Subtelomeric rearrangements of dysmorphic children with idiopathic mental retardation reveal 8 different chromosomal anomalies

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SUMMARY: Mıhçı E, Özcan M, Berker-Karaüzüm S, Keser İ, Taçoy Ş, Hapsolat Ş, Lüleci G. Subtelomeric rearrangements of dysmorphic children with idiopathic mental retardation reveal 8 different chromosomal anomalies. Turk J Pediatr 2009; 51: 453-459.

Subtelomeric rearrangements are an important cause of both sporadic and familial idiopathic mental retardation (MR) and/or congenital malformation syndromes. We report on a cohort of 107 children with idiopathic MR and normal karyotype 450–550 band level by GTG banding screened for subtelomeric rearrangements by multiprobe fluorescence in situ hybridization (FISH). In these cases, five patients had de novo deletions (1p deletion was found in 2 cases; 3q deletion, 9p and 9q deletions were found in 1 case each) and four patients had unbalanced rearrangements [der(5)t(5;15)(pter;qter)pat in 2 patients who were siblings, rec(10)dup(10p)inv(10)(p13q26)mat in 1 patient and der(18)t(18;22)(qter;qter) de novo in 1 patient].

Our study confirms that the subtelomeric rearrangements are a significant cause of idiopathic MR with dysmorphic features.

Key words: mental retardation, fluorescence in situ hybridization, subtelomeric FISH.

Mental retardation (MR) affects approximately 1.2% of the population, and its cause is unexplained in the majority of cases[1]. An important cause has been shown to be chromosomal rearrangements, reported in up to 40% of individuals with severe MR and in only 5-10% of patients with mild MR[2-4].

The subtelomeric regions are believed to be the most gene-rich regions of the genome and are susceptible to copy number changes, owing to repeat-rich sequences that show a high frequency of recombination. Because the telomere regions of the chromosomes are G-band negative and morphologically similar, a number of techniques have been applied for subtelomeric screening such as fluorescence in situ hybridization (FISH) with subtelomere probes, high resolution comparative genome hybridization (HR-CGH), multiple ligation probe amplification (MLPA) and array CGH[5]. It is now clear that unbalanced cryptic subtelomeric rearrangements resulting in segmental aneusomy and gene-dosage imbalance are a significant cause of idiopathic MR and congenital anomalies[2,6,7]. The incidence of cryptic subtelomeric chromosomal aberrations remains unclear, although it ranges from 2 to 29% of moderate or severe MR cases in some studies[4,5].

The aim of our investigation was to detect the incidence of subtelomeric abnormalities in children with idiopathic MR and to compare the clinical phenotype in our patients to those in the literature.

Material and Methods

Study Population

In this study, we investigated 107 patients with idiopathic MR who admitted to the Pediatric Genetic Division of Akdeniz University School of Medicine between 2003 and 2008. A few

patients had developmental delay in the first application and follow-up revealed MR by age-related tests. If the patient's age was below six years, we used Goodenough-Harris drawing test. For those above six years, Wechsler Intelligence Scale for Children Revised test was used. An intelligence quotient (IQ) score below 70 was used as MR criterion for age-appropriate applicable patients.

All the patients were preselected by clinical geneticists using the five-item checklist of De Vries et al.[6]. The checklist includes: 1) Family history of MR, 2) Prenatal growth retardation, 3) Postnatal growth abnormalities, 4) ≥2 facial dysmorphic features, and 5) ≥1 non-facial dysmorphic features and/or congenital abnormalities. All of the patients should have had at least four of these criteria and a normal karyotype on the GTG-banded cytogenetics at the 450-550 band resolution. We ruled out recognizable syndromes and metabolic diseases in patients as the etiology of MR.

Cytogenetic and FISH Studies

Metaphases were prepared from peripheral blood lymphocytes according to standard cell cultures techniques. Chromosomes were analyzed using GTG banding 450-550 band resolution levels according to ISCN 2005[8]. For each patient, a minimum of 20 metaphases were analyzed.

Fluorescence in situ hybridization (FISH) studies of the subtelomeric regions were performed using Chromoprobe Multiprobe-T System kit (Cytocell, UK) according to the protocol recommended by the manufacturer. Hybridized metaphase spreads were analyzed using Zeiss Axioplan 2 epifluorescence microscope. Images were captured by CCD camera and analyzed using an imaging system with MacProbe software v.4.1. For each chromosome, at least five metaphases were examined. More than 10 cells were analyzed for the particular chromosome if an aberration was detected. In all positive cases, the karyotype was also analyzed retrospectively by conventional cytogenetic study.

When positive cases were detected, FISH analyses with subtelomeric probes were performed in the proband's parents and in the relatives with idiopathic MR and dysmorphic features. In those patients who were shown to have subtelomeric rearrangements, written informed consent was provided for medical presentation.

Results

In this study, we analyzed 107 children who had normal karyotype by GTG banding using subtelomeric region-specific FISH probes. Each patient had idiopathic MR and dysmorphic features. Subtelomeric chromosomal rearrangements were detected in 9 of 107 (8.4%) patients (2 of them were siblings). Except for one case, retrospective cytogenetic analysis of all FISH-positive patients was normal. We investigated parental subtelomeric chromosomal regions by FISH, using subtelomeric region-specific probes. The subtelomeric chromosomal rearrangements were found to be familial in three patients, two of whom were siblings. In all others, the chromosomal rearrangements appeared to be de novo. The clinical and FISH findings of 9 patients are presented in Table I. Facial appearances of the patients are shown in Figure 1 and FISH images of the patients are shown in Figure 2.

Discussion

Cryptic unbalanced subtelomeric rearrangements represent a significant cause of MR associated with congenital anomalies. Despite a number of studies, the prevalence of these rearrangements in clinic populations remains unclear[9,10]. According to clinical inclusion criteria and the size of the study populations, the incidence ranges from 2% to 29% in developmental delay populations[5,6]. We previously reported the frequency of the subtelomeric rearrangements as 20% in a smaller study[11]. In the present study, all patients (n=107) were selected by clinical geneticists using the five-item checklist provided by de Vries et al.[6]. We found eight different subtelomeric rearrangements in nine patients, and the prevalence of subtelomeric chromosomal rearrangements was found to be 8.4%. Our results confirm that a clinical checklist can improve the detection rate of cryptic subtelomeric chromosomal aberrations in the subtelomeric FISH studies. Until recently, multiprobe FISH was used to detect deletions and duplications in the patients with balanced or unbalanced chromosomal rearrangements. However, it was recognized that using multiprobe FISH for the screening led

Table I. The Clinical and FISH Findings of 9 Patients (Part 1)

Patients	1	2	3	4	5
Subtelomeric FISH	46, XX, ish del (1)(pter–)	46, XX, ish del (1)(pter–)	46, XX, ish del(3)(qter–)	46,XX, ish del (9)(pter–)	46,XX, ish del(9)(qter–)
Parental karyotype	Normal	Normal	Normal	Normal	Normal
Age	11 months	12 months	5 years	7 years	5 years
Sex	Female	Female	Female	Female	Female
Weight kg/(centile)	7/(3)	11/ (90)	16/(10-25)	20.5/(10-25)	19/ (50)
Height cm/(centile)	67/(10-25)	70/ (25–50)	107 (50)	117/(50)	108/(25–50)
Head circumference cm/(centile)	42.5/ (3)	42/ (<3)	46.2 (<3)	40.5/(<3)	47.2/(<3)
Craniofacial features	• Large anterior fontanel • Small and deep-set eyes • Synophrys • Downslanting palpebral fissures • Long eyelashes • Micrognathia	• Large anterior fontanel • Coarse and round face • Synophrys • Epicanthal folds • Microphthalmia • Deep–set eyes • Downslanting palpebral fissures • Midfacial hypoplasia • Low hairline • Short neck	• Sparse hair • Narrow frontal area • Deep–set eyes • Prominent nose • Sparse eyebrows	• Trigonocephaly • Prominent forehead • Flat occiput • Upslanting palpebral fissures • Hypertelorism • Arched eyebrows • Epicanthal folds • Short nose with flat bridge • Highly–arched palate	• Downslanting palpebral fissures • Synophrys • Midfacial hypoplasia • Low–set ears
Extremity abnormalities	• Small hands and feet • Clinodactyly • Drumstick terminal phalanges • Nail hypoplasia • Proximal implantation of thumbs	• Small hands and feet • Bilateral single transverse crease • Clinodactyly	• Clinodactyly	• Long toes • Bilateral metacarpophalangeal shortness • Hyperconvex nails • Bilateral toe anomalies*	• Clinodactyly • Sidney line on left palmar area
Other	• Widely spaced nipples	• Widely spaced nipples • Hyperphagia • Self–abuse	–	• Widely spaced nipples	• Absent deep tendon reflexes
Mental retardation	+***	+***	+	+	+
Hypotonia	+	+	–	–	+
Score	4	4	4	4	4
ECHO	ASD, PDA**	ASD, PDA**	–	ASD**	Tricuspid and mitral valves insufficiency
Cranial MRI	Non–communicating hydrocephalus	Frontal lobes atrophy and myelination defect	Normal	?	Normal

FISH: Fluorescence in situ hybridization. MRI: Magnetic resonance imaging. ASD: Atrial septal defect. PDA: Patent ductus arteriosus.

Patients	6	7	8	9
Subtelomeric FISH	46, XX,ish der (5) t(5; 15)(pter-; qter+)pat	46, XY,ish der(15) t(5; 15)(pter+; qter-)pat	46,XX.ish rec(10)dup(10p)(inv)(10)(p13q26)mat	46, XX, ish der (18) t(18; 22) (qter-; qter+)
Parental karyotype	Father: 46,XY.ish t(5;15)(pter;qter)	Father: 46,XY.ish t(5;15)(pter;qter)	Mother: 46,XX,inv(10)(p13q26)	Normal
Age	3 years	2 years	12 months	2 months
Sex	Female	Male	Female	Female
Weight (kg/centile)	13.5/(10-25)	4.8/(<3)	6.8/(<3)	2.4/(<3)
Height (cm/centile)	92/(25-50)	60/(<3)	71 (<3)	49/(<3)
Head circumference (cm/centile)	43/ (<3)	39.5/(<3)	43.5 (<3)	34/(<3)
Craniofacial features	• Downslanting palpebral fissures • Hypertelorism • Strabismus • Broad nasal bridge • Prominent nasal root • Epicanthal folds • Malocclusion • Posterior rotated pinnae • Preauricular tags	• Large anterior fontanel • Hypertelorism • Upslanting palpebral fissures • Highly arched palate	• Flattened palpebral fissures • Prominent epicanthus • Short and broad nose • Cleft palate • Micrognathia • Low-set ears • Flat occiput • Short neck	• Large anterior fontanel • Prominent forehead • Hypertelorism • Epicanthal folds • Downslanting palpebral fissures • Short eyelids • Short nose • Thin upper lip • Cleft palate • Micrognathia • Low-set and dysplastic ears
Extremity abnormalities	• Unilateral simian line • Bilateral pes planus • Hyperactive deep tendon reflexes	• Pectus carinatum	• Clinodactyly	• Small hands
Other	• Umbilical hernia • Fusion on the 2nd-3rd cervical vertebrae	–	• Labia major hypoplasia	• Sacral dimple
Mental retardation	+	+	+***	+
Hypotonia	–	–	+	+***
Score	5	5	4	5
ECHO	Normal	Normal	?	ASD, PS
Cranial MRI	?	Thin corpus callosum	Normal	?

* 3rd and 4th toes of both feet were short and back.

** FISH: Fluorescence in situ hybridization. sASD: Secundum atrial septal defect. ASD: Atrial septal defect. PDA: Patent ductus arteriosus. SubAoVSD: Subaortic ventricular septal defect defect. PS: Pulmonary stenosis.

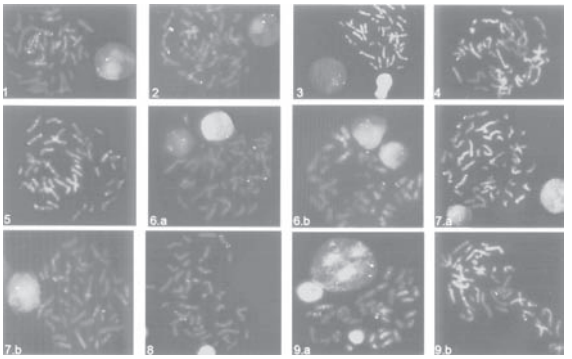

Fig. 1. Overview of nine cases.

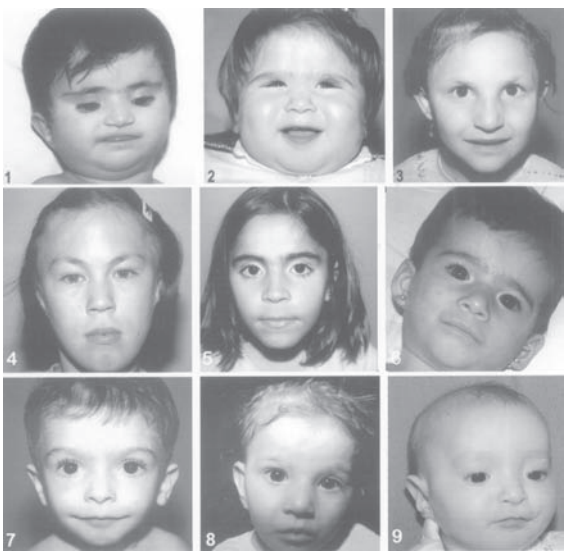

Fig. 2. FISH images of the subtelomeric rearrangements described in this study: (1 and 2) 1p subtelomere deletion; (3) 3q subtelomere deletion; (4) 9p subtelomere deletion; (5) 9q subtelomere deletion; (6a) monosomy of subtelomeric region of 5p; (6b) trisomy of subtelomeric region of 15 q; (7a) trisomy of subtelomeric region of 5 p; (7b) monosomy of subtelomeric region of 15q; (8) duplication of the subtelomeric region of 10p (9a) monosomy of subtelomeric region of 18q; (9b) trisomy of subtelomeric region of 22q.

to a considerably high rate of false positivity[12]. Hence, Park et al.[12] suggested that if any cryptic subtelomeric anomalies were found using multiprobe FISH, this rearrangement should be confirmed using single probe FISH with specific targeting. However, in our study, we did not perform single probe FISH for confirmation. There are a few methods that can be used such as comparative genome hybridization, MLPA and microsatellite marker analysis[4]. Even if these methods may be more sensitive than multiprobe FISH, they can only define unbalanced rearrangements, while multiprobe FISH method can define both balanced and unbalanced rearrangements, making it a more advantageous method.

The frequency of the deletion of short arm of chromosome 1 (1p36) is known as recurrent chromosomal microdeletion syndrome[13,14]. Deletion of this chromosomal band can be difficult to detect by GTG banding. Our two patients had findings consistent with the most characteristic dysmorphic features of 1p deletion (Table I)[14-16]. In the literature, hydrocephalus and hearing loss were noted frequently in monosomy 1p[15]. However, our cases had non-communicating hydrocephalus without hearing loss.

A subtelomeric deletion of chromosome 3q was present in one case. Thus far, only eight cases of 3q microdeletion syndrome have been reported[17-19]. Our case has MR, dysmorphic features and microcephaly (Table I), similar to the reported cases.

Trigonocephaly and upward-slanting palpebral fissures are usually noted in patients with 9p deletion syndrome[20], and these findings were present in our case (Table I). Variable types of congenital heart disease such as ventricular septal defect (VSD), patent ductus arteriosus (PDA) and pulmonic stenosis (PS) are reported in one-third to one-half of patients with 9p deletion syndrome[21]. Our case had an isolated atrial septal defect (ASD).

Until now, 22 patients have been reported with a cryptic subtelomeric deletion of 9q. It has been suggested that microdeletion 9qter represents a novel MR syndrome. The minimum critical region responsible for 9q subtelomeric deletion syndrome (9q-) is approximately 1.2 Mb and encompasses at least 14 genes. Some striking similarities between cytogenetically visible 9qter deletion and a subtelomeric deletion of 9q suggest the presence of a common critical region in the subtelomeric domain[22,23]. Our case (Case 5) had all of the clinical findings observed with 9q deletion (Table I), and also had minimal tricuspid and mitral valve insufficiency.

The occurrence of subtelomeric chromosomal rearrangements can be de novo or can be derived from familial translocations. In this study, we detected a cryptic familial unbalanced translocation between subtelomeric regions of

chromosome 5p and 15q, inherited from their father, in two siblings. In approximately 90% of patients, 5p deletion occurs de novo, and in 10%, it results from a parental balanced translocation[24-26]. In one of the two siblings, partial monosomy for subtelomeric region of chromosome 5p and partial trisomy for subtelomeric region of chromosome 15q resulting from inheritance of chromosomes derived from a paternal balanced translocation. Our case had clinical findings characteristic of 5p deletion syndrome (Cri-du chat). In addition, she had fusion on the 2nd-3rd cervical vertebrae. This finding in monosomy 5p is the first in the literature. The other sibling had a partial trisomy for subtelomeric region of chromosome 5p and partial monosomy for subtelomeric region of chromosome 15q. To our knowledge, partial trisomy of subtelomeric region of 5p has not been reported before. This patient had some dysmorphic features (Table I).

Distal deletions of the terminal long arm of chromosome 15 have been rarely described. Only five patients with pure terminal 15q deletion have been reported in the literature[27]. All of the 15qter deletion cases and ours had similar dysmorphic features. Prenatal and postnatal growth retardation related to the loss of one copy of the IGF1R gene was present in all the 15qter deletion cases and our patient. The IGF1R gene localizes in the 15q26.3. IGF1 receptor is a transmembrane tyrosine kinase receptor that transduces signals corresponding to IGF1 and IGF2. It is well known that IGF1 plays a key role in growth development[27].

Several patients have been reported with terminal 10p duplication/10q deletion resulting from inheritance of a recombinant chromosome derived from a maternal pericentric inversion[28,29]. The clinical findings of dup(10p)/del(10q) syndrome are more similar to dup(10p) syndrome than to del(10q) syndrome. Some authors report that hypotonia, high-arched/cleft palate, frontal bossing, clubfoot, and nasal abnormalities are described in 50% or more of the cases. Dolichocephaly, wide sutures, frontal bossing, micro/retrognathia and renal defects are frequently seen in patients with dup(10p)/del(10q)[28]. We detected duplication of 10p13→pter and deletion of 10q26→qter in one patient whose clinical findings were consistent with a case reported by Nomoto et al.[30] with duplication 10p13→pter.

In one patient, we detected a cryptic unbalanced de novo translocation between subtelomeric regions of chromosome 18q and 22q. This translocation resulted in a partial monosomy for subtelomeric region of chromosome 18q and partial trisomy for subtelomeric region of chromosome 22q. Terminal deletion of long arm of chromosome 18 is a well-characterized deletion syndrome. Our case had all of the findings with partial trisomy 22 (Table I). In addition, our patient had ASD defect, which is not a classical cardiac finding with partial trisomy 22[31].

In summary, our study confirms that the defined clinical selection criteria for the pre-selection of children with idiopathic MR and dysmorphic features leads to a diagnostic yield of about 8.4% for subtelomeric alterations. In both familial and sporadic cases, the detection of subtelomeric rearrangements is of great importance in offering genetic counseling and prenatal diagnosis. Regardless of whether the use of telomeric FISH may be replaced by CGH array technologies, subtelomeric deletions, if detected, will continue to account for a significant proportion of diagnoses made in this clinical population.

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