49,XXXXY: a distinct phenotype. Three new cases and review

Jennifer Peet, David D Weaver, Gail H Vance

Abstract

Over 100 cases of 49,XXXXY syndrome have been published to date. Classic findings include radioulnar synostosis, hypogonadism, and mental retardation. The majority of reported cases have not distinguished the 49,XXXXY syndrome from Klinefelter syndrome (47,XXY), and these patients are frequently labelled as having Klinefelter syndrome or as being a "Klinefelter variant." Because of distinct clinical features, we delineate the 49,XXXXY syndrome as separate from Klinefelter syndrome, and emphasise the prevalence of congenital heart defects. We also report three new cases of 49,XXXXY syndrome and briefly discuss patient management.

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The 49,XXXXY syndrome was first reported in 1960 by Fraccaro *et al*¹ and represents a rare sex chromosome aneuploidy syndrome with an approximate incidence of 1 in 85 000 male births.² A 49,XXXXY karyotype is thought to arise from maternal non-disjunction during both meiosis I and meiosis II.³⁻⁶ Such successive non-disjunction theoretically produces an egg with four X chromosomes, which, when fertilised by a Y bearing sperm, results in an embryo with 49,XXXXY syndrome.³⁻⁶ Interestingly, the occurrence of this syndrome does not appear to be related to maternal age. Several suggestions have been made to account for the phenotype associated with a 49,XXXXY genotype, as well as for other X chromosome aneuploidies. Two prevalent theories for the abnormal phenotype include (1) increased dosage of active genes in regions which escape X inactivation, and (2) asynchronous replication of the extra X chromosomes.⁷⁻⁸ In either case, the amount/

timing of genes expressed on the X chromosome is altered.

The classic clinical findings reported in persons with a 49,XXXXY karyotype have included radioulnar synostosis, mental deficiency, and hypogonadism.⁹⁻¹¹ Because these findings are not distinctive from the clinical findings in Klinefelter syndrome, subjects with 49,XXXXY syndrome are often labelled as having Klinefelter syndrome (47,XXY) or as being a "Klinefelter variant". There are a few reports, however, which do make a point of differentiating this sex chromosome aneuploidy from Klinefelter syndrome.¹²⁻¹³ After reviewing published reports on 49,XXXXY and examining the three subjects reported in this paper, we have concluded that the 49,XXXXY syndrome should be classified separately from Klinefelter syndrome. People with 49,XXXXY syndrome have characteristic facial features, particular habitus, multiple skeletal anomalies, cardiac defects, genital abnormalities, variable degree of mental impairment, and speech problems apart from those classically seen in Klinefelter syndrome.

Case reports

CASE 1

Case 1 (Fam No 87398), now a 3½ year old white male, was referred to the medical genetics service as a neonate following postnatal identification of a 49,XXXXY karyotype. He was born by caesarean section to a non-consanguineous, 23 year old, G(2)P(1)Ab(1) mother and a 26 year old father. The pregnancy reportedly was complicated by oligohydramnios and intrauterine growth retardation. Apgar scores were 7 at one minute and 8 at five minutes. Length and weight were <5th centile and OFC was greater than 2 SD below the mean (table 1). On examination after birth there were upward slanting palpebral fissures, telecanthus, prominent maxilla, bilateral clinodactyly of the 5th fingers with converging

Table 1 Measurements of the three patients reported here

Case 1	Case 2	Case 3
Birth	Birth	Birth
Wt 1880 g (<5%)	Wt 3450 g (50%)	Wt 2380 g (<5%)
Ht 43.18 cm (<5%)	Ht 48.26 cm (3-10%)	Ht 47 cm (<5%)
OFC 30.48 cm (<-2SD)	OFC N/A	OFC 31 cm (<-2SD)
3 mth	1 y	1½ y
Wt 4.06 kg (<5%)	Wt 9.37 kg (10-25%)	Wt 7.2 kg (<3%)
Ht 56 cm (3-10%)	Ht 73.5 cm (10-25%)	Ht 73 cm (<3%)
OFC 37 cm (<-2SD)	OFC 45 cm (<-2SD)	OFC 45 cm (<-2SD)
2½ y	14½ y	
Wt 9.9 kg (3%)	Wt 48.4 kg (25-50%)	
Ht 86 cm (25-50%)	Ht 158.7 cm (25-50%)	
OFC 44.6 cm (<-2SD)	OFC 54 cm (<-2SD)	

Wt=weight, Ht=height, OFC=occipitofrontal circumference.

Department of
Medical and Molecular
Genetics, Indiana
University School of
Medicine, 975
W Walnut Street,
Room IB-264,
Indianapolis,
IN 46202-5251, USA
J Peet
D D Weaver
G H Vance

Correspondence to:
Dr Vance.

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Figure 1 Case 1 aged 3 months.

Figure 2 Case 1 aged 2½ years.

creases, and prominent plantar creases running between the first and second toes bilaterally. There was no limitation to extension or rotation of the elbows. Genital abnormalities included a hypoplastic foreskin, scrotalisation of the penis, small testes, and bilateral hydroceles. Bilateral inguinal hernias and atrial and ventricular septal defects were detected at birth and subsequently repaired successfully. The family history included hyperthyroidism in the father resulting in thyroidectomy, and pectus carinatum in the mother and several of her uncles.

At the age of 3 months, inner and outer canthal distances (3 cm and 6 cm, respectively) were both between the 3rd and 25th centile and palpebral fissure lengths were both 1.5 cm

(greater than 2 SD above the mean). Additionally, plagiocephaly, a depressed nasal bridge, asymmetrical chest, and clinodactyly of the 2nd toes were noted (fig 1). At the age of 2 years 2 months, both his inner and outer canthal distances were above the 97th centile. Further examination showed an open metopic suture, facial asymmetry, underdeveloped orbital bones, intermittent strabismus, narrow but normally positioned ears, genu valgum, hyperextensible elbows, dermal hyperkeratosis, and generalised hypotonia (fig 2).

Chest radiographs showed stable cardiomegaly, levoscoliosis of the lower thoracic and upper lumbar spine, and a right cervical rib. The scoliosis, thought in part to be secondary to neuromuscular hypotonia, has gradually improved with time, decreasing from 20° at the age of 1 year to 6° at the age of 3.

Case 1 received physical, occupational, and speech therapy from the age of 6 months. Both hearing and vision have been tested and are within normal limits. Developmental assessment at several stages of his life indicated global developmental delay. At 6 months, the Bayley Scales of Infant Development rated the mental development index as <50 (age equivalent of 3 months). The behavioural age was assessed at 2.2 months using the Wisconsin Behavior Rating Scale, and between 0-3 months on the Rossetti Infant-Toddler Language Scale. At the age of 1 year, case 1 was evaluated to have gross motor skills at a 4 month level and fine motor skills at a 9 month level. Behavioural age was estimated at 7 months by the Wisconsin Behavior Rating Scale. At a chronological age of 36 months, the Peabody Developmental Motor Scales-Fine Motor Scale estimated an age equivalence of 15 months. Case 1 sat unassisted at 1 year and scooted and stood with help at 2 years of age. At 3 years, his only words were "Mama" and "Dada."

CASE 2

Case 2 (Fam No 54754) was last evaluated by us at the age of 15½ years. He is a white male who was born at term to a non-consanguineous, 22 year old, G(1)P(1) mother and a 24 year old father. The pregnancy was uncomplicated. Birth weight was 3450 g (50th centile) and length was 48 cm (3rd-10th centile) (table 1). Postnatally, he was found to have tetralogy of Fallot and subsequently underwent ventricular septal defect repair.

Case 2 was ascertained at 1 year of age by karyotype analysis for dysmorphic features and developmental delay. On examination at 1 year, his height and weight were at the 20th to 25th centile range for age and head circumference was greater than 2 SD below the mean (table 1). Physical features included plagiocephaly, low anterior hairline, right preauricular pit, short neck, abnormal palmar creases with bilateral fifth finger clinodactyly, small penis and testes, and delayed bone age. He was lost to follow up until the age of 14 years 2 months, during which time he was reported to have had frequent upper respiratory tract infections with multiple episodes of pneumonia. On physical

Table 2 A comparison of Klinefelter syndrome, 49,XXXXY syndrome, and the three new patients reported in this paper

	Klinefelter syndrome*	49,XXXXY syndrome†	Case 1	Case 2	Case 3
Intelligence	Normal/slightly reduced	Variable, low normal/MR	DD	DD	DD
Speech	Delay	Severe delay, absent	Absent	Absent	Absent
Stature	Average height $\geq$ 184 cm + (90-97%)	Average birth length 48.6 cm (25-50%), average adult height 181 cm (75-90%)	25-50%	25-50%	<3%
Skeletal abnormalities	Scoliosis, 5th finger clinodactyly	Many anomalies, delayed ossification, cartilage degeneration	Plagiocephaly, asymmetrical chest, levoscoliosis, right cervical rib, 5th finger clinodactyly, genu valgum	Plagiocephaly, elbow contracture, exaggerated lordosis, 5th finger clinodactyly, phalangeal hypoplasia, knee enlargement, genu valgum, pes planus	Trigonocephaly, hip subluxation
Cardiovascular defects	Increased incidence of MVP	14-20%‡§	ASD,VSD	TOF	PDA
Genital abnormalities	Small penis, small testes	Small penis, small testes	Hypoplastic foreskin, penile scrotalisation, small testes, bilateral hydroceles	Small penis, small testes	Normal genitalia

*Paulsen and Plymate.²⁹†Sijmons *et al.*²³‡Karsh *et al.*⁹§Linden *et al.*¹⁸

ASD=atrial septal defect, DD=developmental delay, MR=mental retardation, MVP=mitral valve prolapse, PDA=patent ductus arteriosus, TOF=tetralogy of Fallot, VSD=ventricular septal defect.

examination at 14 years 2 months, his outer canthal distance was 9.25 cm (75th-97th centile) and inner canthal distance was 3.75 cm (greater than 2 SD above the mean) with a palpebral fissure length of 2.75 cm (greater than 2 SD below the mean). Plagiocephaly, epicanthic folds, upward slanting palpebral fissures, prominent nasal bridge, broad and flat nose, left malar flattening, thick superior helices, right sided preauricular pit, mandibular hypoplasia, and micrognathia were noted. Skeletal abnormalities included a raised left shoulder, exaggerated spinal lordosis, contracture of the right elbow, bilateral 5th finger clinodactyly, thin tapering legs with genu valgum, thin and narrow feet with pes planus, and increased sandal gap between toes 1 and 2 bilaterally. Bilateral thenar eminence hypoplasia, clubbing of the finger and toenails, and small penis and testes were also observed. Dermatoglyphic examination showed bilateral hypoplasia of the distal flexion creases of the thumb and fingers with a bridged simian crease on the right palm. Sexual development was Tanner stage II. Both serum LH and FSH were markedly raised, indicating primary gonadal failure. X ray evaluation of the hands showed hypoplasia of the distal phalanx of each finger and a normal bone age. Testosterone therapy was refused by the parents.

Developmental delay of 6-8 months was assessed at a chronological age of 17 months. Case 2 crawled at 2 years and walked at 2½ years. He has severe speech impairment and communicates primarily by sign language. Hearing and vision are reported as normal.

CASE 3

Case 3 (Fam No 88585) is a 3½ year old, Amish, white male born by spontaneous vaginal delivery to a 25 year old, G(6)P(3)Ab(3) mother and a 27 year old father. Consanguinity was denied and the pregnancy was uncomplicated. Apgar scores were 8 at one minute and 9 at five minutes. Birth weight and length were at the 5th centile and his OFC measured greater than 2 SD below the mean (table 1). A patent ductus arteriosus was identified at birth and ligated at 15 months. He had pneumonia at 17 months.

He was referred to the medical genetics clinic following a peripheral blood karyotype report of 49,XXXXY. On examination at the age of 18 months, he was a small, pale, and shy child with a triangular shaped head. Both his height (73 cm) and weight (7.2 kg) were below the 3rd centile. Head circumference was greater than 2 SD below the mean (table 1). He had a prominent forehead, horizontal palpebral fissures with drooping lower lids, normal inner and outer canthal measurements, broad nasal bridge, downturned corners of the mouth, an inverted left nipple, and a sacral dimple. Subluxation of the right hip and eversion of the lower legs bilaterally were also noted. He had normal reflexes and truncal hypotonia. He sat independently but did not walk or speak.

Discussion

Reports describing subjects with 49,XXXXY syndrome have emphasised the "classic triad" of mental retardation, radioulnar synostosis, and hypogonadism.⁹⁻¹¹ We, and a few others before us, suggest that patients with 49,XXXXY syndrome actually have a more distinctive phenotype consisting of a characteristic facies and habitus, multiple skeletal anomalies, cardiac defects, genital abnormalities, a variable degree of mental impairment, and severe speech impairment (table 2). The clinical phenotype changes as the person grows to an adult. Therefore, certain features present in children are not necessarily present in adults and vice versa.

The characteristic facial appearance of a child with 49,XXXXY syndrome includes a full, round face, epicanthic folds, upward slanting palpebral fissures, ocular hypertelorism, telecanthus, a broad and depressed nasal bridge, and micrognathia.¹⁴⁻¹⁶ With age, the fullness of the face gives way to coarsening of features and prognathism becomes apparent.^{10 17 18} Patients may also have microcephaly, cleft palate, and abnormally shaped or positioned ears.^{12 18 19} All three of our patients have characteristic facial features and microcephaly (table 3). Cases 1 and 2 also have plagiocephaly and facial asymmetry. To our knowledge, plagiocephaly in association with 49,XXXXY syndrome has not been

Table 3 Facial features observed in the 49,XXXXY syndrome and the three reported patients

49,XXXXY	Case 1	Case 2	Case 3
Microcephaly	+	+	+
Full/round face (childhood)	+	?	–
Epicanthic folds	+	+	+
Upward slanting palpebral fissures	+	+	–
Ocular hypertelorism	+	+	+
Telecanthus	+	–	–
Broad, depressed nasal bridge	+	+	+
Micrognathia	+	+	+
Abnormally shaped/positioned ears	+	+	–

reported previously, and we found only one published case describing facial asymmetry.¹⁶

The general adult habitus of a person with 49,XXXXY syndrome is eunuchoid. The neck is short, the shoulders and chest are narrow, and frequently the nipples are widely spaced.^{10 18} Patients often have long, thin tapering arms and legs with bilateral cubitus valgus, genu valgus, and pes planus. As with facial features, the body habitus of a subject with 49,XXXXY syndrome changes over his lifetime. Infants with a 49,XXXXY karyotype are generally small for gestational age yet may show “catch up” growth later in life. For example, the birth length of case 1 was below the 5th centile but measured between the 25th and 50th centiles at the age of 2½ years. However, the birth length of case 3 was also below the 5th centile and remained so at 18 months of age. Case 2 had a normal birth length and measured between the 25th and 50th centiles for height at the age of 14½ years. A review of heights and weights of published cases of 49,XXXXY syndrome (not including our three cases) showed an average birth weight of 2551 g (<10th centile, n=29) and average birth length of 48.6 cm (25th–50th centile, n=8). The average adult height was 181 cm (75th–90th centile, n=6) and average adult weight was 71 kg (75th–90th centile, n=4).

Multiple skeletal anomalies occur in people with 49,XXXXY syndrome and include radioulnar synostosis, delayed bone age with lack of closure of bone growth plates into adulthood, congenital hip dislocation, early degeneration of articular cartilage (especially at the elbows), and hypertrophy of epiphyses.^{20–23} The skeletal anomalies of the three cases reported are listed in table 2. Case 1 had plagiocephaly, a right cervical rib, asymmetrical chest, scoliosis, and bilateral 5th finger clinodactyly. Case 2 had plagiocephaly, a raised left shoulder, exaggerated spinal lordosis, contracture of the right elbow, hypoplasia of the phalanges, bilateral 5th finger clinodactyly, genu valgum, and pes planus. Case 3 had congenital hip subluxation.

Congenital heart and vascular disease is also observed in subjects with a 49,XXXXY karyotype. In fact, the first case report by Fraccaro *et al*¹ described a child with a patent ductus arteriosus (PDA). Fifteen years later, Karsh *et al*⁶ reviewed published reports and found that 13 of 88 (14%) reported cases of 49,XXXXY syndrome had a cardiovascular defect with the most common defect being a PDA. Several reports since 1975 have also described congenital heart defects.^{4 5 18 19} To these reported

cases we add three new patients. Case 1 was born with atrial and ventricular septal defects, case 2 was born with tetralogy of Fallot, and case 3 with a PDA. Interestingly, Meschede *et al*²⁴ reviewed published reports of another sex aneuploidy syndrome, 48,XXYY, and found that 8% of those examined had a congenital heart defect.

Genital abnormalities are consistently found in males with a 49,XXXXY karyotype. These anomalies include small penis and testes, undescended testes, bifid scrotum, ambiguous genitalia, and scrotalisation of the penis.^{1 3 18 25 26} Two of our patients had hypogonadism and case 1 also had scrotalisation of the penis, hypoplastic foreskin, and bilateral hydroceles.

Another feature of 49,XXXXY syndrome is cognitive impairment. Most authors of older publications predicted a bleak prognosis of moderate to severe mental retardation in these subjects with an estimated mean IQ of 35.^{2 13 26} While patients with moderate to severe mental retardation and this karyotype do exist and will continue to be reported, the above prediction of IQ range probably is based on biased data. Many of the patients in the earlier reports were institutionalised and did not receive sufficient early intervention or personal interaction which might have enabled them to function at a higher level. More recently, several patients have been reported with IQs in the borderline to low normal range. Sheridan *et al*²⁶ described a patient with IQs of 76 and 70 when assessed by the Stanford Binet and Weschler Preschool and Primary Scale of Intelligence (WPPSI) tests, respectively. Borghgraef *et al*¹³ reported two patients, both of whom had IQs of 72 as measured by WPPSI scale. Kleczkowska *et al*² reported two additional patients with borderline IQs of 70 and 72. Lomelino and Reiss²⁷ reported a child with 49,XXXXY syndrome who was ascertained only as a control to a research study. This child had an IQ of 78±6 as measured by the Stanford-Binet test at 4 years 10 months. Of the three cases reported here, formal developmental data were available only from case 1. However, all three were documented to have developmental delay.

Additionally, speech impairment or even speech aphasia is uniformly found in persons with 49,XXXXY syndrome.^{12 15 26–28} Each patient reported here had significant speech impairment. Neither cases 1 nor 2 attempt purposeful verbal communication. Case 2 has successfully learned and uses sign language. Case 3, at 18 months, also had significant speech delay.

In conclusion, we believe that 49,XXXXY syndrome is a distinct clinical entity and should not be “lumped” together with Klinefelter syndrome. People with 49,XXXXY syndrome have distinctive facial features, are more mentally handicapped, and have greater speech difficulty than those with Klinefelter syndrome. In addition, males with 49,XXXXY syndrome are generally shorter, have distinct skeletal anomalies, and an increased incidence of congenital heart defects when compared to males with a 47,XXY karyotype. The presence of congenital heart defects in subjects with

49,XXXXY syndrome suggests special attention be given to the cardiac evaluation. Conversely, males with congenital heart defects who fit the phenotypic description of 49,XXXXY syndrome or who have significant speech impairment or both are candidates for chromosome analysis.

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