

# Two cases of deletion 5p syndrome: one with paternal involvement and another with atypical presentation

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## ABSTRACT

**We report two cases of deletion 5p or cri du chat syndrome (CdCS) with different presentations and risks of transmission: one case with paternal chromosome 5 involvement and another, a *de novo* case with atypical clinical presentation. Cytogenetic analysis was performed on the two cases and their parents. GTG-banded karyotype analysis of Cases 1 and 2 revealed abnormal 46,XY,del(5)(p13-15) male karyotypes. For Case 1, the mother showed normal female karyotype while the father showed an abnormal karyotype involving a balanced translocation 46,XY,t(5;10)(p13;p15). For Case 2, however, both parents showed a normal karyotype pattern. In Case 1, the clinical features, particularly the distinct facial phenotype in combination with a characteristic cat-like cry and hypotonia, aided in the diagnosis at birth and the karyotype analysis was resolute. The boy in Case 2 presented with atypical clinical features. Even though this patient had multiple syndromic features, the typical high pitched cat-like cry was not prominent. Instead, the patient manifested persistent stridor (from day three of life), which might have prevented the clinician from suspecting CdCS at birth. However, when this patient was presented at seven months of age for cytogenetic analysis, a confirmatory diagnosis of CdCS was established. For children with congenital abnormalities, an early clinical diagnosis confirmed through cytogenetic and molecular investigations, is important for providing personalised diagnostic and prognostic evaluation, and also for genetic counselling on the reproductive risk, particularly for patients with parental chromosome translocation involvement.**

**Keywords:** cri du chat syndrome, deletion 5p syndrome, paternal chromosome 5 involvement

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## INTRODUCTION

Deletion 5p syndrome (cri du chat syndrome [CdCS]) is considered the commonest autosomal deletion syndrome resulting from variable hemizygous deletions in the short arm of human chromosome 5 (5p). It has a prevalence of one in 15,000 to one in 50,000 live births.<sup>(1,2)</sup> The characteristic cat-like cry is a diagnostic feature of CdCS, apart from other clinical features.<sup>(2)</sup> About 85% of the 5p deletions are *de novo*, whereas 10%–15% of CdCS cases are familial, with the overwhelming majority due to parental translocations. We report two cases from Malaysia—one familial case with paternal chromosome 5 involvement, and the other, a *de novo* case with an unusual presentation.

## CASE REPORTS

### Case 1

A Malay boy presented to the Hospital Universiti Sains Malaysia (HUSM) with multiple syndromic features associated with peripheral cyanosis at day two of life. He was born full-term, with a birth weight of 2.5 kg and suffered birth asphyxia due to prolonged labour. The proband is the first child of a non-consanguineous second marriage of apparently healthy Malay parents (father 40 years, mother 29 years of age). Their children from previous marriages were all in good health. The cat-like cry was prominent, including the other syndromic features such as microcephaly, micrognathia, flattening of occiput, long philtrum, high-arched palate, hypertelorism, low set ears, rocker-bottom feet, small contracted pelvis, transverse palmar crease, short-webbed neck and widely-spaced nipples. We followed-up with this patient at 13 months of age, and noted a gross development delay (weight 5.2 kg, height 66.3 cm and head circumference 38.7 cm). He could neither walk nor stand up, and was incapable of speech.

### Case 2

A full-term Malay boy, born as a first child of non-consanguineous parents, with a birth weight of 2.8 kg and a good Apgar score, was admitted to HUSM for persistent stridor at day 27 of life and was treated as laryngomalacia. There was no prominent dysmorphic

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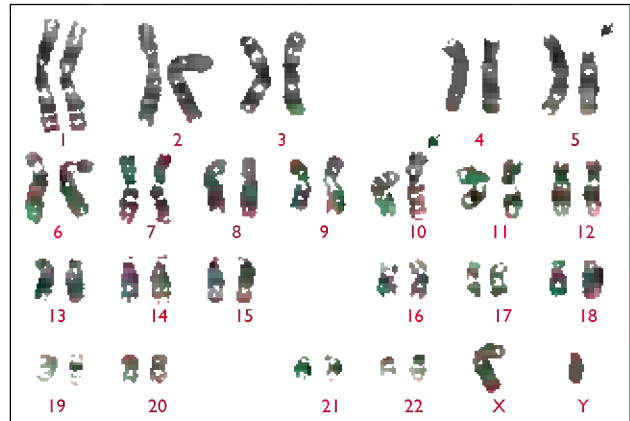
feature noted during this admission. At seven months of life, he was evaluated for failure to thrive, and he was also noted to have multiple syndromic features, such as triangular facies, hypotelorism, flat occiput, low-set ears and hypotonia. Currently, at one year of age, he suffered growth and mental retardation with head circumference 37.6 cm, weight 4.7 kg and height 65 cm.

Cytogenetics analysis was performed on the two cases and their parents at the Human Genome Centre, Universiti Sains Malaysia, employing standard cytogenetic procedures and karyotyped following ISCN (1995). GTG-banded karyotype analysis of Cases 1 and 2 revealed an abnormal male with 46,XY,del(5)(p13–15) karyotype. For Case 1, the mother showed normal female karyotype, while father showed an abnormal karyotype involving a balanced translocation 46,XY,t(5;10)(p13;p15) (Fig. 1). For Case 2, both parents showed a normal karyotype pattern.

## DISCUSSION

In our reported Case 1 and in other reported cases of CdCS, the clinical features, in particular the distinct facial phenotype in combination with a characteristic cat-like cry and hypotonia, led to the suspicion of such a diagnosis from the time of birth. The karyotype analysis on the peripheral blood was resolute. But in our reported Case 2, the child presented with atypical clinical features. Even though the patient had multiple syndromic features, such as triangular facies, flat occiput, low-set ears, hypertelorism and hypotonia, the typical high-pitched cat cry was not prominent. Instead, the patient manifested persistent stridor (since day three of life), which might have prevented the clinician from suspecting the CdCS at birth. This patient was presented only at seven months of age for cytogenetic analysis. For the children with congenital abnormalities, the clinical diagnosis should be confirmed as soon as possible, with cytogenetic and molecular investigations to provide more personalised diagnostic and prognostic evaluation, which may be helpful for rehabilitative and educational interventions.

Some CdCS patients may have deletion of the entire 5p. However, the pertinent region for the clinical phenotype involves the critical region 5p15.2. The high-pitched cat-like cry maps to 5p15.3 while the remaining features map to a small region of 5p15.2. It is estimated that about 100 genes reside in this region. The gene hTERT (human telomerase reverse transcriptase), the catalytic subunit of telomerase enzyme, is located on the deleted 5p15.33 region and loss of one copy of hTERT has been suggested as a cause or contributing factor of CdCS.<sup>(3)</sup> In a study of ten CdCS patients, Zhang et al demonstrated concomitant deletion of hTERT allele in



**Fig. 1** Chromosomes of the father of the Case 1 patient shows an abnormal karyotype, 46,XY,t(5;10)(p13;p15), involving a balanced translocation (arrows).

all ten patients. They concluded that hTERT is limiting and haploinsufficient for telomerase maintenance in humans *in vivo*. The hTERT deletion may be the one genetic element contributing to the phenotypic changes in CdCS. Their findings also suggested that hTERT is strictly required for normal cell growth and development in humans.<sup>(3)</sup>

It is unclear as to what extent the loss of hTERT allele contributes to the clinical features of CdCS. During early stages of embryonic development, hTERT and telomerase are commonly activated to prevent telomerase attrition so that high cellular proliferation capacities necessary for organ growth are maintained.<sup>(4)</sup> Insufficient or suboptimal hTERT expression resulting from the hTERT deletion in CdCS may affect normal foetal development. According to Mainardi et al, growth retardation and mental deficiencies observed in CdCS patients could be attributable to accelerated telomerase shortening during early development.<sup>(5)</sup> It is also possible that haploinsufficiency for telomerase stabilisation leads to premature grey hair and small testes with spermatogonia, as well as other related conditions in adult patients with CdCS. However, it should be emphasised that deletion of hTERT allele could not explain all characteristics of CdCS. Concomitant loss of other genes at the end of the 5p region also plays a crucial role in the development of CdCS.

Deletions that do not include 5p15.2 and 5p15.3 present varying clinical phenotypes from severe mental retardation and microcephaly to clinically normal. The increased severity of dysmorphism and developmental delay have been reported to be corresponding to the increased size of deletion. In both the cases reported here, the deletion was identified as deletion at 5p13-15. This deletion corresponded to the severity of clinical findings and the anticipation of profound mental retardation in these patients. About 85%–90% of the

CdCS patients have a *de novo* deletion of the short arm of chromosome 5, while 5%–10% of cases are due to unbalanced segregation of a parental translocation<sup>(6-8)</sup> and only about 5% of deletions are due to a recombinant from a parental inversion of chromosome 5,<sup>(2)</sup> mostly of paternal origin.<sup>(5)</sup> Case 1 reported here is a familial case due to unbalanced segregation of paternal translocation 46,XY,t(5;10)(p13;p15). The father was clinically and mentally normal because of the balanced translocation, but mental subnormality is expected to be expressed in the child as he grows older. The reproductive risk for carriers of translocations involving 5p, as defined by evaluation of personal and reviewed data from 54 pedigrees, has been reported to range from 8.7%–18.8% with both genders having a similar risk.<sup>(5)</sup> Early diagnosis is important for a correct evaluation of medical problems and for genetic counselling on the reproductive risk, particularly to identify patients with a deletion caused by familial rearrangement, which has a higher recurrent risk.

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