Published in final edited form as:

Hum Genet. 1996 June ; 97(6): 802–807. doi:10.1007/bf02346193.

Familial double pericentric inversion of chromosome 5 with some features of cri-du-chat syndrome

Sheryl A. Goodart,

Department of Biochemistry and Molecular Biology, Thomas Jefferson University, 233 S. 10th Street, Philadelphia, PA 19107, USA

Merlin G. Butler,

Departments of Pediatrics, Pathology and Orthopedics, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

Joan Overhauser

Department of Biochemistry and Molecular Biology, Thomas Jefferson University, 233 S. 10th Street, Philadelphia, PA 19107, USA

Abstract

Fluorescence in situ hybridization analysis was performed to characterize a complex pericentric inversion involving chromosome 5 in a mother and son. The mother had hypertelorism, epicanthal folds, and mild mental deficiency while the son had additional anomalies that have been observed in patients with cri-du-chat syndrome. Both individuals were found to have an identical double pericentric inversion [inv5(p15.1q31(inv5(p14q12)))]]. Neither inversion breakpoint mapped near the chromosomal regions implicated in the cri-du-chat syndrome. The phenotype of the son suggests that the inversion process may have affected the expression of some of the cri-du-chat syndrome genes, suggestive of a genomic imprinting or penetrance effect.

Introduction

Cri-du-chat syndrome is one of the more common deletion syndromes, with an incidence of 1 in 50000 live births. This syndrome is typically associated with a deletion of the short arm of chromosome 5 and the clinical features include a high-pitched monochromatic cry, microcephaly, hypertelorism, a round face, hypotonia, and severe psychomotor and mental retardation (Lejeune et al. 1963; Niebuhr 1978a, b; Carlin 1990). Recently, two separate critical regions have been delineated that, when rendered hemizygous, correlate with the disease phenotype (Overhauser et al. 1994). A deletion of 5p15.3 results in the manifestation of the cat-like cry from which the syndrome derived its name (Gersh et al. 1995), while a deletion of 5p15.2 results in the presentation of the other major clinical features of the syndrome (Goodart et al. 1994).

Pericentric inversions are among the most frequent chromosomal rearrangements with a frequency of 1–2% (Kaiser 1984; Mattina et al. 1989) and involve all chromosomes (de la

Chapelle et al. 1974; Kaiser 1984). While most pericentric inversions do not result in an abnormal phenotype, the presence of the inversion usually leads to an increased incidence of reproductive failure, stillbirths or congenital anomalies in live births due to recombinant events leading to duplications and deletions of chromosome material.

In this report, we describe a complex rearrangement involving chromosome 5 in a mother and son. The mother is mildly affected, while the son has features suggestive of the cri-du-chat syndrome. Extensive fluorescence in situ hybridization (FISH) experiments were performed to determine the nature of the rearrangement as well as to determine a cytogenetic reason for the clinical phenotype present in the son. No differences in the rearranged chromosome 5 could be detected between the mother and son.

Materials and methods

Cytogenetic analysis and cell line establishment

Standard cytogenetic protocols were followed for G-banding of prepared prometaphase chromosomes from stimulated peripheral blood lymphocytes (Verma and Babu 1989). Lymphoblastoid cell lines were established from whole blood according to standard procedures.

Fluorescence in situ hybridization

Although the initial interpretation was a simple pericentric inversion, the banding pattern was suggestive of a more complex re-arrangement. To determine the nature of the rearrangement, numerous FISH experiments were performed using DNA probes that had been previously mapped to chromosome 5. Emphasis was placed on 5p markers because of overlap of the clinical features in our patient with the cri-du-chat syndrome. DNA probes that had been mapped to distinct regions of 5p using a somatic cell hybrid deletion mapping panel were used (Overhauser et al. 1994). The location of these markers with respect to the cri-du-chat critical regions have been previously determined (Goodart et al. 1994; Gersh et al. 1995). Yeast artificial chromosome (YAC), lambda phage, and cosmid clones that had been previously mapped to distinct regions of 5p (Goodart et al. 1994; Overhauser et al. 1994; Gersh et al. 1995) were used as probes for FISH analysis. In addition, cos-mid clones mapping to different regions of 5q that have been described by (Takahashi et al. 1993) were provided by the Human Genome Center at the University of California, Irvine for additional mapping studies.

FISH analysis was performed using chromosome spreads prepared from both peripheral blood and lymphoblastoid cell lines. The probes were labeled with either biotin or digoxigenin by nick translation using the appropriate labeled dNTP and a Bionick kit (Bethesda Research Laboratories). An alpha-satellite probe D5Z2/D1Z7/D19Z3 (Oncor), which hybridizes to the centromere of chromosomes 1, 5, and 19, was simultaneously hybridized with the chromosome 5-specific probes. Hybridization was performed as previously described (Boghossian-Sell et al. 1994). Briefly, 400 ng of labeled probe was hybridized to prepared chromosomes in the presence of 5 ng sonicated salmon sperm DNA and 4.5 μ g of human Cot-1 DNA in 50% formamide, 1 $\times$ SSC, and 10% dextran sulfate.

After overnight hybridization at 37° C, the slide was washed in a series of three washes: (1) 50% formamide, 2 × SSC at 4°C; (2) 1 × SSC at 42° C; and (3) 0.1 × SSC at 65° C. Detection of the probe was performed with either fluorescein isothiocyanate (FITC)-labeled avidin for biotin-labeled probes or a mixture of FITC-labeled avidin and rhodamine-labeled avidin for two-colored FISH. Chromosomes were counterstained with propidium iodide for biotin-labeled probes or 4',6-diamidino-2-phenylindole (DAPI) for two-colored FISH. Photographs were taken with Kodak Ektachrome 100 film. A minimum of 30 spreads was analyzed for each FISH experiment.

The whole chromosome painting system (Bethesda Research Laboratories) was used according to the manufacturer's instructions.

Case report

This is a 6-week-old white male presenting with dysmorphic features. He weighed 3430 g (60th%) and was 49.5 cm (40th%) at birth and was born at 38-weeks gestation to a 23-year-old G₃P₀₀₃ single white female by vaginal delivery but with feet presentation. He was hospitalized for 1 week due to jaundice and hypoglycemia. The pregnancy history was unremarkable but a kidney infection was noted during the pregnancy and resolved after treatment. The mother did not report a history of smoking, alcohol or illicit drug use during the pregnancy. A poor weight gain was noted while on regular formula (3–4 ounces every 4 h) and multiple minor anomalies were seen, thus the reason for referral for a genetics evaluation.

At 6 weeks of age his height was 53 cm (15th%), weight 3.3 kg (< 3rd%), head circumference 38 cm (40th%), inner canthal distance 2.5 cm (90th%), outer canthal distance 6.2 cm (30th%), ear length 3.4 cm (30th%), mid-finger length 2.7 cm (30th%), and hand length 6.8 cm (50th%). Prominent features included down-slanting palpebral fissures, downturned corners of the mouth, epicanthal folds, telecanthus, prominent occiput, small external auditory canals, strabismus, short up-turned nose, prominent-appearing forehead, transverse palmar simian crease of left hand, a weak cry, hypotonia, and failure to thrive.

A karyotype was obtained from peripheral blood cells and a complex rearrangement was found. The karyotype was interpreted as 46,XY, inv(5)(p15.2q21), although the G- banding was suggestive of a more complex rearrangement.

Chromosome studies of the parents were then performed and the mother appeared to have the same complex rearrangement of chromosome 5. There was no evidence of mosaicism in the mother. The family history was remarkable in that the mother had a similar facial appearance (e.g., hypertelorism, epicanthal folds) and mild learning impairment (she graduated from high school but required special education classes). The mother did not have strabismus. Other facial features seen in the son, such as eye-slanting and prominent-appearing forehead, were absent. No simian creases were observed. No information was available with regard to an unusual cry at birth. There were no miscarriages, other birth defects, or consanguinity. Chromosome studies of the maternal grandmother were normal

but the paternal grandfather was not available for analysis. Figure 1 shows partial karyotypes of the mother and proband.

The child was reevaluated at 15 months of age, when he appeared well nourished and well developed and was being cared for by foster parents. He began to crawl by 1 year of age, walking at 15 months, and had a vocabulary of approximately ten words. His height was 82.5 cm (75th%), weight 12.4 kg (75th%), head circumference 49 cm (75th%), inner canthal distance 3.5 cm (> 95th%), outer canthal distance 7.1 cm (40th%), ear length 4.8 cm (40th %), mid-finger length 4 cm (50th%), and hand length 9.1 cm (30th%). Prominent features included those observed at 6 weeks of age but, in addition, a flattened nasal bridge, round-appearing face, overfolding of the right ear, dolichocephaly with ridging of the sagittal sutures, right accessory nipple, and diastasis recti (Fig. 2). Significant negatives included no heart murmur, no cutaneous lesions or ear tags, and no cryptorchidism or hernias.

Results

To determine whether the son had a different chromosomal rearrangement than the mother that could not be detected using high resolution G-banding, extensive FISH analysis was performed.

Lymphocytes from the mother and child were immortalized with Epstein-Barr virus (EBV). The mother's lymphoblasts were first examined by FISH using whole chromosome 5 painting probes to determine whether her rearranged chromosome 5 was completely of chromosome 5 origin and to determine whether she had a cryptic translocation. As shown in Fig.3A, both chromosome 5 homologues hybridized along the entire length of the chromosome. Furthermore, hybridization to other chromosomes could not be detected, ruling out a cryptic translocation. Similar analysis of the child's chromosome gave identical results.

Because of the clinical features suggestive of the cri-du-chat syndrome present in our patient, a YAC clone that spans the 5p15.2 cri-du-chat critical region (CDCCR) and several cosmid clones that map within this region were used as probes in FISH analysis (Goodart et al. 1994). The results using metaphase spreads derived from both the mother and the son were identical. All of the probes mapping to the CDCCR as well as probes mapping to 5p15.3 and part of 5p15.1 hybridized to the telomeric end of the long arm of the derivative 5 chromosome as shown in Fig. 3B. Probes that mapped to the proximal portion of 5p 15.1 and the distal half of p14 (D5S16, D5S758, D5S796, D5S28), hybridizing to the short arm of the derivative 5 chromosome, are shown in Fig. 3C. DNA probes from the proximal portion of p14 and p13 mapped to the centromeric portion of the long arm of the derivative chromosome 5, as shown in Fig. 3D. None of the 5p probes used were deleted or duplicated. Because of the presence of 5p material in three different locations, the results suggested that multiple chromosomal rearrangements were present, as had been suggested by the banding pattern.

To determine the nature of the rearrangement, additional FISH experiments were performed using the cosmids mapping to the long arm of chromosome 5. Cosmids were identified that

mapped to the distal portion of the short arm, the middle portion of the long arm, and the proximal portion of the short arm of the rearranged chromosome 5 (data not shown). One inconsistency with previously reported mapping data (Takahashi et al. 1993) was found. Two-color FISH using cCI5–16 and cCI5–23 revealed that cCI5–16 mapped distal to cCI5–23 on the normal chromosome 5, thus cCI5–16 mapped more telomeric than the reported location in q22.

Based on the physical mapping of the markers, it was determined that the rearranged chromosome 5 consisted of two pericentric inversions, a smaller inversion with breakpoints at p14 and q12, and a larger inversion with breakpoints at p15.1 and q31. The final karyotype present in both the mother and the son was determined to be inv(5) (qter→q31::p15.1→p14::q12→p14: :q 12-q31 : :p 15.1 →pter). An ideogram of the rearranged chromosome is shown in Fig. 4.

Discussion

A majority of pericentric and paracentric inversion genotypes are accompanied by a normal phenotype. These inversions are often found due to a reproductive failure, often characterized by numerous spontaneous abortions (D'Alessandro et al. 1991; Bianchi et al. 1992; Haagerup and Hertz 1992; Lindberg et al. 1992; Boyd et al. 1994). Inversions are also found when karyotyping is performed because of advanced parental age (Chodirker et al. 1992; Haagerup and Hertz 1992) or because of the presence of congenital malformations and/or dysmorphologies (Fryns et al. 1986; Kleczkowska et al. 1987; Lopez-Rangel et al. 1993; Schnur et al. 1993; Estop et al. 1994). The inversions found are usually singular in nature with only one inversion event resulting in the inverted chromosomes. Once an inversion has been identified, a study of the karyotypes of a whole family often reveals that the inversion has been inherited. Often the inversion is inherited without any adverse consequences as long as additional chromosomal aberrations have not occurred (Fryns et al. 1986; Kleczkowska et al. 1987; D'Alessandro et al. 1991; Bianchi et al. 1992; Chodirker et al. 1992; Haagerup and Hertz 1992; Lindberg et al. 1992; Boyd et al. 1994). However, children can inherit an inversion from a phenotypically normal parent without any other apparent chromosomal abnormality and be affected. In a study by Kleczkowska et al. (1987), 7.1% of liveborn pericentric inversion carrier offspring were affected in some way. Another study by the same group (Fryns et al. 1986) showed that 2% of the paracentric inversion carrier off-spring of phenotypically normal parents were affected. For some unknown reason, paracentric inversion inheritance carries a greater risk of an affected phenotype than pericentric inversions, even though no evidence can be found that any new deletion or duplication has occurred in either type of inversion. Although the mother of our study was mildly affected, her son presented with additional clinical findings that are also observed in patients with the cri-du-chat syndrome.

There have been several reported cases of an infant presenting with the cri-du-chat syndrome and a parent with a pericentric inversion (Dobbs et al. 1988; Chernos et al. 1992), however, in both cases, a meiotic recombination event resulted in an unbalanced karyotype with a 5p deletion.

The familial inheritance of the pericentric inversion presented in this report was discovered due to features (e.g., round face, relative hypertelorism, epicanthal folds, downturned corners of the mouth, cat-like cry) suggestive of cri-du-chat syndrome in our male child. FISH analysis using 5p- and 5q-specific probes was performed on both the child's and the mother's sample and no differences in the location of the probes between the two samples were observed. However, because probes encompassing all of 5p and 5q were not used, we cannot completely rule out the possibility that the child may have a small deletion or rearrangement not present in the mother that is not detected by the DNA probes used in this study. It was originally postulated that the child's phenotype was due to an undetectable submicroscopic deletion not present in the mother. Such a deletion in the CDCCR would be consistent with the cri-du-chat phenotype, however, extensive analysis using probes known to map within the CDCCR as well as additional probes mapping adjacent to the CD-CCR did not detect such a deletion.

This report is another example of a rare case of an inherited pericentric inversion in an affected child. The pattern of inheritance is consistent with a possible imprinting effect with the child, who presented with additional clinical findings to the mother who carries the same apparent chromosome 5 rearrangement and who had epicanthal folds, relative hypertelorism, and a similar facial appearance when she was of comparable age. Although the maternal grandfather's chromosomes were unavailable for study, the normal karyotype and phenotype of the maternal grandmother suggests that the mother's inversion was either a de novo occurrence or was inherited from her father.

In a reported case where imprinting was clearly not the cause for a clinically affected offspring, an affected female child had a familial paracentric inversion of chromosome 7, but also presented with cardio-facio-cutaneous syndrome (Lopez-Rangel et al. 1993). In that case, the inversion was inherited from her grandmother through her mother. No loss or gain of chromosomal material could be detected in the affected child, but it was suggested that a submicroscopic deletion could be the cause for the syndrome phenotype in the affected child.

It is of interest to note that when the parental origin of deletions resulting in cri-du-chat syndrome was investigated, over 80% were of paternal origin (Overhauser et al. 1990). The reason for the increased incidence of paternal deletions is not clear. It is possible that there may be a genomic imprinting effect or a penetrance effect of at least some genes mapping within 5p15. This is further supported by the description of two-generation families with multiple members with deletions, where a subset of the individuals with a 5p deletion have clinical features (Bengtsson et al. 1990; Gersh et al. 1995). Another possibility for the clinical differences between the mother and her child is uniparental disomy of the chromosome 5 homologues in the child.

Familial inheritance of a pericentric inversion involving 5p have been previously reported (see Kaiser 1984 for a review). Of the nine cases reported, three were inherited with the appearance of clinical symptoms (Crawford and Mason 1973; Jacobs et al. 1975; Eberle et al. 1982), however, none had a phenotype remotely resembling cri-du-chat syndrome.

Although our patient had a weak cry, it was not a cat-like cry. Recent analyses of patients that presented with only the cat-like cry identified a region within 5p15.3 that is specifically associated with this clinical feature of the syndrome (Gersh et al. 1995). Furthermore, patients with an interstitial deletion of 5p that did not delete this region had all of the features of cri-du-chat syndrome except for the cat-like cry (Overhauser et al. 1994). Our patient has no disruption or deletion of 5p15.3, explaining the lack of the characteristic cat-like cry. However, many of the other features of the syndrome are present, suggesting that the maternal inheritance of the double paracentric inversion may affect the expression of genes that are also deleted in cri-du-chat syndrome.

Our report of a son with an inherited double pericentric inversion with the clinical features of cri-du-chat syndrome from a mildly affected mother with the same chromosome rearrangement suggests that mechanisms other than deletion of 5p material can lead to the appearance of features of the cri-du-chat syndrome. Thus, care will need to be taken when prognoses are made with regard to the inheritance of a supposedly innocuous chromosomal re-arrangements involving 5p.

Acknowledgements

This work was supported by NIH grant HG0237 to J.O.

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Fig.1A, B.

Partial karyotypes of a familial pericentric inversion. The chromosome 5 homologues are shown. **A** Mother; **B** son

Fig.2. Clinical photographs of the male proband at 15 months of age. Findings consistent with cri-du-chat syndrome include failure to thrive, hypotonia, epicanthal folds, down-slanting palpebral fissures, strabismus, and a simian crease

Fig.3A, B.

Fluorescence in situ hybridization (FISH) of the re-arranged chromosome. Metaphase spreads from the mother are shown. The *small arrow* points to the normal chromosome 5 and the *large arrow* points to the inv(5). **A** Whole chromosome 5 painting; **B** FISH with the centromeric probe and probes mapping to 5p15.3 (D5S725, D5S750, D5S752, D5S10, D5S794, D5S11); **C** FISH with the centromeric probe and a probe mapping to 5p15.1 (D5S758); **D** FISH with the centromeric probe and probes mapping to 5p14 (D5S711 and D5S700)

Fig.4.

Location of DNA probes on chromosome 5. An ideogram of chromosome 5 is shown on the *left*. The location of the DNA probes used in FISH experiments are shown on the *left*. The sites of the inversion breakpoints are also shown. An ideogram of the double inversion chromosome 5 is shown. The *arrows* point to the inversion breakpoints and the origin of each chromosome region is shown