—Case Reports—

A Case of Severe Mental and Developmental Retardation Associated with 14q Terminal Monosomy/5q Terminal Trisomy

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Abstract

I previously described the case of a 19 year-old female with severe mental retardation, developmental retardation, microcephalus, short stature, bilateral microphthalmia, ptosis and blepharophimosis[1]. Now, I present clinical descriptions of her half-siblings, who have a different father. Subtelomeric fluorescence *in situ* hybridization (FISH) analysis of the proband demonstrated 5q terminal trisomy and 14q terminal monosomy. I presume that her mother harbors a balanced translocation between the terminal of chromosome 5q and 14q. I suggest that familial cases of mental retardation and dysmorphic features should be screened for terminal chromosomal abnormalities by FISH or comparative genomic hybridization (CGH), even if G-banding analysis or high-resolution chromosome analysis is normal.
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Key words: subtelomere, 5q terminal trisomy, 14q terminal monosomy, chromosomal aberration, fluorescence *in situ* hybridization

Introduction

Recently, chromosomal micro-aberrations have been documented by fluorescence *in situ* hybridization (FISH) or comparative genomic hybridization (CGH) in individuals with mental retardation. Additionally, cryptic subtelomeric chromosome anomalies have been recognized as a significant cause of dysmorphology and mental retardation[1–3]. Baker *et al.*[4] reported that subtelomeric anomalies were found in 1/53 (1.9%) of an idiopathic mental retardation/developmental delay group and in 8/197 (4.1%) of a second group in which the mental retardation was associated with dysmorphic features and/or malformations in the absence of a recognized syndrome. All nine patients had different subtelomeric chromosomal anomalies.

Here, I used FISH to identify a 5q terminal trisomy and a 14q terminal monosomy in a female with severe mental retardation. Multiple dysmorphic features and various malformations are also present in her family. I discuss the phenotypes observed in her full and half-siblings (some siblings have different fathers).

Case Presentation

Proband (Individual III-7 in Fig. 1): 19 Year-old Female

The proband was born by Caesarian section at 38 weeks gestation, as the younger sister of dizygotic

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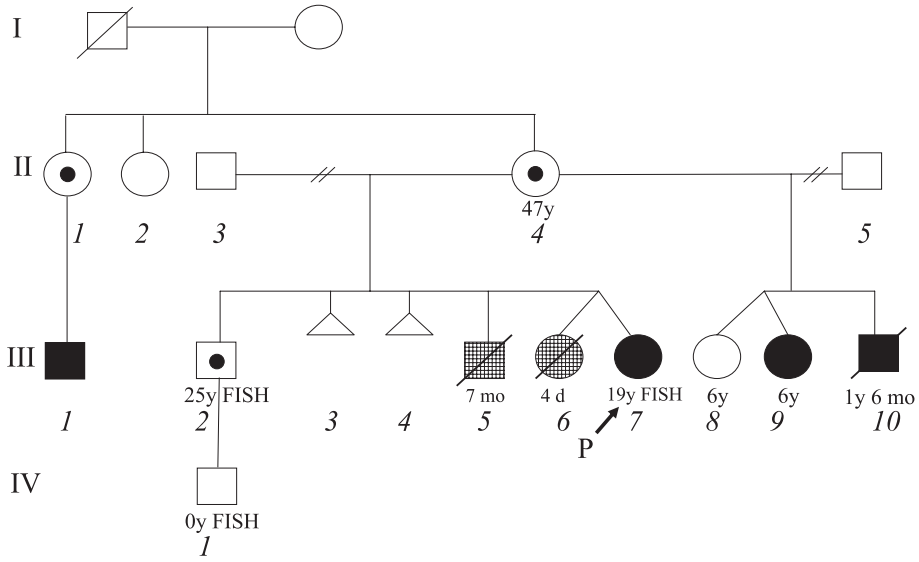

Fig. 1 The family pedigree.
Square symbol is male, and circle symbol is female. Black symbol is affected, and triangle symbol is spontaneous abortion. Black circle in the symbol is the carrier with a balanced translocation suspected.
I did not know the details as facial dysmorphlogies of III-5 and III-6 (cross stripes symbol), but suspected as affected.
"FISH"symbol was performed subtelomeric fluorescence *in situ* hybridization (FISH) analysis.The brother of proband (III-2) demonstrated a balanced translocation between the terminal of chromosome 5q and 14q. Prenatal FISH diagnosis of individual IV-1 and his wife's unborn fetus revealed no abnormalities.

twins. Her Apgar score was 6–9 points and her birth weight was 2,270 g (small for gestational age). From the postnatal period, she has demonstrated microcephalus, bilateral ptosis, blepharophimosis and microphthalmia (more prominent on the right side). She was in hospital for heart failure from 10 months to 3 years old. It is unknown when she gained head control, but she sat at 5 years old, was able to stand with support at 6 years old but cannot yet walk alone. She has severe psychomotor delay, and cannot communicate by language or behavior. Her height, body weight and head circumference are 120 cm (−4.5 SD), 17 kg (−3.1 SD) and 48 cm (−3.4 SD) respectively at present. Recently, she has undergone slight somatic changes related to puberty. Her laboratory and radiological examinations including cranial CT scan were normal, and her bone age corresponded to the chronological age. Her karyotype was normal (46,XX) by G-banding (400–550-band level) and high resolution analysis (550-band level). However, subtelomeric FISH analysis with informed consent (using a TelVysion Multi-color FISH Probe™, Abbott Molecular, U.S.) demonstrated 5q terminal trisomy and 14q terminal monosomy. Her FISH pictures was demonstrated in **Figure 2** (ish der (14) t (5;14) (q35.3+, q32.3−) (D5S 2907+, D14S1420−).

Individual III-2: 25 Year-old Male, Brother of the Proband

This individual is healthy and does not have any malformations. However, subtelomeric FISH analysis (conducted with informed consent) demonstrated a balanced translocation between the terminal of chromosome 5q and 14q (ish t (5;14) (q35.3+, q32.3−; q35.3−, q32.3+) (D5S2907+, D14S1420−) (D5S2907−, D14S1420+)). His wife was 15 weeks pregnant at the time, and the fetus was sampled by amniocentesis with informed consent of them. Subtelomeric FISH analysis of the fetus revealed no abnormalities (ish 5p15.3 (5pSUBTEL×2), 5q35.3 (DS2907×2), 14q32.3 (D14S308×2)) and the baby was born healthy (individual IV-1).

The parents of the proband and individual III-2

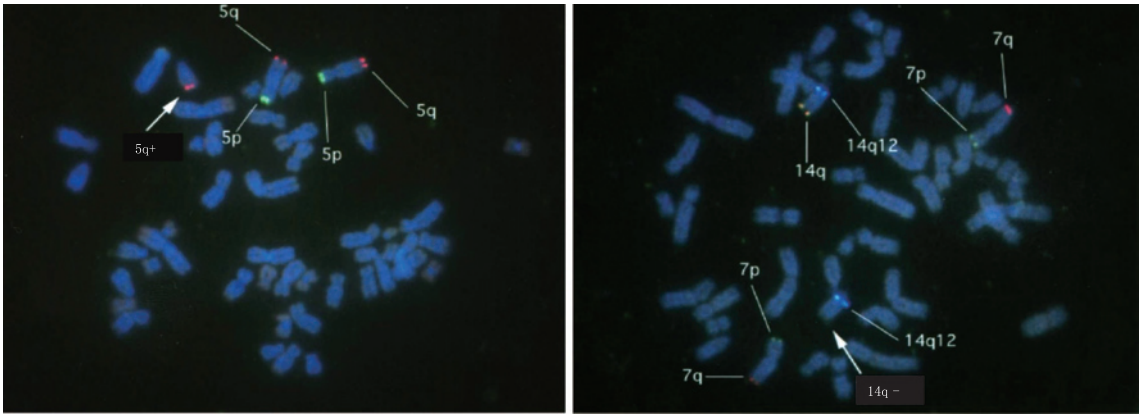

Fig. 2 Subtelomeric fluorescence *in situ* hybridization (FISH) analysis (using a TelVysion Multi-color FISH Probe™, Abbott Molecular, U.S.) of the proband (III-7) demonstrated 5q terminal trisomy and 14q terminal monosomy (ish der (14) t (5;14) (q35.3 +, q32.3 −) (D5S2907 +, D14S1420 −).

divorced 10 years ago. The mother re-married 7 years ago and has had a further three children with her new husband.

Individual III-9: 6 Year-old Female, half-sister of the Proband

Individual III-9 was born by Caesarian section at 35 weeks 6 days gestation, as the younger sister of dizygotic twins. Her birth weight was 1,362 g (small for gestational age). From the postnatal period, she has demonstrated a narrow palate, single palmar crease, flat nose and developmental delay, but not ptosis, blepharophimosis or microphthalmia. At 1 year old, her body weight and height were 6,700 g (−3.2 SD) and 74.3 cm (−2.0 SD) respectively. She could stand with support at 2 years old, walk alone, albeit unstably, and speak a few words at 3.5 years old and run at 4 years old. Now, she can speak only simple sentences. Her body weight is 9.8 kg (−2.8 SD) at present.

Individual III-10: Male, Died at 1.5 Years Old, Half-brother of the Proband

This individual was born by Caesarian section at 37 weeks 3 days gestation. His birth weight was 1,772 g (small for gestational age). His Apgar score was 7–8 points. From the postnatal period, he demonstrated a high arched palate, hypertelorism, blepharophimosis and flat nose. Cranial CT scans revealed large lateral ventricles and hypoplasia of the corpus callosum. His karyotype was normal (46, XY) by G-banding analysis (400–550-band level) with informed consent. Right side hearing loss was detected by an auditory brainstem response test. He has severe developmental delay and congenital laryngeal stridor. At 1.5 years old, he was barely able to lift up his head while lying prone, and could not speak any words. He had very severe growth retardation: his body weight, height, chest circumference and head circumference were 4,530 g (−5.6 SD), 66.6 cm (−4.9 SD), 35.2 cm (−6.5 SD) and 38.5 cm (−6.0 SD) respectively. He died suddenly of respiratory failure after hospitalization for pneumonia.

Family History

Upon examination, the mother of the proband (individual II-4) is 47 years old and healthy at present. She has had two spontaneous abortions (individuals III-3 and III-4). Both her sisters (individuals II-1 and II-2) were healthy. The child of her elder sister (individual III-1) had facial dysmorphology with blephalophimosis and cerebral palsy (his age, sex and detailed phenotype are unknown).

The proband's twin sister (individual III-6) died 4 days after birth of cardiomegaly and herniation of the diaphragm. Her brother (individual III-5) died 7 months after birth of neonatal asphyxia. The facial dysmorphologies of individuals III-5 and III-6 were unknown. Chromosomal examinations were not performed on these individuals. The proband's sister (III-8) had a normal delivery and was healthy.

Table 1. Clinical features of nine 14q terminal deletion cases (adapted from Maurin *et al.* [5]) and the correlation with phenotypes of our three cases (the proband, individuals III-9 and III-10)

Symptoms	Parental origin of deletion: Mat 4, Pat 1, ND 4	*Proband*	*Individual III-9*	*III-10*
Mental Retardation:	9/9	+ +	+	+ +
Hypotonia:	7/9	−	−	±
IUGR:	3/8	+	+	+
Postnatal growth retardation:	6/9	+	+	+ +
Microcephaly:	4/8	+	+	+
Dolichocephaly:	2/6	−	−	−
High forehead:	5/7	−	−	±
Prominent forehead:	3/7	−	−	−
Hypertelorism:	2/6	−	−	−
Strabismus:	3/6	−	−	−
Blepharophimosis:	6/8	+	−	+
Ptosis:	4/8	+	−	−
Downslanding palpebral fissures:	3/7	−	−	−
Telecanthus:	7/9	−	−	−
Broad/flat nasal bridge:	6/7	+	+	+
Anteverted nares:	2/6	−	−	−
Short bulbous nose:	6/7	−	−	−
Long philtrum:	5/7	+	+	+
Broad philtrum:	6/7	−	−	−
Thin upper lip:	5/6	+	±	+
Small mouth:	4/7	+	+	+
Highly arched palate:	6/8	−	Narrow palate	+
Low-set ears:	3/7	−	−	−
Malformed helices:	3/5	−	−	−
Micrognathia:	3/7	−	−	−
Pointed chin:	2/8	−	−	−
Congenital heart disease:	1/5	−	−	−

Discussion

Because the proband's karyotype was 5q terminal trisomy and 14q terminal monosomy, and her brother's karyotype was a balanced translocation between the terminal of chromosome 5q and 14q, we assume that the proband's mother also harbors a balanced translocation between the terminal of chromosome 5q and 14q. I suggested performing FISH analysis on the proband's affected sisters, but their mother declined.

Baker *et al.*[4] reported a 17 year old, moderately mentally retarded male with pre- and postnatal growth retardation and microcephaly, facial dysmorphism (low set simple ears, mild facial asymmetry, hypertelorism, blepharophimosis, broad prominent nose, high arched palate), slender hands and absence of the distal interphalangeal creases of the third and fourth fingers. This patient's karyotype was 46,XY. ish der (14) t (9;14) (q34.3; q32.33). The balanced form of the translocation was found in the mother and three maternal relatives. Maurin *et al.*[5] reported a female infant presenting with psychomotor retardation and facial dysmorphism (round face, short forehead with low hairline, hypertelorism, epicanthus, telecanthus, upslanted palpebral fissures, short bulbous nose, long philtrum, smooth Cupid's bow, round upper lip with thin vermillion border, protruding lower lip, downturned corners of the mouth, small chin and low-set ears). Cytogenetic studies showed a terminal 14q32.33 deletion. The parents' karyotypes were normal. A review of the patient of Maurin *et al.*, and the eight cases with pure terminal 14q32.3 deletions, has demonstrated that the critical region for mental

retardation, hypotonia, epi-telecanthus, short bulbous nose, long philtrum, thin upper lip and small mouth comprises the subtelomeric 1.6 Mb of chromosome 14q. The phenotypes of the three affected individuals (the proband, individuals III-9 and III-10) and the patients of Maurin *et al.* are summarized in **Table 1**. All our three cases showed mental retardation, microcephalus, flat nose and growth retardation.

Clinical features of 5q34/35-qter duplication[6,7] and 5q terminal deletion[4] differ from our cases. Besides, the most frequent findings in distal trisomy for 14q are a low birth weight, retarded growth, mental retardation, microcephaly, facial asymmetry, facial dysmorphism with frontal bossing, hypertelorism, bulbous nose, a prominent upper lip, sparse eyebrows and eyelashes, ear malformation and micrognathia, congenital heart defects, genital hypoplasia and finger anomalies[8]. The two untested affected siblings of the proband may be 5q terminal monosomy and 14q terminal trisomy. The phenotype of the proband's brother (individual III-10) was similar to that of 14q distal trisomy, but I could not confirm this by FISH.

In summary, I suppose that the proband's phenotype is caused by the 14q terminal deletion. I have previously discussed this case in relation to Ohdo blepharophimosis syndrome[1]; in this report I hypothesized that some cases of Ohdo blepharophimosis syndrome (OBS; MIM 249620) might be due to subtelomeric chromosomal aberrations like the proband. OBS is a multiple malformation syndrome characterized by blepharophimosis, ptosis, dental hypoplasia, hearing impairment and intellectual disability. Wide ranges of dysmorphic features and congenital abnormalities have been described in cases reported as OBS and Ohdo-like syndromes. White *et al.*[9] reported two cases of OBS, and subtelomeric FISH studies of all chromosome arms on the two cases showed no abnormality. I could not find any documents performed subtelomeric FISH studies of OBS without this one.

I now suggest that familial cases of mental retardation and dysmorphic feature should be screened for terminal chromosomal abnormalities by FISH or CGH, even if G-banding analysis or high-resolution chromosome analysis is normal. In the future, I hope more origins of the genetic diseases and dysmorphic syndrome will be found with the popularization of subtelomeric FISH and CGH.

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