

histological characteristics, and uni or bilateral ovarian tumor, as well as favorable or unfavorable prognosis during the course of the disease.⁴

Our patient had only left ovary involvement with a tumor of teratomatous characteristics; WBS after ablation therapy with radioiodine (¹³¹I) only showed uptake in the cervical bed, but no advanced metastatic disease; finally, thyroglobulin levels before thyroid ablation with radioiodine were not excessively high (16 g/mL). After six years of clinical monitoring, the patient remains free of tumor recurrence. All of the foregoing suggests that this case had the clinical characteristics of two synchronous primary tumors.

Although the therapeutic management of malignant struma ovarii is controversial, it is advisable to perform neck ultrasonography and thyroid FNA if any thyroid nodule is detected. Total thyroidectomy is recommended if there is any suspicion of a malignant thyroid nodule.⁵

The synchronous presence of malignant struma ovarii and papillary thyroid cancer is usually associated with a favorable prognosis, unlike in the presence of metastatic disease having one or the other origin. The main barrier for making recommendations on the clinical management of these synchronous tumors is the rarity of their coexistence and the lack of sound scientific evidence.

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Reproductive options in osteogenesis imperfecta. A two cases report in the same family with a new mutation in *COL1A1*[☆]



Opciones reproductivas en pacientes con osteogénesis imperfecta. A propósito de 2 casos de la misma familia con una nueva mutación en *COL1A1*

Osteogenesis imperfecta (OI) is a genetic disorder characterized by bone fragility, usually due to a mutation in the *COL1A1* or *COL1A2* genes that encode for the α chain of type 1 collagen, the main bone protein.^{1–4}

Two patients with OI (father and daughter) in whom a genetic study showed a c.3607C>T (p.Gln1203*) change in the *COL1A1* gene not previously described are reported here. The potential reproductive options are reviewed.

Case 1

This was a 55-year-old male diagnosed with OI after his affected daughter was born (Fig. 1). He had sustained at least 10 fractures and several dislocations before reaching 14 years of age. The patient had been diagnosed with mixed hearing loss. Physical examination findings showed the following: height 158 cm, blue sclerae, normal teeth, no bone deformities. Laboratory test results showed: normal calcium, phosphorus and creatinine levels; 25OH-vitamin D, 16 ng/mL; iPTH, 65.7 pg/mL (NR, 15–65); 24 h calcium levels, 260 mg.

Normal bone density as measured by densitometry (DEXA) gave a mean T-score in the lumbar spine (LS) –2.2 (–3.7 in L4). Treatment with alendronate plus calcium and vitamin D was administered with a good response (T-score in LS after four years of treatment, –0.9).

A genetic study revealed a c.3607C>T (p.Gln1203*) mutation in the *COL1A1* gene.

Case 2

This was a 21-year-old female, the daughter of the above patient, who was diagnosed with OI at birth. During pregnancy, curved tibiae and intrauterine growth retardation were detected (birth weight, 2 kg). She sustained her first fracture at four days of life, and subsequently had several fractures, especially in the lower limbs, before the age of 16 years.

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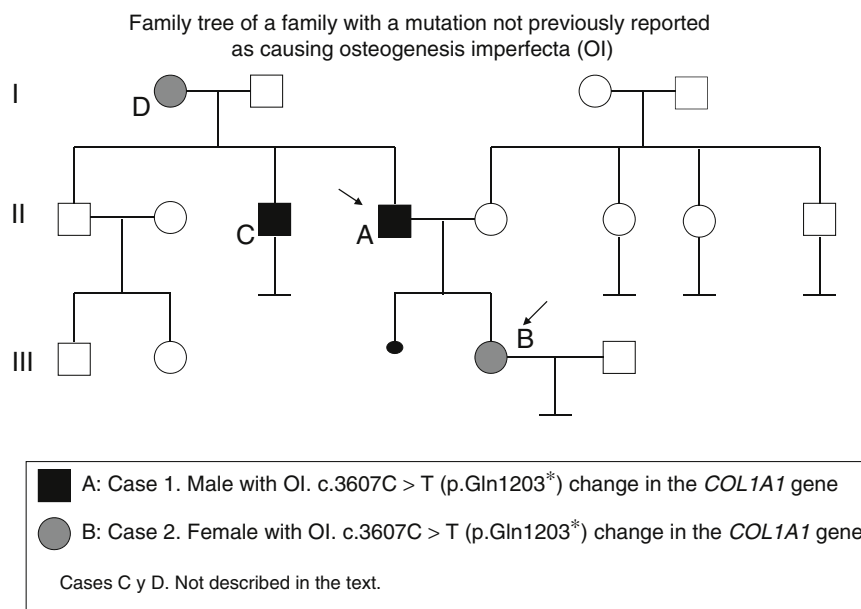


Figure 1 Family tree of a family with a mutation not previously reported as causing osteogenesis imperfecta (OI).

At the age of seven years, DEXA showed a Z score -2.83 in LS; intravenous pamidronate and subsequently oral alendronate were administered until 14 years of age and an increased Z score to $+1.2$. Z score has remained normal since then. Physical examination findings were as follows: height 157 cm, blue sclerae, normal teeth, no deformities, and normal hearing.

As she was concerned both about the way in which her disease was inherited and about her options for a future maternity, a directed genetic study was conducted, which confirmed that she carried the mutation previously detected in her father. Genetic counseling was provided.

Bone fragility is the main characteristic of OI, causing multiple fractures with no or minimal trauma, and progressive deformities in more severe cases. Other signs include low height, blue sclerae, dentinogenesis imperfecta, and hypoacusis in adults.

Diagnosis is usually made at an early age. In children and adolescents, intravenous bisphosphonates have been shown to be effective for decreasing fractures and improving pain, mobility, and final height. However, many patients reach adult age undiagnosed. Most adults affected have osteoporosis, for which bisphosphonates are the treatment of choice.⁵⁻⁷

OI is usually caused by mutations in genes that encode for the $\alpha 1$ and $\alpha 2$ chains of type 1 procollagen (*COL1A1* and *COL1A2* genes) and is inherited as a dominant autosomal disorder, although other genes have also been identified as being involved, including *CRTAP* and *LEPRE-1*, which result in uncommon forms of the disease with a recessive autosomal heredity. At least other 11 related genes are known, including *OSX*, *SERPINH1*, *PPIB*, *FKBP10*, *BMP1*, *CREB3L1*, *IFITM5*, *SERPINF1*, *SPARC*, *TMEM38B*, and *WNT1*.^{3,4,8}

More than 1500 different mutations have been reported. Our patients were found to have a c.3607C>T (p.Gln1203*) mutation in the *COL1A1* gene that implies a change in amino acid and glutamic acid by a stop codon at

position 1203, resulting in a truncated protein. This nucleotide substitution has not previously been reported in the literature as being associated with OI, but based on the harmful effect it has on the protein, it is likely to be its cause.

The woman was informed of the dominant inheritance and of the risk of transmission of the disease (50% in each pregnancy). In cases where this condition is identified, genetic counseling is followed by information about reproductive options.^{9,10} In this case, the alternatives were as follows:

Preimplantation genetic diagnosis (PGD): after *in vitro* fertilization treatment, this allows for genetic embryo testing and for selecting healthy embryos. The mutation responsible for the disease is known, and one of two embryonic blastomeres is taken by embryo biopsy. Molecular genetic diagnosis is performed to search for the known mutation in the embryos, and non-affected embryos are selected to be transferred to the uterus, which allows for a child to be born without the genetic disease. PGD has been possible in Spain since the approval of Act 14/2006, of May 26, on assisted human reproduction techniques, and is available on the national health system. The main argument for performing PGD is that it prevents the trauma of miscarriage and decreases the stress associated with waiting for the results of prenatal diagnosis. It is however a long process associated with low effectiveness rates (15–20%) and high multiple pregnancy rates, potential embryo handling, controversy regarding the safety of embryo biopsy, and high cost.

***In vitro* fertilization with donor oocytes:** the gamete of the affected parent is replaced by an anonymous healthy gamete. Oocytes and sperm are fertilized outside the uterus, and the embryo is transferred to the uterus of the mother, where it is implanted, free of disease.

Conception and the performance of prenatal diagnosis using procedures such as chorion biopsy and genetic

amniocentesis, which allow for taking fetal cells on which genetic studies of OI may be performed. If the fetus carries the mutation, no cure exists. The only possibility is therapeutic abortion.

Non-invasive procedures such as the detection of fetal circulating DNA in maternal blood, are promising.

Other options for having a child include natural pregnancy accepting the risks entailed, or adoption.

Our patient is currently considering the pros and cons of these alternatives.

Women with OI who receive treatment with bisphosphonates during childbearing age also worry about their safety in future pregnancies, because these drugs remain for years in the bone matrix and cross the placental barrier. Bone turnover suppression may cause fetal hypocalcemia. Data in females are sparse, but no serious adverse effects have so far been reported.¹¹ However, the safety period has yet to be established.

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Glucocorticoid resistance syndrome caused by two novel mutations in the *NR3C1* gene



Síndrome de resistencia a los glucocorticoides causado por dos nuevas mutaciones en el gen *NR3C1*

Glucocorticoid resistance (GCCR, OMIM #615962) is a rare condition characterized by generalized, partial, target tissue resistance to glucocorticoids. Cortisol action mediated by the glucocorticoid receptor (GR) is decreased, with a compensatory elevation of circulating ACTH. This increases the production of glucocorticoids, mineralocorticoids and adrenal androgens.¹ The diurnal rhythm of cortisol is maintained but in an elevated level and no adequate cortisol suppression is observed after 1 mg dexamethasone (DXM) test.¹

The molecular basis of GCCR has been related to mutations in the *NR3C1* gene, located on 5q31–q32, which encodes for the GR (Fig. 1A).

In this letter, we report two novel heterozygous mutations in the *NR3C1* gene in two unrelated patients in whom glucocorticoid resistance was suspected.

Biochemical values obtained from the patients are shown in Table 1. In both cases, these pointed to an ACTH-dependent Cushing's syndrome. No pituitary lesion was observed in either patient's magnetic resonance imaging (MRI). Bone densitometry was also normal in both cases.

Patient 1 was a 12-years old girl referred to the endocrinologist after her pediatrician observed a clinically irrelevant white stretch mark on the right thigh and, afterwards, a high basal cortisol level. Menarche occurred at the age of 11 and she referred regular periods. Physical evaluation was normal (weight in percentile 75, height in percentile 90 and Tanner stage IV for pubertal development). Her blood pressure was normal. She presented mild hirsutism. Physiological causes for elevated cortisol levels were excluded. As she remained asymptomatic, no therapeutic attitude was taken. Subsequent evaluations showed no physical or biochemical changes. Hormone studies were performed in the patient's parents. Her mother had slightly elevated cortisolemia (27 µg/dl), with normal DHEA-S, testosterone and 17-Hydroxyprogesterone values. Plasma cortisol level after 1 mg oral DXM administration overnight was 3.7 µg/dl. Father's results were normal.

Patient 2 was a 41-years-old woman referred to the endocrinologist for hirsutism in 1998. She presented regular menses with no other symptoms or signs of Cushing's