

## CASE REPORT

### Inherited t(9;22) as the cause of DiGeorge syndrome: a case report

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#### Abstract

DiGeorge syndrome is associated with microdeletion of chromosome 22q11.2. Most cases occur sporadically although vertical transmission has been documented. We report a rare case of DiGeorge syndrome in an 8-year-old girl. Blood sample of the patient was cultured and harvested following standard procedure. All of the 20 cells analysed showed a karyotype of 45,XX,-22,t(9;22)(p23;q11.2). Cytogenetic investigation done on the patient's mother revealed that she was the carrier for the translocation. Her karyotype was 46,XX,t(9;22)(p23;q11.2). Fluorescence *in situ* hybridisation (FISH) analysis using TUPLE1 and N25 (Vysis, USA) probes showed deletion of the 22q11.2 region in the patient, confirming the diagnosis of DiGeorge syndrome. FISH analysis showed no deletion of the region in the mother.

**Keywords:** DiGeorge syndrome, deletion 22q11.2, fluorescence *in situ* hybridisation (FISH), t(9;22)

#### INTRODUCTION

DiGeorge syndrome (DGS) is characterised by neonatal hypocalcemia which may present as tetany or seizures, due to hypoplasia of the parathyroid glands and susceptibility to infection due to a deficit of T cells. A variety of cardiac malformations are also seen in particular those affecting the outflow tract. Learning disorders and developmental delay affect 70%-90% of individuals with DGS. Ninety-four percent of DiGeorge cases are *de novo* deletions and only a small percentage (<1%) have chromosomal rearrangements involving 22q11.2, such as a translocation between chromosome 22 with another chromosome.<sup>1</sup> In most cases, the deletion (del22q11) eliminates 3 Mbp of DNA encoding for approximately 30 genes.<sup>2</sup> 22q11.2 deletion is detected by using fluorescence *in situ* hybridisation (FISH) analysis.<sup>3,4,5</sup>

#### CASE REPORT

SY, an 8-year-old girl was referred to the Paediatric Clinic for learning disability. She was clinically dysmorphic with generally coarse facies. There was hypertelorism with down slanting palpebral fissures, a bulbous nose, low set ears,

long tapering fingers and she had a hypernasal speech. Other systemic examinations were normal. SY attended special school from Standard One. Her mother did not appear dysmorphic but was treated for an underlying psychiatric illness. A clinical diagnosis of DiGeorge syndrome was made and cytogenetic investigations were requested. FISH analysis confirmed that SY had microdeletion of 22q11.2 region. A blood sample of the patient's mother was taken for cytogenetic investigations. The father's sample was not available for the test.

For karyotyping, twenty metaphases spreads were analysed. FISH analysis using locus specific probes: TUPLE1 and N25 (Vysis, USA) were applied to detect the deletion on 22q11.2 region. Absence of orange-pink signal on one chromosome 22 indicates a deletion on the loci.

#### Cytogenetics

The patient has a karyotype of 45,XX,-22,t(9;22)(p23;q11.2). In addition to the translocation involving the long arm of chromosome 22 and the short arm of chromosome 9, monosomy of chromosome 22 was also seen in the karyotype (Figure 1).

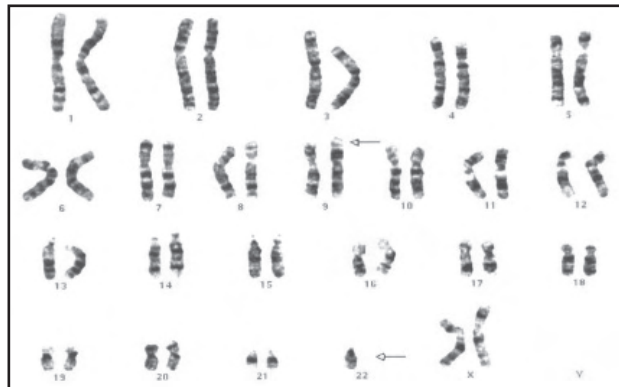


FIG. 1: A Giemsa banded karyotype of the patient shows a translocation of the long arm of chromosome 22 and the short arm of chromosome 9. Monosomy 22 is also seen in the karyotype (G-banding X1000)

The karyotype of the mother was 46,XX,t(9;22) (p23;q11.2). Translocation involving chromosomes 9 and 22 and partial monosomy of chromosome 22 was also identified (Figure 2).

Further analysis by FISH was then carried out on samples of both the patient and her mother. The purpose was to identify a deletion of the 22q11.2 locus in both subjects. Deletion of the loci was detected in the patient (Figure 3) but not in the mother (Figure 4).

**DISCUSSION**

DiGeorge syndrome (DGS) which is also known as velocardiofacial syndrome is caused by a submicroscopic chromosome deletion of band 22q11. It is associated with a disturbed development of the pharyngeal arches. DGS which affects approximately 1 in 4000 births, usually occurs sporadically.<sup>6</sup> Provided both

parents are phenotypically and genotypically normal, the recurrence risk in future siblings will be low.<sup>6</sup>

DGS associated with chromosomal rearrangements is however very rare; less than 1% of such cases has been reported.<sup>1</sup> In our report, conventional analysis i.e. karyotyping has revealed that the rearrangement in this patient was inherited from the phenotypically normal mother. Due to the translocation in the mother, unbalanced gametes may be produced during gametogenesis which results in recurrent miscarriage or birth of an abnormal child. Similar findings of unbalanced translocation involving chromosome 20;22 and 4;22 have also been reported in individuals which show features of DGS.<sup>7,8</sup> The risk to offspring depends on whether and how the chromosomal rearrangement interferes with the process of meiosis.<sup>6</sup>

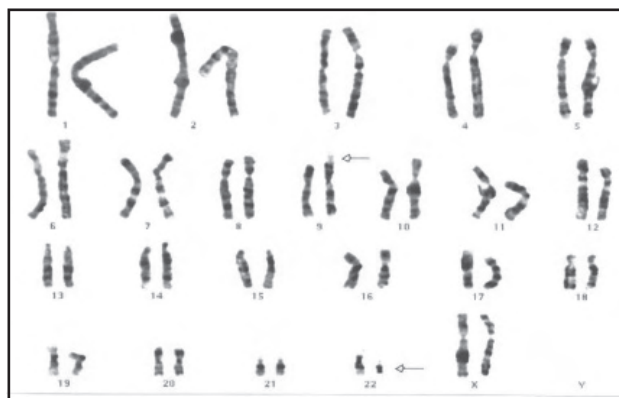


FIG. 2: A Giemsa banded karyotype of the mother shows a translocation between the long arm of chromosome 22 and the short arm of chromosome 9. Partial monosomy of chromosome 22 is also seen in the karyotype (G-banding X1000)

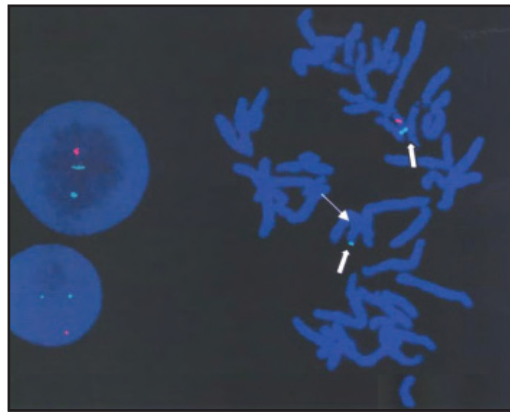


FIG. 3: Metaphase and interphase cells hybridized with LSI DiGeorge N25 region probe. Absence of orange-pink signal on one chromosome 22 (thin arrow) indicates deletions of the N25 locus at 22q11.2. LSI ARSA gene probe which maps at 22q13.3 acts as a control (thick arrows).

Theoretically, twelve possible chromosomal combinations can be produced in the gametes of a heterozygous individual with autosomal translocation. Most unbalanced combinations would produce such enormous genetic imbalance that the conceptus would be lost very early in pregnancy (occult abortion) or even fail to implant. Moderate imbalances would proceed to the stage of recognizable miscarriage or to late foetal death. Conceptuses with lesser imbalance may result in the birth of an abnormal child. Following the Pachytene-Diagram Model of Jabert *et al*, the mode of segregation in our patient was 3:1 segregation which gave rise to the tertiary monosomy 22.<sup>9</sup> Reports have shown that tertiary monosomy in a 45 chromosome conceptus is extremely rare.<sup>10</sup>

In our case, it is important to counsel the mother of her risks of having recurrent miscarriages or another abnormal child. In addition, prenatal testing such as amniocentesis, chorionic villus sampling or percutaneous umbilical cord blood sampling to detect chromosomal abnormality may be suggested to the mother in her subsequent pregnancies. It has been reported that the risk of miscarriage for a translocation carrier is in the range of 20% to 30%.<sup>11</sup>

This case illustrates the need to check for parental chromosomes in cases of chromosomal anomalies as there may be implications for future siblings. Both conventional karyotyping and FISH methods play an important role in providing a complete picture as clearly

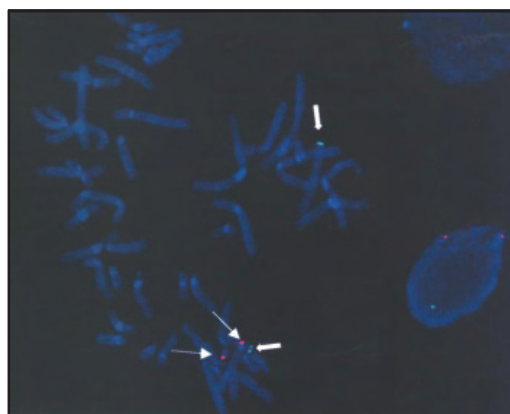


FIG. 4: Metaphase cells hybridized with LSI DiGeorge TUPLE1 region probe. Presence of two signals of orange-pink (thin arrows) indicates that the locus TUPLE1 is present but one is separated from chromosome 22. LI ARSA gene probe which maps at 22q13.3 acts as a control (thick arrows)

seen in this report. FISH provides a reliable enhancement to conventional cytogenetics. However, it cannot replace the gold standards of conventional chromosomal analysis as it cannot exclude other chromosomal aberrations for which the specific probe is not used.

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