



## Xp22.33 Deletion: A Cause of Fetal Demise in a Male Fetus

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### Abstract

We describe a pedigree in which a couple had one healthy boy and two pregnancies of male fetuses with fetal demise at 18 weeks, respectively 22 weeks of gestation. Both fetuses presented dysmorphic features at expulsion and were found to have an Xp22 deletion, encompassing 9 genes among which the SHOX gene. The mother carries this deletion and presents very mild phenotypic features. We believe this deletion is responsible for intrauterine demise in male fetuses.

### Introduction

Miscarriages occur in about 5 to 10% of all pregnancies. In approximately 50% of the cases a chromosomal anomaly is found to be the cause of the miscarriage. Unfortunately, in up to 50% of the cases the etiology remains unknown [1].

For couples with repetitive miscarriages, it is very important to find the underlying problem, in order to give a useful counseling, as their wish for a healthy child is not fulfilled yet and anxiety for another miscarriage grows.

From a genetic point of view, new perspectives are rising with the development of new techniques in cytogenetics, such as the CGH-array, especially in a prenatal setting. By using array-CGH an additional 5% of submicroscopic chromosomal rearrangements can be detected, enabling a correct diagnosis for a miscarriage that would otherwise be classified of unknown etiology.

In this case report we describe a pedigree in which a couple had one healthy boy and two pregnancies which ended in late miscarriages. These were pregnancies of male fetuses with fetal demise at 18 and 22 weeks of gestation. Both fetuses presented dysmorphic features and an Xp22 deletion, encompassing 9 genes among which the SHOX gene.

### Materials and Methods

After diagnosis of fetal demise in the second fetus, thorough examination of both mother and fetus was carried out, following the available guidelines.

**Personal and familial history**, with assessment of the pedigree and clinical examination of both fetus and parents were carried out.

**Radiological examination** involved prenatal ultrasound, a total skeletal X-ray, MRI en CT-scan of the fetus post-miscarriage.

**Pathological examination** of the fetus was performed subsequently.

**Karyotyping** was performed on cultured amniotic cells, obtained by a 10 ml amniotic fluid sample in a syringe. Chromosomal banding in metaphases was acquired by Giemsa staining. At least nineteen metaphases were analyzed.

**CGH-array** was performed with a 180k Agilent array. Only submicroscopical deletions/duplications of at least 100 kb, derived from 3 consecutive divergent reporters were reported. The reported positions and CNV information were based on Human Genome Build 36. Presumable benign CNV's were not reported.

**Fluorescence in situ hybridisation (FISH)** was performed on metaphase cells following the standard technique using the direct- marked subtelomeric-specific probes (ToTe/Vision probes- Abott Molecular Inc.).

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Figure 1:



Figure 2:



Figure 3:



Figure 4:



Figure 5:



Figure 6:

## Results

### Clinical case

A 26 year old woman was referred to the prenatal team because of intrauterine demise of her fetus. This was seen during routine second trimester ultrasound examination by her gynecologist. At that time it concerned a pregnancy of 22 weeks of gestation.

Pedigree examination revealed short stature in the patient (152 cm), her mother (150 cm) and maternal grandmother (140 cm). The grandmother had several miscarriages, but no detailed information was available. The patient has one younger healthy brother, who has no child wish yet. The couple has a healthy son, who is almost 3 years old and developing well. Clinical examination of both parents shows normal findings and stature for the father. Examination of

the mother, our patient, shows short but proportionate stature and discrete Made lung deformity of her wrists (Figure 1 and 2).

In our center an expertise ultrasound was performed and fetal demise was confirmed. It was a male fetus, who presented acrocrania due to distinct hydrocephaly and intracranial hemorrhage. Schizencephaly could not be totally excluded. Labor was induced and a male fetus was stillborn with following parameters: weight 495 g (P12-25), length 260 mm (P25), HC 210 mm (> p97), femur length 32 mm (p5), humerus length 30 mm (p5) and AC 190 mm (>p97).

At clinical examination the fetus was found to have several dysmorphic features. The face was round with a high forehead, telecanthus with narrow palpebral fissures, small nose with anteriorly rotated nostrils, smooth philtrum, short broad neck, small dysplastic ears, short but proportionate aspect of the limbs with chubby hands and a distended abdomen (Figure 3-5). Skeletal dysplasia was suspected and X-rays showed moderate shortening of the long bones, but no morphological anomalies of the skeleton, besides a subtle bell shaped thorax (Figure 6-8).

Subsequently a CT-scan and MRI were performed (Figure 1). CT-scan showed definite nuchal edema, flat nose, short long bones



Figure 7:

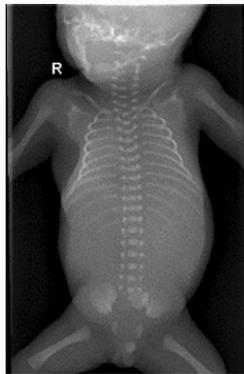


Figure 8:



**Figure: 9** Post Mortem Imaging a) Computed Tomography showing nuchal oedema and short long bones without any associated pathological pattern. MRI b) sagittal and c) coronal images show severe destructive ischemic and hemorrhagic lesions of the cerebral and cerebellar cortex.

without associated bulging nor pathological pattern. The fingers were quite slender. The MRI showed explicit anomalies of the brain, probably caused by several cerebral infarctions with associated hemorrhage in regions with porencephaly. Recent infarctions were described in the cerebellum. There were however no arguments for shizencephaly (Figure 9).

At pathological examination of the fetus, clinical and radiological

findings were confirmed. No other associated organ anomalies were found. Placental examination showed normal findings for the age of pregnancy.

### Genetic results

Prenatal conventional karyotyping on amniotic cells revealed 46, XY normal karyotype with G-banding in nineteen metaphases.

Array-CGH on amniotic cells revealed an aberrant male  $arrXp22.33(60701-2730700)x1; arr Xp22.33(2741300-3419600)x0$ . A 3.4 Mb terminal deletion of chromosome band Xp22.33 was thus detected. This terminal deletion was also found in the mother and confirmed by FISH technique. Consequently, we considered this 3.4 Mb Xp22.33 deletion as an inherited deletion from the mother, probably responsible for lethality in male fetuses.

### Discussion

In the present report we describe a pedigree marked by several miscarriages in females with short stature. Our patient was diagnosed twice with fetal demise in the second trimester of pregnancy, both times concerning male fetuses. At the time of the second miscarriage thorough examination was carried out and a 3.4 Mb Xp22.33 terminal deletion was found by array-CGH on amniotic cells. This region encompasses 9 genes, including the SHOX gene. Terminal Xp deletion leads to SHOX haplo insufficiency, and when it exceeds Xp22.33 it causes a variant of Turner syndrome in which gonadal function is preserved and short stature constitutes the major clinical feature [2]. Other Turner-like stigmata may be present, such as a high-arched palate, abnormal auricular development, cubitus valgus, genu valgum and short metacarpals. Heterozygous defects in the pseudoautosomal SHOX gene or deletion of the SHOX downstream regulatory domain are known to cause Leri-Weil Dyschondrosteosis (LWD) [3,4]. LWD is a dominantly inherited skeletal dysplasia characterized by short stature, mesomelia, and Madelung wrist deformity. Although the disorder occurs in both sexes, it is usually more severe in females, perhaps due to sex difference in estrogen levels. However, pubertal development and fertility are generally normal in both sexes with the disorder [3]. Deletion of this gene is unlikely to be responsible for all phenotypic features in the fetus, but can be correlated to the phenotype of the mother. Up to now there are no cases described in literature with fetal demise due to LWD. One of the other genes concerned in this deletion is the ARSE gene, in which mutations are responsible for Chondrodysplasia Punctata 1 (CDPX1). This is an X-linked recessive disorder characterized by failure to thrive, mental retardation, and atypical facies [5]. Dysmorphic features include short stature, depressed nasal bridge and hypoplasia of the distal phalanges, which is a distinctive feature. These features were all found in both fetuses. In previous reports describing families with CDPX1, fetal demise of male fetuses has been reported a few times. Male patients with deletion of both SHOX gene and ARSE gene have also been reported, having a severe but not a lethal phenotype [6]. Nevertheless, we believe that in this case the Xp22.33 deletion is probably responsible for the fetal demise, as it is giving rise to a contiguous gene syndrome with recognizable features of LWD and CDPX1 on one hand [7], but being lethal due to interactions with other genes included in the deleted region or perhaps epigenetic factors. Nevertheless, this case beautifully shows the difference in phenotypic feature expression between affected males and females for some genetic entities [7].

This couple was counseled and prenatal diagnosis and pre-

implantation genetic diagnosis was discussed. In a subsequent spontaneous pregnancy array-GCH was performed on chorionic villi sampling. The female fetus did not carry the deletion and showed normal evolution on consecutive ultrasound examinations.

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