, OI type I; (7) c.4338dupC, duplication, frameshift mutation, p.Val1447Argfs*104, OI type IB; (8) c.4343G>A, substitution, missense mutation, p.Gly1448Asp, OI type I/IV; (9) c.4358_4362del, deletion, frameshift mutation, p.Glu1453Argfs*96, OI type I; and (10) c.4391T>C, substitution, missense mutation, p.Leu1464Pro, OI type III. Rugolotto et al [13] reported OI type II in a neonate with a missense mutation in exon 52 of *COL1A1* (T>A, g.16310AF_017178), which converts the codon 1437 from leucine (CTG) to glutamine (CAG) along the proα1(I) carboxyl-terminal peptide. Fuccio et al [14] reported a missense mutation of c.4292C>T, p.T1432I (Thr_Ile) in exon 52 of *COL1A1* in a patient with OI type IV. The present case was associated with OI type III, which is severe and progressively deforming with grayish sclerae, DI, short stature, and moderate deformity at birth [1,5,15]. The severity of autosomal dominant OI increases in the order of type I < type IV < type III < type II. OI type II is perinatally lethal, and type I is mild and nondeforming with no limb deformity.

The affected living girl in this presentation had upper limb paralysis at birth, mimicking shoulder dislocation or subluxation, birth trauma of the upper limbs, brachial plexus injury and clavicle fractures. OI may be undetected prenatally, and the postnatal manifestations may be mistaken as birth trauma. Rapid diagnosis of OI after birth is necessary for proper pediatric management and parental counseling, to avoid medical legal problems under such a circumstance. Recent studies have suggested that cesarean delivery might not protect against fractures in infants with OI, and whenever vaginal delivery is chosen, instrumentation should be minimized to avoid intracranial trauma of the affected fetuses [16].

The peculiar aspect of the present case is the recurrence of autosomal dominant OI in the offspring of unaffected parents with paternal gonadal mosaicism. Genetic counseling of recurrent autosomal dominant OI should include a thorough mutational analysis of the family members, and mutational analysis of the sperm may detect paternal gonadal mosaicism for the mutation. It has been suggested that in familial autosomal dominant OI with one affected parent, the recurrent risk is 50%; in the presence of carriers of an autosomal recessive mutation in both parents, the recurrent risk is 25%; in the case of parental mosaicism, the recurrent risk for autosomal dominant OI is variable, but can be up to 50%; in the case of unaffected parents with parental gonadal mosaicism, the empirical risk of recurrence ranges from 1% to 3%; and in the absence of parental somatic mosaicism, gonadal mosaicism, or recessive or dominant inheritance, the recurrent risk is probably <1% [17–21].

In summary, we present prenatal diagnosis of recurrent autosomal dominant OI associated with a mutation in the *COL1A1* gene arising from paternal gonadal mosaicism in the unaffected father. Our case adds to the examples of recurrent autosomal dominant OI caused by paternal gonadal mosaicism for a mutation in the *COL1A1* gene.

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