Another patient with an interstitial deletion of chromosome 9: case report and a review of six cases with del(9)(q22q32)

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Abstract

We report a case of del(9)(q22q32) in a severely mentally retarded boy. The most prominent clinical features are short stature, microcephaly, dysmorphic facies, and delayed bone age. Although six cases of this deletion have now been reported, confirmation of a definite syndrome is not yet possible.

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A severely mentally retarded boy with dysmorphic features was referred to our clinic. Chromosome studies showed an interstitial deletion of chromosome 9 in the q22q32 region. Other cases of del(9)(q22q32) have previously been reported by Ying *et al.*,¹ Robb *et al.*,² and Farrell *et al.*³ In a review of interstitial deletions in the 9(q22q34) region, Farrell *et al.*³ reported two new cases and a previously unpublished case described by Sekhon *et al.*⁴ of del(9)(q22q32). When the six cases now on record are compared, no distinct pattern of clinical features emerges. Our case comes closest to one of the cases described by Farrell *et al.*³

Case report

The patient was the first son of a G1,P1 22 year old mother and a 26 year old father, both white. The family history was unremarkable and the parents were not related. The pregnancy was uncomplicated and delivery was at 42 weeks of gestation. Birth weight was 2600 g ($\approx$ 3rd centile) and length was 46 cm ($<$ 3rd centile).

The patient first came to our clinic at the age of 14 months because of retarded psychomotor development. Length then was 73 cm ($<$ 3rd centile), weight was 9.5 kg ($\approx$ 10th centile for age), and head circumference was 45 cm ($\approx$ 3rd centile).

He was slightly hypotonic and could not sit up or roll over. He did not babble like normal children of his age. His skull showed brachycephaly and frontal bossing. Inner and outer canthal distances were 3.5 cm ($>$ 97th centile) and 8 cm (75th to 97th centile), respectively and the palpebral fissures were downward slanting. There were slight epicanthic folds on both sides. The left eye showed divergent strabismus. The ears were small and primitively formed without ear lobes, and the neck

was short. Internipple distance was increased (measurements not recorded). The patient had a hypoplastic scrotum and a small penis, and no testes were palpable. His fingers were tapered and his toes were small, with partial cutaneous syndactyly of the second to fourth toes on both feet, and with hypoplastic toenails. There was marked medial deviation of the toes.

On further investigation, the EEG showed some epileptic activity, though the patient had no clinical seizures. Later EEGs showed a similar pattern. A CT scan showed a slightly dilated ventricular system with minimal cerebral atrophy. Physical examination of the patient showed no abnormalities of internal organs. *x* rays of the thorax, spine, and hips were normal, but an *x* ray of the hand showed marked delay in skeletal age by as much as 10 months. Because of an overly short frenulum, frenotomy was performed, but speech did not improve. Audiometry was normal.

The patient first walked at the age of 3 years. However, at 8 years orthopaedic surgery had to be performed to correct a developing non-spastic pes equinovarus of the left foot.

At 10 years an *x* ray of the hand again showed delayed skeletal age, this time by 2.5 years.

Figure 1 The patient at the age of 9 years 6 months.

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Clinical features of different cases of *del(9)(q22q32)*

Features	Cases					
	1	2	3	4	5	6
Sex	M	?	F	F	M	M
Stature (centile)	25th		25th	90th		< 3rd
Skin						
Generalised hirsutism	+					
Hypopigmented macules (abdominal)			+			
Skull						
Head circumference (centile)	25th		< 3rd	75th		< 3rd
Brachycephaly				+		+
Trigonocephaly			+			
Frontal region						
Frontal bossing						+
Supraorbital ridge hypoplasia	+	+				
Deep vertical groove	+					
Synophrys				+		
Eyes						
Hypertelorism						+
Telecanthus				+		
Hypotelorism	+					
Downward slanting palpebral fissures	+		+			+
Narrow palpebral fissures		+				
Epicanthic folds			+	+		+
Ptosis			+	+		
Strabismus				+		+
Sclerocornea	+					
Dysmorphic ears	+		+	+		+
Nose						
Depressed nasal bridge	+					
Broad tipped nose		+				
Long philtrum	+	+				
Mouth						
Wide mouth						+
Small mouth			+			
High palate			+			
Short frenulum						+
Irregular dentition						+
Thorax						
Asymmetrical	+					
Pectus excavatum					+	
Genitalia						
Cryptorchidism					+	+
Hypoplastic scrotum and penis						+
Hands						
Tapered fingers						+
Abnormal position of fingers					+	
Polydactyly	+					
Feet						
Pes equinovarus						+
Hallux valgus				+		
Syndactyly (cutaneous)	+					+
Medial deviation of toes						+
Short second toes			+			
Hypoplastic toenails						+
Internal organs						
Small muscular VSD				+		
PDA				+		
Duodenal atresia	+					
Meckel's diverticulum	+					
Malrotation of gut	+					
Multilobulated spleen	+					
Accessory spleens					+	
Dysplasia of right kidney	+					
Focal glomerulosclerosis					+	
Hydronephrosis		+				
Bilateral hydronephrosis	+					
Neurological symptoms						
Psychomotor retardation			+	+		+
Hypertonia	+					
Hypotonia		+	+			+
Abnormal EEG	+					+
Seizures	+					
X ray abnormalities						
Delayed skeletal age						+
Skull						
Wide occipital synchondrosis	+					
Angulated clavicles	+					
Ribs						
Accessory pair (C7)			+			
Fluted	+					
Ribbon-like					+	
Unspecified		+				
Vertebrae						
Partial fusion					+	
Unspecified		+				
Hands						
Ankylosis of phalangeal joints					+	
CT scan						
Dilatation of ventricles				+	+	+
Asymmetry of ventricles					+	
Cerebral atrophy (minimal)						+
Necropsy						
Multiple cerebral anomalies					+	
Parental origin of deleted chromosome	M			P		M

1 = case of Ying *et al.*¹ 2 = case of Sekhon *et al.*⁴ 3 = first case of Farrell *et al.*³ 4 = second case of Farrell *et al.*³ 5 = case of Robb *et al.*²
 6 = present case.

* ICD > 97th centile, OCD = 75th–97th centile. † ICD > 97th centile, OCD = 50th centile.

‡ Consistent with race.

Figure 2 Partial karyotypes of the patient: 9qh+ (left) and del(9)(q22q32) (right).

We examined the boy again at the age of 14 years. His height of 145 cm (<3rd centile) and head circumference of 51 cm (<3rd centile) were still far below normal. The eyebrows were broad (1 cm). The mouth was wide with thick lips and complete but irregular dentition. His feet were short and stubby with a slight equinovarus deviation most pronounced in the left foot. Pubic hair growth indicated the onset of puberty, but both penis and scrotum were hypoplastic. The patient still did not talk. He functioned at the level of a 1½ year old child, and seemed to live in a world of his own.

Fig 1 shows the patient at the age of 9 years 6 months.

CYTOGENETIC STUDIES

Peripheral lymphocytes were cultured and CTG banded using standard techniques. Seven metaphases were analysed. All showed a 46,XY,9qh+,del(9)(q22q32) karyotype (fig 2). Chromosomal investigation of the mother showed a normal 46,XX karyotype and the father had a 46,XY,9qh+ karyotype. As the father and our patient both have the same 9qh+ chromosome, the deleted chromosome is probably maternal in origin. No cell line is available from the patient.

REVIEW OF PUBLISHED CASES

The clinical findings of the six cases of del(9)(q22q32) now on record are shown in the table. Eye anomalies were reported in five out of six patients, as were anomalies of the hands and feet and neurological symptoms. Four out of six cases had dysmorphic ears, abnormal shape of the skull, aberrations of internal organs, and x ray abnormalities of the ribs and vertebrae. Other symptoms are less frequent. However, within the various categories the symptoms vary considerably and no consistent pattern is apparent in the distribution of individual symptoms reported more than once.

Discussion

Our patient most closely resembles the first patient described by Farrell *et al*³ (patient 3

in the table). Shared symptoms are microcephaly, epicanthic folds, downward slanting palpebral fissures, dysmorphic ears, various abnormalities of the toes, psychomotor retardation, and hypotonia. The two cases differ in several other aspects, however.

At this stage, explanations for the diversity of symptoms in the six reported cases must remain speculative. The most probable explanation is a difference in the exact breakpoints of the deletions. There also may have been structural variations of the deleted segment by inversions or duplication of DNA, not detectable by cytogenetic studies. The similarity of the last two bands of chromosome 9 may hamper accurate cytogenetic assessment.

Genomic imprinting was suggested by Farrell *et al*³ as a cause for the differences observed, but in our opinion this is unlikely. With the genomic imprinting, one would expect a division of cases into two distinct groups with similar features, corresponding to a deletion of either maternal or paternal DNA. In three cases the origin of the deleted chromosome is known, namely in one case described by Farrell *et al*³ (paternal), in the case of Ying *et al*¹ (maternal), and in our case (maternal). However, the phenotypes of the two cases with the maternally derived deleted chromosome are not similar. On the contrary, our case (maternal origin) most resembles the case of Farrell *et al*³ (paternal origin).

For clarification of this matter precise DNA analysis is needed to find out the exact position and structure of the deletions.

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