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Correspondence to K A Fagan, Cytogenetics Laboratory, Mater Hospital, Waratah, NSW 2298, Australia.

Features of Turner's and DiGeorge's syndromes in a child with an X;22 translocation

MAXIMINA R PINTO*, ROSARIO PINTO LEITE*, AND AUGUSTA AREIAS†

*Cytogenetics Unit, Instituto de Genetica Medica Jacinto de Magalhaes; and †Maternidade Julio Dinis, Porto, Portugal.

SUMMARY We describe the clinical and cytogenetic findings in an infant who presented with the features of both Turner's and DiGeorge's syndromes associated with a unique translocation between chromosomes X and 22.

DiGeorge's syndrome (DGS) is a rare condition in which, despite some degree of variability, the clinical features usually include neonatal hypocalcaemia, defective cellular immunity, absent or hypoplastic thymus and parathyroid glands, cardiovascular anomalies, and a typical facies. Dysmorphic features include downward slanting palpebral fissures, ear anomalies, hypertelorism, and a short philtrum. Recently DGS has been shown to be

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FIG 1 Appearance of the proband.

associated with deletions involving the proximal long arm of chromosome 22.¹⁻⁵

Turner's syndrome variants caused by differing deletions of the short arm of the X chromosome have an incidence of 1:25 000 live births. The clinical features include short stature, webbed neck, cardiac defects, broad chest with widely spaced nipples, and transient lymphoedema.⁶

As far as we know this is the first case where both syndromes are present in the same infant.

Case report

CLINICAL FINDINGS

The proband was a female infant born at 38 weeks' gestation to young, healthy, unrelated parents. The couple had an older normal son and a previous male stillborn of unknown cause. The patient was delivered by caesarean section owing to fetal distress and hydramnios. At birth she weighed 3070 g (>50th centile), her length was 45 cm (<5th centile), and the head circumference was 35 cm (>50th centile).

She presented with microphthalmia, small, downward slanting eyes, choanal atresia, very low set, simple ears, a short neck with bilateral skin folds, a broad chest with widely spaced nipples, normal female genitalia, and generalised lymphoedema (fig 1). She was placed in a ventilator at birth and developed convulsions on the second day. Repeated infections led to neonatal septicaemia and subsequent death at 18 days of age.

Blood tests showed hypocalcaemia (1.75×10^{-3} mol/l), anaemia (Hb 8.5 g/l), leucopenia ($5000/\text{mm}^3$), neutropenia (33%), and thrombocytopenia ($80\,000/\text{mm}^3$).

FIG 2 Idiograms and GTG banding pattern of chromosomes X, 22, and t(X;22).

FIG 3 (a) Partial metaphase showing the X, 22, and t(X;22) with sequential GTG and CBG banding. (b) Inactive abnormal X chromosome (arrowed).

TABLE Enzyme activities in nmol/h/mg protein in cultured fibroblasts from the patient and in healthy controls.

Enzyme	Proband	Controls
β -galactosidase	479	259–684
α -iduronidase	7.8	15–22 (n=4)

CYTOGENETIC STUDIES

Chromosome analyses were performed on peripheral blood and fibroblast cultures according to standard techniques. GTG, RBG, and CBG banding showed a karyotype that was interpreted as 45,X,-X,-22,+t(X;22)(p21.3;q11.2) (figs 2 and 3). BrdU replication studies showed inactivation of the abnormal X in all 50 cells analysed.

Both parents had normal karyotypes.

ENZYME STUDIES

After identification of the cytogenetic abnormality, the activities of α -iduronidase, localised to 22q11 (HGM9),⁷ and β -galactosidase, localised to 3p21-cen (HGM9),⁷ were assayed in cultured fibroblasts from the patient using standard techniques (the second enzyme was assayed as a laboratory control). The results showed a normal activity for β -galactosidase but an activity of only 50% for α -iduronidase (table). Fibroblast cultures from the parents were not available for comparison.

NECROPSY

No thymus or parathyroid glands were found at necropsy. The lymph nodes showed a marked depletion in the T zone. There was a small accessory spleen. Mild adrenal hypoplasia was noted (both glands weighed 3.5 g). The ovaries showed normal infantile primary follicles with no evidence of dysgenesis.

Discussion

This female infant, investigated because of dysmorphic features, which included those typical of Turner's syndrome as well as other atypical features, was found to have an unbalanced chromosome translocation with loss of material from one X homologue and from a chromosome 22. After identification of the karyotype, the atypical features were retrospectively consistent with DiGeorge's syndrome, which has been localised to 22q11 (HGM9).⁷ The laboratory findings supported this diagnosis, which was eventually confirmed by necropsy findings.

Cytogenetically, it was not easy to assess the extent of the loss of material from either chromo-

some. The finding that α -iduronidase activity was only half of the normal value suggests that one of the alleles coding for this enzyme is included in the deletion and that the breakpoint on 22 is therefore distal to q11 (the localisation of the α -iduronidase gene). Unfortunately, previous reports on deletion of 22q11 and DGS do not mention α -iduronidase activity. In fact, it may prove useful to measure such activity in all cases suspected of DGS with or without the microscopically visible deletion.

It could be argued that the clinical features of DGS and the reduced α -iduronidase activity are a consequence of the spreading of inactivation from Xp onto 22 and does not necessarily imply a deletion of 22q. This seems unlikely, however, since no chromosome 22 C band positive centromere was observed on the aberrant X.

On the abnormal X chromosome it appears that the whole, or at least most of band p21 is present. Based on the adrenal hypoplasia (AHC) found at necropsy, it is tempting to assume that the breakpoint involved the region p21.2 and p21.3, to which the AHC gene has been assigned (HGM9).⁷ This would explain an X linked condition in a female, implying that the patient's mother is a carrier for this condition and that the chromosomal rearrangement was therefore a paternal meiotic event.

From these observations the AHC gene is likely to be located on distal p21.3.

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Correspondence to Dr Maximina R Pinto, Cytogenetics Unit, Instituto de Genetica Medica Jacinto de Magalhaes, Praca Pedro Nunes 74, Porto, Portugal.