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Partial Deletion of the Short Arm of Chromosome 3

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Abstract. A case of deletion of the short arm of chromosome 3 (46,XY,del(3)(p253) is described. The patient is a youth of 18 years in an institution for the mentally retarded. Phenotypically, he presents congenital heart disease, hypertelorism, ptosis, epicanthus, blepharophimosis, strabismus, nystagmus, synophrys, low-set ears, frequent infections, epilepsy (abnormal EEG and grand mal seizures), "rocker bottom" feet, flat occiput and muscular hypotonia. The parents are healthy and with normal karyotypes. A silent allele in the GPT system was found in the mother, the propositus and 4 of the 5 siblings.

Key words: Deletion syndrome – Chromosome 3 – Mental retardation – Malformations – GPT silent allele

Introduction

Although chromosome 3 shows relatively frequent chromosome breakages, particularly on the short arm at 3p2 (Aula and von Koskull 1976), only few patients have been reported with deletions of chromosome 3 (Verjaal and De Nef 1978; Fineman et al. 1978; Gonzales et al. 1980). We now report a further case. In 1962, this patient was diagnosed as having normal chromosomes.

Case Report

The proband, a male, was born in March 1962 as the fifth of six siblings (the three sisters and two brothers are normal). The mother had a barium meal in the 7th week of gestation. The pregnancy was otherwise uneventful. The mother was 36 and the father 41 years at the time of the proband's birth. The parents are of the Catholic faith.

The proband was described as "spastic" immediately after birth. His appearance was peculiar. The birth weight was 2800 g and length 48 cm. He was admitted to a paediatric department at the age of five days on account of aspiration of amniotic fluid and various malformations including a sixth finger originating from the middle phalanx of the right fifth finger. Bilateral ptosis was obvious at birth.

He was admitted again at the age of eight months on account of suspicion of mental retardation, congenital heart disease (abnormal vessels) and cerebral dysrhythmia. Angiography revealed right-sided aortic arch with crossing of the descending aorta to the left, crossing posterior to the oesophagus while the left innominate artery crossed anterior to the trachea. Stridor was frequent during childhood.

The proband developed slowly and did not learn to walk until the age of eight years.

Febrile convulsions occurred in 1965, 1969, 1970 (parotitis epidemica) and 1973. He has received anticonvulsive treatment with phenytoin since 1975. The EEG showed a severely abnormal curve with diffuse low-frequency activity and discharges of spikes (1975). Occasional seizures still occur when he is pyrexial.

There have been numerous infections (otitis media, otitis externa, sinusitis) treated by operative measures and antibiotics.

Ophthalmological examination revealed congenital blepharophimosis, intermittent slight divergent and convergent strabismus, nystagmus, vitreous opacities and bilateral ptosis. No slanting of the eyes was present.

"Rocker bottom" feet were diagnosed in 1973 and treated by orthopaedic footwear.

On examination at the age of 18 years (S.B. and L.H.) he was a well-nourished adolescent of strikingly short stature, height 148 cm and weight 42,5 kg (corresponding to the average for a boy of 12–13 years). He is good natured and placid. He can help with dressing and undressing. He has no active speech but understands simple instructions. The mental development is considered to be low in the imbecile range. The cranium is asymmetrical with a flat occiput: circumference 55 cm. The hairlimit is low both anteriorly and posteriorly and the neck is broad and short. Bilateral epicanthus, ptosis and hypertelorism are present. Convergent strabismus is observed in the left eye and spontaneous horizontal nystagmus was found in both eyes.

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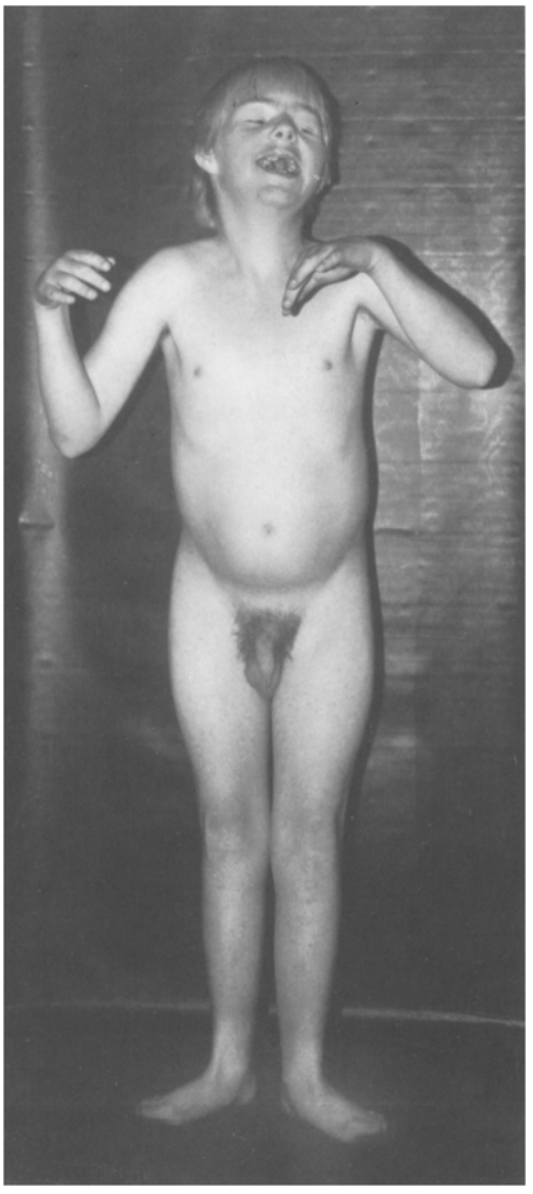


Fig. 1a–c. The proband at the age of 18. Note: ptosis, synophrys, low-set ears and "rocker bottom" feet

The eyebrows meet in the mid-line. The face is expressionless. It is difficult to assess his sight. He shows no interest in sweets of 1 cm in diameter but handles small toys and uses sight for orientation. The glabella is broad and the nose is of normal form with purulent secretions at the time of examination. The ears are small, prominent and low-placed but of normal form. He listens to bells and reacts to conversation and relevant noises. The teeth are slightly discoloured. An upper incisor is missing. There is a tendency to bruxism. His appearance is shown in Fig. 1.

Stethoscopic examination of the heart reveals normal findings. There is a tendency to hyperventilate. Abdomen: Diastasis of approximately 3 cm between the rectus abdominis muscles is found. Both testes are in the scrotum and are of normal size. Pubic hair and penis are normal.

The triceps and biceps tendon reflexes are brisk and equal. The hands are small and soft with short pointed fingers with very little pulp. No contractures, deformities nor four-finger line are present. The grasp is clumsy and no pincer grip is present.

He walks without support alternately on heels or toes with the feet in extreme valgus position. The feet assume varus position when sitting. The gait is stiff and inelastic. Both feet show "rocker bottom" deformity and both achilles tendons are tense. The patellar and ankle tendon reflexes are brisk and equal and there is no clonus. The great toe is longest on both feet. The left fifth toe overlaps.

He uses a diaper both day and night.

Radiographic Examination

The cranium is markedly flattened posteriorly and almost tower-shaped. No intracranial calcification nor impressiones digitatae were observed. The sella turcica is normal.

The left hand shows retarded bone development (approximately 15 years compared with the chronological age of 18 years).

A pronounced S-shaped scoliosis is observed in the thoracolumbar spine. Intravenous urography shows normal conditions on the right side. The left kidney is situated in the pelvis and its drainage is free.

Cytogenetic Findings

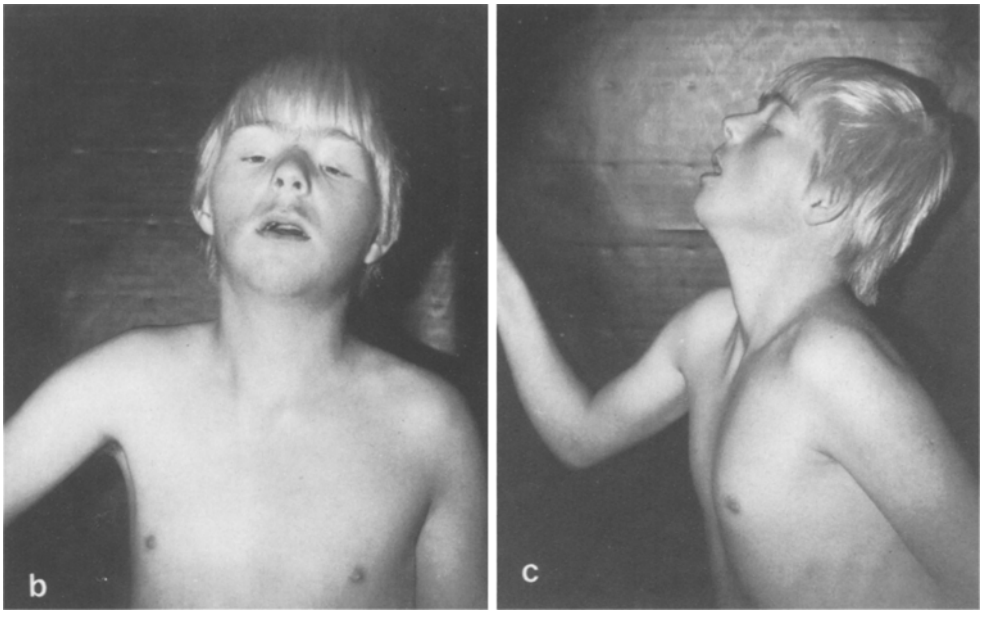
Chromosome investigation was carried out on the first occasion in 1962 on account of the proband's peculiar facies and malformations. A normal karyotype was found by the standard Giemsa technique. In 1974, a new chromosome investigation was carried out in connection with screening of patients under the Service for the Mentally Retarded and the chromosome aberration was diagnosed.

Lymphocytes were cultured in the usual manner for 72 h with addition of PHA. Harvest and slide-preparation followed the usual procedure and air-dried slides were stained with QM for 20 min (Caspersson et al. 1970). R-banding was carried out be the method described by Mikkelsen (1976). For prometaphase chromosomes, lymphocytes were cultured by the method described by Yunis (1976). Suitable cells were photographed and karyotypes prepared. A 46,XY,del(3)p(253) karyotype was found. The band delineation followed the diagram of Francke and Oliver (1978). Partial karyotypes are given in Fig. 2.

The parents had normal chromosomes. Comparison of the proband's and the parent's variable regions on chromosome no. 3 were non-informative as both parents had a strongly fluorescing marker on one of their chromosomes no. 3 (Fig. 3).

Marker Gene Studies

Blood group, serum type and enzyme studies for the family are given in Table 2. The investigation revealed normal types and segregation with one exception, the GPT-system, in which the phenotype of the proband was found to be incompatible with the mother's. The finding of the same discrepancy in 3 normal sisters together with a normal karyotype in the mother virtually excludes any causal relation between this phenomenon and the chromosome 3 deletion and indicates the existence of a coincidental, silent GPT allele. The fact that the suspected silent GPT gene segregates together with the PGM_12 gene in 5 and possibly all of 6 sibs may well be accidental and does nor appear to have any bearing on the chromosomal anomaly.



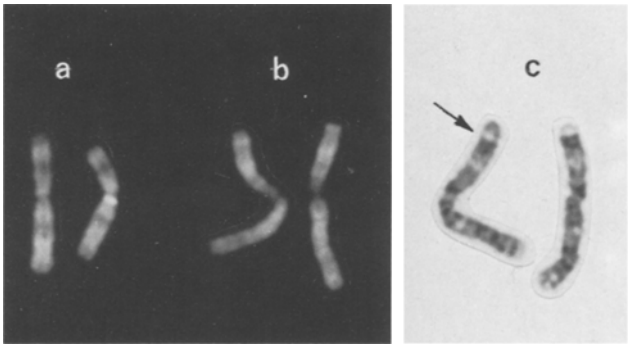


Fig. 2. Chromosome no. 3 from the proband in **a** Q-banding, **b** R-banding, **c** trypsin-Giemsa-staining. Note: deletion at band p253. Arrow on band p253 of the normal chromosome

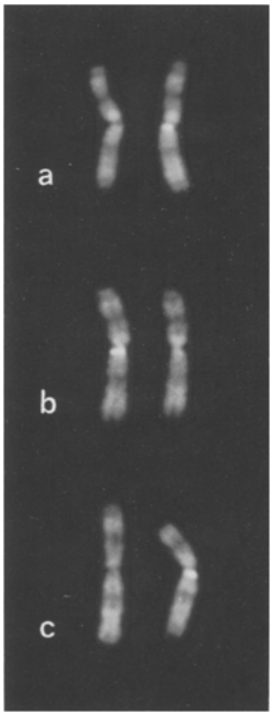


Fig. 3. Chromosomes 3 from **a**) father, **b**) mother, **c**) proband in Q-banding. Note: both parents have one chromosome 3 with a fluorescing variant, so has the proband's deleted chromosome

Discussion

Only relatively few patients with chromosome 3 deletion have been reported. This is interesting as the region 3p2 is apparently one of the most common sites for spontaneous chromosome breakage in lymphocyte cultures. Aula and von Koskull (1976) found 13% of the total breaks in this region. In the zygote such deletions might be associated with fetal death. However, in studies of spontaneous abortions 3p– has not been reported (Kajii et al. 1980). A zygote containing a deleted chromosome 3 might generally be aborted before a pregnancy could be recognized clinically.

Three cases of 3p– previously described together with the present case are summarized in Table 1. In all the cases the deletion occurred de novo. It is apparently accompanied by serious clinical symptoms. The similar appearance of the four cases favours the delination of a 3p– syndrome characterized by severe mental, psychomotor and growth retardation, a peculiar facial appearance with flat occiput, synophrys and low-set ears, ptosis, epicanthus and anomalies of the extremities. The patients with a deletion of the short arm of

Table 1. Partial deletion of the short arm of chromosome 3. Tabulation of the characteristic features

	Verjaal and De Nef (1978)	Gonzales et al. (1980)	Fineman et al. (1978)	Present case (1980)
Sex	male	female	female	male
Cytogenetic findings	46,XY,del(3)(p25)	46,XX,del(3)(p25)	46,XX,del(3)(p25)	46,XY,del(3)(p253)
Parental age	Father: 42 years, normal Mother: 38 years, normal	Father: 25 years, normal Mother: 25 years, normal	Father: ?? years, normal Mother: 24 years, normal	Father: 41 years, normal Mother: 36 years, normal
Birth weight	2470 g	1915 g	2700 g	2800 g
Birth length	47 cm	?? cm	?? cm	48 cm
Psychomotor retardation	Yes	Yes	Yes	Yes. Low imbecile
Retardation of growth	Yes	Yes	Yes	Yes. Chronological age 18 years. Bone age 15 years
Epilepsy	?	Yes	?	Yes, severely abnormal EEG with diffuse low-frequency activity and spikes
Malformation of head				
a. asymmetry	Yes, flattened posteriorly on left side	?	?	Yes.
b. flat occiput	Yes	?	Yes	Yes, almost tower-shaped head
c. microcephaly	?	Yes	?	No
d. x-ray of skull	?	PEG: normal ventricles	No digital impressions	No digital impressions
e. forehead	?	flat forehead	frontal bossing	?
Face and mouth				
a. eyebrows	curved	synophrys	synophrys	synophrys
b. hair limit	?	low hair limit	?	low hair limit anteriorly and posteriorly
c. nose	prominent with bulging apex	large and flat with round apex	broad and flat	broad glabella, otherwise normal
d. harelip/cleft palate	no/no	no/yes	?/?	no/no, teeth discoloured
e. micrognathy/ retrognathy	yes/yes	?/?	?/?	no/no
f. malformation of ears	Yes, placing of ears?	small, low-placed	?	small, low-placed
Eyes				
a. mongoloid slits	Yes, slightly mongoloid	No	?	No, blepharophimosis, stabismus, nystagmus
b. ptosis	Yes	Yes	Yes	Yes
c. epicanthus	Yes	Yes	Yes	Yes
d. opacities in corpus vitrium	No	No	?	Yes
e. opacities in cornea	No	No	?	No
f. hypertelorism	No	Yes	?	Yes
Neck	?	?	short neck	broad short neck
Spine	No spina bifida	?	Defective segmentation of C 2–3	No spina bifida

Table 1 (continued)

	Verjaal and De Nef (1978)	Gonzales et al. (1980)	Fineman et al. (1978)	Present case (1980)
Malformation of internal organs				
a. cardiovascular	VSD	No	No	Yes, see text.
b. alimentary canal	?	caecum at left side, vulvular anus	?	?
c. urinary tract	?	no anomalies on urography	?	left pelvic kidney, otherwise normal urographic findings
External genitalia	underdeveloped bilateral cryptorchism	normal sexual hair (no breast development, long distance between nipples)	?	normal external genitalia and sexual hair
Extremities				
a. malformations of hands	second finger overlaps third and fifth overlaps fourth, bilaterally	fourth metacarpal short and of same length as fifth	fifth finger short and incurved, postaxial extra anlage on left hand	extra anlage originating from middle phalanx of right fifth finger
b. malformations of feet	rockerbotton feet, extra anlage lateral on both feet	?	?	rockerbotton feet
c. tone	normal	hypertonic lower limbs	hypertonic	hypotonic

Table 2

Grandmother born 1900	OMNS−	C+CW−D+E+c+P_1−K−Fya+ Hp 2-1 Gc 2-1 Gm(a−x−b+) Km− PGM_1 1-1 EAP BC GPT 2-1 EsD 1-1 GLO 2-2 AK 1-1 PGD A ADA 1-1 Gt 1-1				
Mother born 1926	OMNS−	C−D+E+c+e−P_1−K−Fya− Hp 2-1 Gc 2-1 Gm(a−x−b+) Km− PGM_1 2-1 EAP B GPT 2-0 EsD 1-1 GLO 2-2 AK 1-1 PGD A ADA 1-1 Gt 1-1	Father born 1921	OMNS−	C+CW−D+E−c+P_1+K−Fya− Hp 2-1 Gc 1-1 Gm(a+x−b+) Km− PGM_1 1-1 EAP BC GPT 2-1 EsD 2-1 GLO 1-1 AK 1-1 PGD A ADA 1-1 Gt 1-1	
		Sister born 1950	OMNS−	C+CW−D+E+c+P_1+K−Fya− Hp 1-1 Gc 1-1 Gm(a+x−b+) Km− PGM_1 2-1 EAP B GPT 2-0 EsD 1-1 GLO 2-1 AK 1-1 PGD A ADA 1-1 Gt 1-1		
		Sister born 1952	OMNS−	C+CW−D+E+c+P_1+K−Fya− Hp 2-1 Gc 1-1 Gm(a−x−b+) Km− PGM_1 2-2 EAP B GPT 2-0 EsD 1-1 GLO 2-1 AK 1-1 PGD A ADA 1-1 Gt 1-1		
		Brother born 1955	OMNS−	C−D+E+c+e+P_1+K−Fya− Hp 1-1 Gc 2-1 Gm(a−x−b+) Km− PGM_1 1-1 EAP B GPT 2-1 EsD 2-1 GLO 2-1 AK 1-1 PGD A ADA 1-1 Gt 1-1		
		Sister born 1960	OMS−	C−D+E+c+e+P_1+K−Fya− Hp 2-2 Gc 2-1 Gm(a+x−b+) Km− PGM_1 2-1 EAP B GPT 2-0 EsD 1-1 GLO 2-1 AK 1-1 PGD A ADA 1-1 Gt 1-1		
		Proband born 1962	OMS−	C+CW−D+E+c+P_1+K−Fya− Hp 2-1 Gc 1-1 Gm(a+x−b+) Km− PGM_1 2-1 EAP BC GPT 2-0 EsD 1-1 GLO 2-1 AK 1-1 PGD A ADA 1-1 Gt 1-1		
		Brother born 1964	OMS−	C−D+E+c+e+P_1+K−Fya− Hp 2-1 Gc 2-1 Gm(a−x−b+) Km− PGM_1 2-1 EAP B GPT 1-1 (O) EsD 2-1 GLO 2-1 AK 1-1 PGD A ADA 1-1 Gt 1-1		

chromosome 3, described by Boué and colleagues (1974) and the deletion p25 and duplication q21→qter described by Allderdice et al. (1975) are not included in the table although the facial appearance of the patients resembled the other cases. The chromosome aberration in Boué's case and the 4 patients described by Allderdice arose from a familial pericentric inversion showing monosomy for the distal part of the short arm of chromosome 3 and trisomy for parts of the long arm. It appears to be difficult to decide whether some of the clinical features occur because of the trisomy of long arm material or the lack of short arm material.

Marker gene studies showed discrepancy between the patient and his mother in the GPT system. As the GPT system has not been localized with certainty, a family study was carried out, showing that the mother's father must have carried a silent allele which is segregating in the family. Recently, the gene for aminoacylase, has been localized to the distal part of the short arm of chromosome 3 (Voss et al. 1980). Analysis of this system, however, was not possible in our case.

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References

Allderdice PW, Browne N, Murphy DP (1975) Chromosome 3 duplication q21→qter deletion p25→pter syndrome in children of carriers of a pericentric inversion inv(3)(p25q21). Am J Hum Genet 27:699–718

Aula P, von Koskull H (1976) Distribution of spontaneous chromosome breaks in human chromosomes. Hum Genet 32:143–148

Boué J, Hirschhorn K, Lucas M, Gautier M, Moszer M, Bach Ch (1974) Aneusomies de recombinaison. Conséquences d'une inversion péricentrique d'un chromosome 3 paternel. Ann Pédiat 21:567–573

Caspersson T, Zech L, Johansson C, Modest EJ (1970) Identification of human chromosomes by DNA-binding fluorescent agents. Chromosoma 30:215–227

Fineman RM, Hecht F, Ablow RC, Howard RO, Breg RW (1978) Chromosome 3 duplication q/deletion p syndrome. Pediatrics 61:611–618

Francke U, Oliver N (1978) Quantitative analysis of high-resolution trypsin-Giemsa bands on human prometaphase chromosomes. Hum Genet 45:137–165

Gonzales J, Lesourd S, Braconnier A (1980) Délétion partielle du bras court du chromosome 3. Ann Genet (Paris) 23: 119–122

Kajii T, Ferrier A, Niikawa N, Takahara H, Ohama K, Avirachan S (1980) Anatomic and chromosomal anomalies in 639 spontaneous abortuses. Hum Genet 55:87–98

Lauritsen JG (1976) Aetiology of spontaneous abortion. A cytogenetic and epidemiological study of 288 abortuses and their parents. Acta Obstet Gynecol Scand Suppl 52:1–29

Mikkelsen M (1976) Identification of active and inactive chromosomes by BrdU incorporation and fluorochrome staining. In: Pearson PL, Lewis KR (eds) Chromosomes Today 5: 409–414

Verjaal M, De Nef J (1978) A patient with a partial deletion of the short arm of chromosome 3. Am J Dis Child 132:43–45

Voss R, Lerer I, Povey S, Solomon E, Bobrow M (1980) Confirmation and further regional assignment of aminoacylase 1 (ACY-1) on human chromosome 3 using a simplified detection method. Ann Hum Genet (Lond) 44:1–9

Yunis JJ (1976) High-resolution of human chromosomes. Science 191:1268–1270

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