

Research Letter

## Prenatal diagnosis and array comparative genomic hybridization characterization of a *de novo* X;Y translocation

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Several types of X;Y translocations have been observed in humans. The first type is an Xp;Yq translocation that produces a derivative X chromosome with a partial deletion of Xp and a partial duplication of Yq such as 46,X,der(X)t(X;Y)(p22.3;q11) [1,2]. The second type is a dicentric Xp;Yp translocation or a dicentric Xq;Yp translocation that produces a dicentric X;Y chromosome with a Y chromosome attaching to the Xp or Xq breakpoint at a Yp distal breakpoint such as 46,X,dic(X;Y)(p22.3;p11.2) [3] with a partial deletion of Xp and a partial deletion of Yp on the dicentric X;Y chromosome, and 46,X,dic(X;Y)(q22;p11) [4] with a partial deletion of Xq and a partial deletion of Yp on the dicentric X;Y chromosome. The third type is an Xp;Yp translocation that produces a derivative X chromosome with a partial deletion of Xp and a partial duplication of Yp such as 45,X male or 46,XX male [5]. The fourth type is an Xq;Yq translocation that produces a derivative Y chromosome with a partial deletion of Yq and a partial duplication of Xq resulting in functional distal Xq

disomy such as 46,X,der(Y)t(X;Y)(q27.3;q11.2) [6]. The fifth type is an Xp;Yq translocation that produces a derivative Y chromosome with a partial deletion of Yq and a partial duplication of Xp resulting in functional distal Xp disomy such as 46,X,der(Y)t(X;Y)(p22.13;q11.23) [7] and 46,X,der(Y)t(X;Y)(p22.3;q11.2) [8]. The sixth type is an Xp;Yp translocation that produces a derivative Y chromosome with a partial deletion of Yp and a partial duplication of Xp resulting in functional distal Xp disomy and sex reversal such as 46,X,der(Y)t(X;Y)(p21.2;p11.3) [9]. The seventh type is an Xq;Yp translocation that produces a derivative X chromosome with a partial deletion of Xq and a partial duplication of Yp and hermaphrodite such as 46,X,der(X)t(X;Y)(q28;p11.31) [10].

Here, we present our experience of prenatal diagnosis and array comparative genomic hybridization (aCGH) characterization of a *de novo* X;Y translocation of 46,X,der(X)t(X;Y)(p22.31;q11.221) in a fetus with a female phenotype and short limbs on prenatal ultrasound.

A 37-year-old, gravida 3, para 1, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 47 years of age. Prenatal ultrasound at 17 weeks of gestation revealed a female fetus with a biparietal diameter (BPD) of 3.9 cm (17 weeks), an

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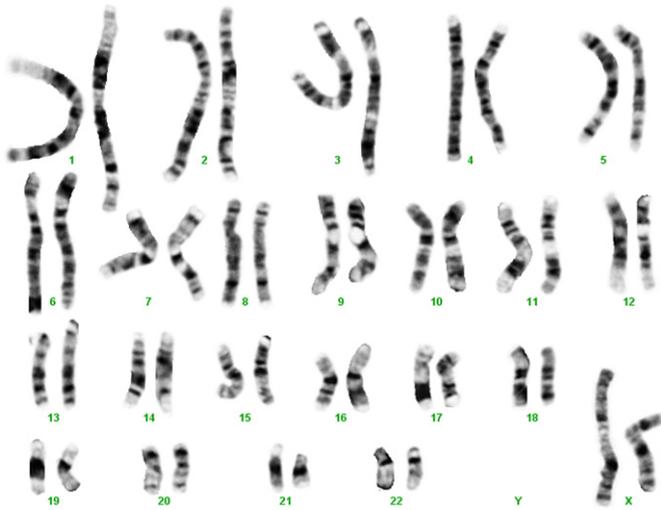


Fig. 1. A karyotype of 46,X,der(X)t(X;Y)(p22.31;q11.221).

abdominal circumference (AC) of 12.36 cm (18 weeks), and a femur length (FL) of 2.19 cm (16 weeks). Cytogenetic analysis of cultured amniocytes revealed a derivative X chromosome with an X;Y translocation involving the p arm of the X chromosome and the q arm of the Y chromosome (Fig. 1). The parental karyotypes were normal. Metaphase fluorescence *in situ* hybridization (FISH) analysis using Xp11.1-p11.21 specific probe RP11-431N15 (56,571,162–56,751,665 bp) and Y centromere specific probe DYZ3 (Vysis, Downers Grove, IL, USA) showed absence of the Y centromere indicating that the derivative chromosome was monocentric (Fig. 2). Molecular analysis of *SRY* gene revealed a negative finding in the

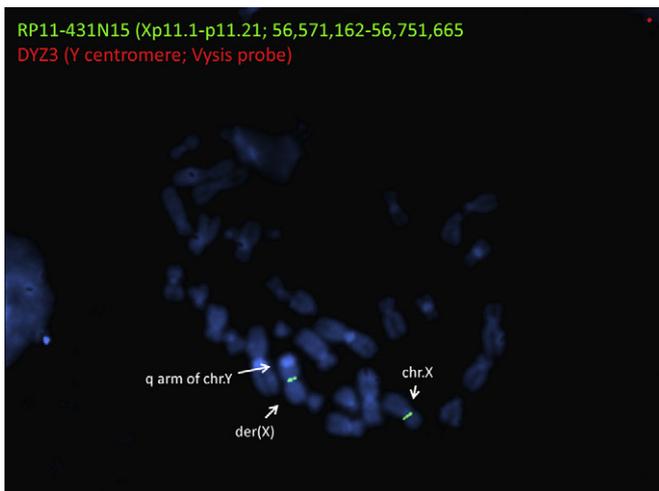


Fig. 2. Metaphase fluorescence *in situ* hybridization analysis using Xp11.1-p11.21 specific probe RP11-431N15 (56,571,162–56,751,665 bp; spectrum green) and Y centromere specific probe DYZ3 (spectrum red) shows absence of the red signal on the derivative chromosome X [der(X)].

cultured amniocytes. The breakpoints on Xp and Yq were precisely mapped by oligonucleotide-based aCGH CytoChip Oligo array (BlueGnome, Cambridge, UK). The aCGH results refined the breakpoint at 8,457,738 bp on Xp22.31 (UCSC hg18, NCBI build 36, March 2008) with an about 5.7-Mb deletion of Xp22.31→pter, and the breakpoint at 14,530,164 bp on Yq11.221 (UCSC hg18, NCBI build 36, March 2008) with an about 12.6-Mb deletion of Yq11.221→pter (Fig. 3). The fetal karyotype was 46,X,der(X)t(X;Y)(Xqter→p22.31::Yq11.221→qter) or 46,X,der(X)t(X;Y)(p22.31;q11.221) (Fig. 1). Prenatal ultrasound at 19 weeks of gestation revealed a BPD of 4.4 cm (19 weeks), an AC of 12.7 cm (18 weeks) and an FL of 2.5 cm (17 weeks). After genetic counseling, the parents elected to terminate the pregnancy. A 358-g fetus was delivered at 21 weeks of gestation with body length of 25 cm, a normal female external genitalia and shortening of the humerus and femur.

The present case had a partial duplication of Yq (Yq11.221→qter) and a partial deletion of Xp (Xp22.31→pter) encompassing the genes of *SHOX* (OMIM 312865), *ARSE* (OMIM 300180), *NLGN4X*, *VCX3A* (OMIM 300533), *STS* (OMIM 300747) and *KALI* (OMIM 308700). Since Yq11.2→qter does not contain the sex determining gene, the phenotype of patients with t(X;Y)(p22;q11) depends on the Xp deletion rather than Yq duplication.

The majority of female patients with 46,X,der(X)t(X;Y)(p22;q11) are phenotypically normal except short stature, whereas male patients with 46,Y,der(X)t(X;Y)(p22;q11) always have phenotypic abnormalities because of nullisomy of partial Xp and may manifest, due to nullisomy of the Xp region, short stature and dyschondrosteosis (related to *SHOX*), chondrodysplasia punctata (related to *ARSE*), hypogonadotropic hypogonadism with anosmia (related to *KALI*) and ocular albinism (related to *OAI*) [2,11–17].

Women with a microscopic or submicroscopic deletion of Xp encompassing the *SHOX* gene region have been known to be associated with the Leri-Weill dyschondrosteosis (LWD, OMIM 127300). LWD is characterized by dyschondrosteosis, short stature, mesomelic shortening of the long bones and bilateral Madelung deformity of the wrists. LWD can be caused by point mutations or haploinsufficiency of the *SHOX* gene [18–21]. The *SHOX* gene is involved in skeletal abnormalities and other stigmata in Turner syndrome such as short stature, cubitus valgus, genu varum, high-arched palate, micrognathia and sensorineural deafness [22]. LWD has been observed in patients with an X;Y translocation [14,17,23–27]. Joseph *et al* [28] reported prenatal diagnosis of 46,X,der(X)t(X;Y)(p22;q11) at amniocentesis because of an elevated level of maternal serum  $\alpha$ -fetoprotein, advanced maternal age and a previous child with trisomy 21, respectively in three pregnancies. In one pregnancy, Joseph *et al* [28] found that the limbs were at the short end of the normal range. The present case provides evidence that short limbs can be a second-trimester ultrasound feature of female fetuses with 46,X,der(X)t(X;Y)(p22;q11).

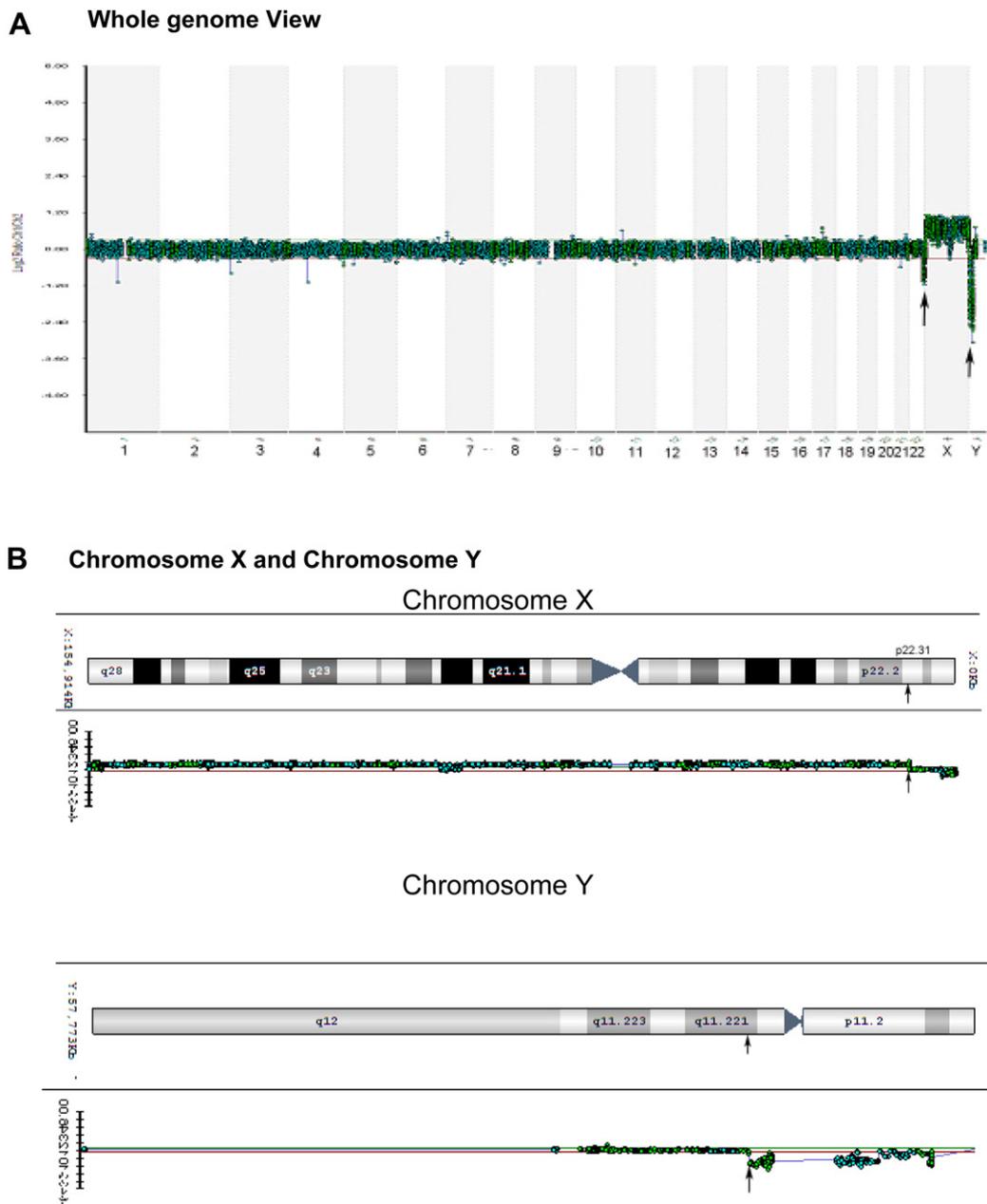


Fig. 3. (A) Oligonucleotide-based array comparative genomic hybridization shows Xp and Yp deletions (arrows) on the whole genome view; and (B) a breakpoint at Xp22.3 (arrow) on X chromosome and a breakpoint at Yq11.221 on Y chromosome.

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