

## CASE REPORT

## Birth of a boy with isolated short stature after prenatal diagnosis of a Xp22.3 nullosomy due to an inherited t(X;15)(p22.3;p10) translocation

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## Introduction

Translocations between X chromosomes and acrocentric chromosomes are rare. These events lead to partial nullosomy of X chromosome genes in males and to premature ovarian failure and Léri-Weill syndrome (MIM 127300) in females (due to nonrandom inactivation of the undelated X chromosome).

Here, we report on what we believe to be the first prenatal diagnosis of a der(X)t(X;15)(p22.33;p10) translocation in a fetus with shortened long bones at a second trimester ultrasound examination. We also demonstrated the utility of array comparative genomic hybridization (aCGH) analysis for clearly defining the size of the X chromosome nullosomy and thus enabling appropriate genetic counseling.

## Case Report

A 30-year-old woman (gravida 2 para 1, III:1) was referred to our unit at 26 weeks of gestation because her

### Key Clinical Message

Translocations between X and acrocentric chromosomes are rare. We report on the inheritance of a familial t(X;15)(p22.3;p10) translocation in a fetus referred for short long bones. Cytogenetic analysis revealed an unbalanced translocation combined with a three-gene nullosomy. After genetic counseling, a prognosis was established and a healthy boy was delivered.

### Keywords

CGH array, genetic counseling, Léri Weill syndrome, t(X; 15) chromosome translocation.

male fetus (IV:2) had abnormally short long bones (below the third percentile at 23 weeks). The patient's previous pregnancy had been uneventful and her second pregnancy had been conceived naturally with a 30-year-old man. The couple was not consanguineous and both individuals were of Caucasian origin. The father's physical examination was normal. The mother presented with Madelung deformity and relatively short stature (1.53 m, which is two standard deviations (SDs) below the mean). No dysmorphic features or mental disabilities were apparent in and the family's medical history was unremarkable. The first-trimester ultrasound scan was normal, with a crown-rump length of 60.0 mm and a nuchal translucency measurement of 1.2 mm. The second-trimester, integrated risk screening for trisomy 21 yielded a value of 1/5000 ( $\beta$ hCG: 0.41 multiple of the median (MoM) and  $\alpha$ FP (feto protein): 1.21 MoM).

A post referral ultrasound scan confirmed these findings but did not identify other anomalies (other than asymmetric ears). A two-dimensional ultrasound examination confirmed the abnormally short femur length, with

a value corresponding to 22–23 weeks of gestation. The biparietal diameter and abdominal circumference were normal for the gestational age. There were no features suggestive of achondroplasia or incomplete osteogenesis (i.e., fracture, curvature or cupping of the edge in the long bones). The amniotic fluid volume and fetal vitality were normal. The couple agreed to undergo an amniocentesis for chromosome analysis. On the basis of (i) a conventional cytogenetic analysis of the fetus, the parents, the maternal grandparents, and the maternal grandmother's parents and (ii) an aCGH analysis of the fetus and the mother, we diagnosed a 46,Y,der(X)t(X;15)(p22.3;q10)mat associated with a terminal PAR1 deletion and a partial Xp22.33 short nullosomy (encompassing the XG, GYG2, and ARSD genes).

On the basis of the literature and in accordance with the French legislation, our institution's clinicians, cytogeneticists, and obstetricians provided the parents with extensive genetic counseling. They notably explained the characteristics of Léri-Weill syndrome and idiopathic short stature (ISS) associated with deletion of the short stature homeobox-containing (SHOX) gene (MIM: 312865), the high probability of infertility and the lack of knowledge concerning the partial nullosomy. Under French law, parents may choose to continue or terminate the pregnancy at any time (regardless of the gestational age); after thought, the parents in this case decided to continue with the pregnancy. After an uneventful pregnancy, a male infant was born at term (birth weight: 3.270 kg [−0.5 SD]; birth length: 47 cm [−1 SD]). The physical examination was normal. At the age of 8 months, the boy's weight was 7.4 kg (−1 SD) and his height was 67 cm (−1 SD). There were no dysmorphic features. Psychomotor development was excellent and all other examinations were normal. Two years and 8 months after birth, the boy's phenotype was normal. The boy is of short stature (height: 86 cm (−1.5 SD), with short limbs; weight: 12 kg (−1 SD) due to SHOX haploinsufficiency but does not have Madelung deformity. There are no mental or psychomotor impairments.

## Cytogenetic Analysis

Given that abnormally short long bones on ultrasound are suggestive of a chromosomal abnormality, fluorescent in situ hybridization (FISH) was performed on 100 interphase nuclei with an Aneuvysion kit (Vysis, Abbott Molecular, Des Plaines, IL). The results were normal.

An analysis of amniotic fluid cells (using standard GTG, RHG, CBG and NOR banding) revealed a 46,Y,der(X) fetal karyotype, with an acrocentric satellite at the top of the short arm of the der(X) chromosome (Fig. 1A). Further FISH analysis (using probes for WCPX [MetaSys-

tems, Altussheim, Germany], SHOX [Kreatech; Amsterdam, The Netherlands] and DXYS130 [Kreatech]) enabled us to better define the fetal karyotype. We hypothesized that the fetus had inherited an unbalanced translocation between an acrocentric satellite and the top of the short arm of the X chromosome (combined with SHOX gene deletion).

The results of parental karyotyping and FISH analyses (Fig. 1B–D) prompted us to diagnose a maternally inherited, unbalanced, derived chromosome (III:1). Karyotyping of the maternal grandparents then enabled us to confirm the unbalanced inheritance of a t(X;15)(p22.3;q10) translocation from the maternal grandmother (II:2) with normal stature (1.61 m). This resulted in a 46,X,t(X;15)(p22.3;q10)dn karyotype, since the great-grandparents' karyotypes were normal (Fig. 2).

We then performed an aCGH analysis, in order to define (i) the size of the fetal deletion and the potentially associated nullosomy and (ii) the mother's deletion on the X chromosome.

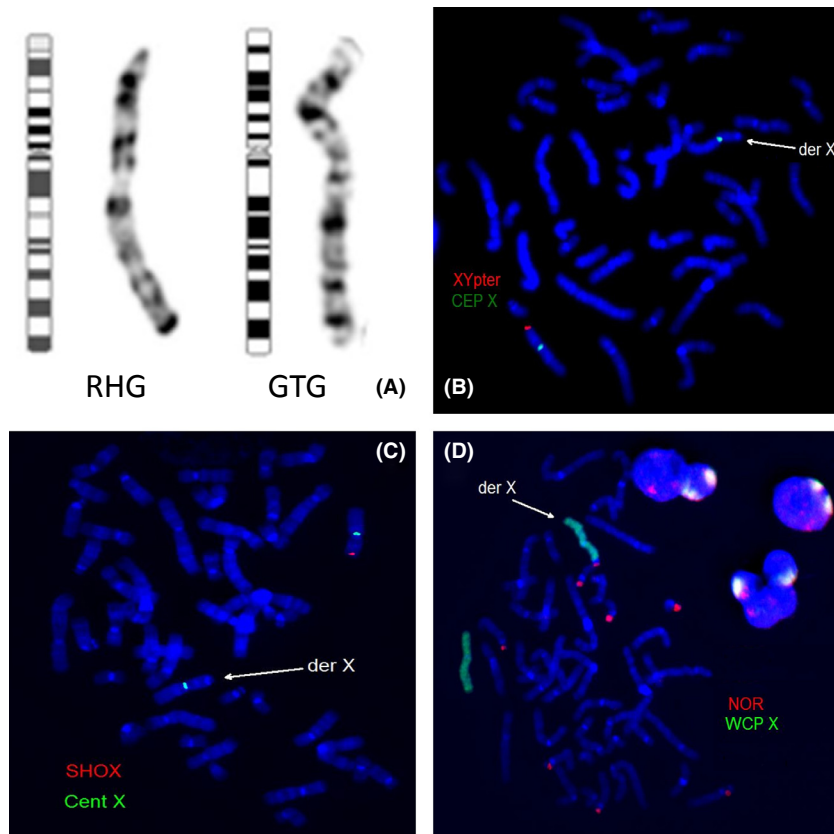
Genomic DNA was extracted from cultured amniotic cells and from the mother's blood using a Perfect Pure DNA blood kit (MagNA Pure, Roche, Indianapolis, IN), according to the manufacturer's instructions. Using a 180-oligonucleotide array (Agilent, Santa Clara, CA; mean resolution: 5 kb), DNA Analytix software (Agilent) and the Hg 19 build, a maternal deletion was confirmed (Fig. 3A). It spanned from 0 (probe: A\_18\_P17041097 (61,091–61,138)) to 2,822,216 (probe: A\_16\_P03642083 (2,822,157–2,822,216)) and encompassed the whole PAR1 region (a 2.6 Mb region containing 24 genes) and its three most proximal genes: XG (chrX: 2,670,093–2,707,747), GYG2 (chrX: 2,746,863–2,800,861), and part of ARSD (2,822,011–2,847,416 pdb).

The PAR1 deletion of X chromosome was detected in fetal DNA. It was associated with a nullosomy encompassing the three above-mentioned genes (Fig. 3B). The final fetal karyotype was, therefore, 46,Y,der(X)t(X;15)(p22.3;q10)mat.arrXp22.33(0–2,689,408)x1mat,Xp22.33(2,701,273–2,822,216)x0mat.

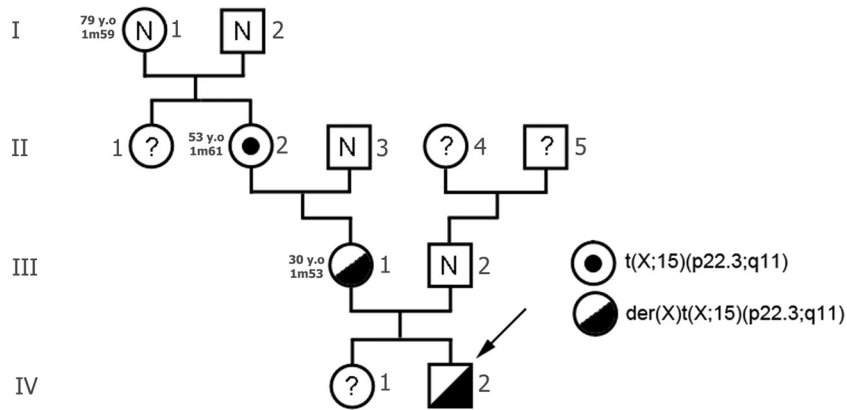
## Discussion

Translocations between chromosomes X and 15 are rare. As is the case for all translocations, different breakpoints lead to the inheritance of unbalanced chromosomes. Inheritance of der(X) (an X chromosome derived from an X-autosome translocation) results in deletion of the X chromosome and duplication of chromosome 15.

When unbalanced chromosomes are inherited in males, der(X) might lead to the partial nullosomy of X chromosome genes – as is observed for the inheritance of partial X chromosome deletions. The nullosomies described to



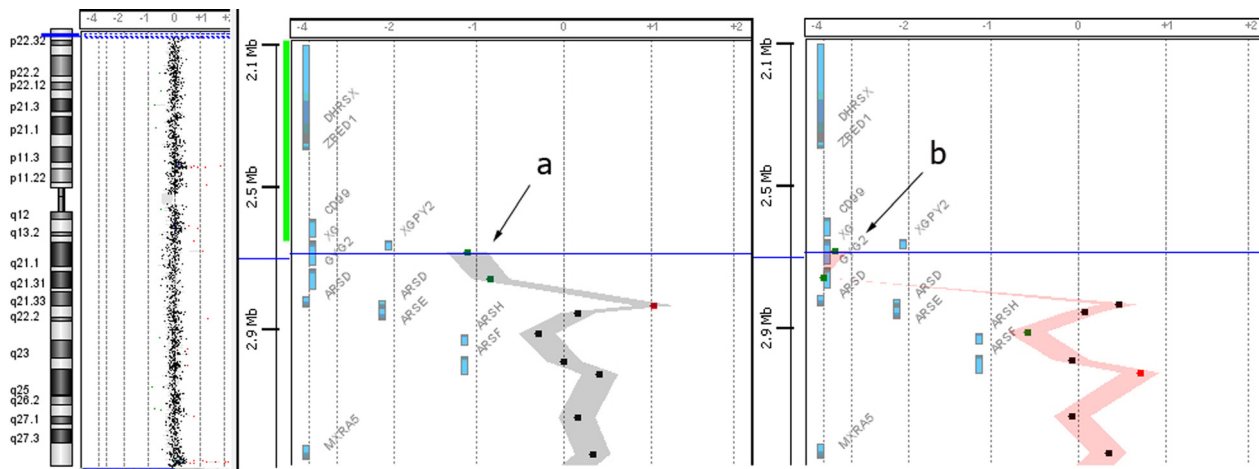
**Figure 1.** Conventional cytogenetic analysis. (A) The proband’s derivative X chromosome, with R and G banding: Fluorescent in situ hybridization on the maternal derivative X chromosome using (B) CEP X (DXZ1) SG and telVysion Xp/Ypter (SO) probes (Abbott Molecular, Vysis), (C) SHOX (SO) and CEP X (SG) probes (Abbott Molecular, Vysis) and (D) a WCP X probe (SG) (Abbott Molecular, Vysis) and a NOR probe (SO).



**Figure 2.** Family tree. The arrow shows the proband (IV:2).

date result in a variety of contiguous gene syndromes, all of which are associated with mental retardation [1]. In general, females with this type of deletion are phenotypically normal, since biased inactivation of the deleted X chromosome is frequently found in this context [2].

However, premature ovarian failure can be caused by haploinsufficiency of genes that are essential for oogenesis and that probably escaped X inactivation. When the deletion encompasses the PAR1 region, Léri-Weill syndrome or ISS results from the SHOX deletion [3].



**Figure 3.** 180K array CGH analysis (Agilent) (A) the mother (III:1) (B) the proband (IV:2).

Here, we report on what we believe to be the first prenatal diagnosis of a  $\text{der}(X),t(X;15)(p22.33;p10)$  in a fetus with abnormally short long bones in a second-trimester ultrasound examination. A conventional cytogenetic analysis of the family clearly showed that the  $\text{der}(X)$  was maternally inherited from a  $t(X;15)(p22.33;p10)$ . Next, aCGH analysis enabled us to define the size of the X chromosome nullosomy, interpret the karyotype and to provide in-depth genetic counseling. However, there was still doubt as to the impact of the partial nullosomy, with a 2.6 Mb deletion and a 200 kb nullosomy encompassing the three most proximal genes in the PAR1 region (*XG*, *GYG2* and *ARSD*).

PAR1 and PAR2 are short, pseudoautosomal (PAR), homologous regions on mammalian X and Y chromosomes (at the top of the short and long arms of these chromosomes, respectively) [4]. PAR1 encompasses 2.6 Mb of the short-arm tips of both X and Y chromosomes in humans and other great apes. To date, 24 genes have been assigned to PAR1 and half of these have a known function. In particular, the *SHOX* gene is involved in height. PAR1 is required for pairing of the X and Y chromosomes during male meiosis and is the only crossing-over point for the gonosomes. Hence, PAR1 is considered to be functionally essential for spermatogenesis [5]. When PAR1 (and thus the *SHOX* gene) is absent, the fetus presents ISS (explaining the ultrasound findings) and short femur length – both of which are classical features of Léri-Weill syndrome [3]. Furthermore, deletion of PAR1 on the X chromosome makes meiotic pairing of the X and Y chromosomes impossible; in turn, meiotic arrest occurs at the pachytene stage. The fetus will be azoospermic, with the absence of spermatozoa in the ejaculate. Spermatozoa are unlikely to be retrieved with a testicular biopsy (with a view to use in intracytoplasmic

sperm injection). For these affected individuals, sperm donation is the only option for paternity.

The *XG* gene is located within the Xp22.32 locus at position 2,670,093–2,734,541, which is at the pseudoautosomal boundary on the short arm of the X chromosome. The three 5' exons are inside the pseudoautosomal region and the remaining exons are within the X-specific end region. The *XG* gene encodes the *Homo sapiens* XG blood antigen (a cell-surface antigen with 48% homology with CD99 and one of the 34 currently known human blood group antigens). No disease or syndrome has been linked to abnormalities in the *XG* locus, even though the latter reportedly escapes X chromosome inactivation [6]. The copy on the Y chromosome is truncated (*XGPY2: Homo sapiens* Xg pseudogene, Y-linked 2 (genomic sequence: chrY:2,620,337–2,643,037)) and transcribed but is not expected to yield a Y chromosome-specific gene product. The *XGPY2* gene testifies to the ancestral homology between the X and Y chromosomes. In fact, the genes on the Y chromosome (other than those in the PARs) can be classified into three categories, (i) X-transposed genes with 99% sequence identity with the homolog on chromosome X, (ii) X-degenerated genes (mainly pseudogenes and relics of autosomal sequences), and (iii) amplicon genes.

The *GYG2* gene encodes a member of the glycogenin family. Glycogenin is a self-glycosylating protein involved in the initiation of glycogen biosynthesis [7]. This X-linked gene is preferentially expressed in liver, heart, and pancreas. The other gene in the family is located on chromosome 3 (*GYG1*, on 3q24) and encodes muscle glycogenin. Both glycogenins are involved in blood glucose homeostasis. To date, no diseases have been linked to *GYG2* abnormalities. A short, 3' truncated version (*Homo sapiens* glycogenin 2 pseudogene 1 (*GYG2P1*),

non-coding RNA) has been identified on the Y chromosome (14,517,915–14,533,389 pdb).

The lysosomal protein encoded by *ARSD* is a member of the arylsulfatase (ARS) family, which is essential for the correct composition of bone and cartilage matrix. The *ARSD* gene (encoding a lysosomal protein) is the most distal in the ARS cluster (*ARSD*, *ARSE*, *ARSF*, and *ARSH*) and has not been linked to a human disease. *ARSD* has the typical features of genes that map to the pseudoautosomal region of the X chromosome: (i) it escapes X inactivation and (ii) it has a related pseudogene (assigned to Yq11) [8]. In contrast, abnormalities in the *ARSE* gene in same cluster have been associated with X-linked recessive punctata chondrodysplasia, (OMIM 302950) [9]. However, *ARSE* had not been deleted in the case described here. Our genetic counseling took account of the absence of reported abnormalities for *XG*, *GYG2*, and *ARSD* and the pregnancy was uneventful. The patient is being monitored regularly in our pediatrics department. He is healthy and the only apparent clinical sign is short stature.

This case has been entered in the ECARUCA database.

## Conflict of Interest

None declared.

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