Subtelomeric rearrangements in mental retardation: Hacettepe University experience in 130 patients

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Recent reports have revealed the presence of subtelomeric rearrangements in 0.5-1.1% of patients with mild mental retardation and in 6.8-7.4% of patients with moderate-severe mental retardation. In the present study, 130 patients with unexplained mental retardation were tested using fluorescence *in situ* hybridization (FISH) analysis for the first time in a large group of Turkish patients, in order to determine the frequency of subtelomeric rearrangements. Three patients had such rearrangements. We present the clinical findings in these patients with (1) coexistent 9p subtelomeric monosomy and 4q subtelomeric trisomy, (2) 22q13.3 subtelomeric monosomy, and (3) coexistent 4p subtelomeric monosomy and 8p subtelomeric trisomy. Mild retardation without dysmorphic features in one of these patients suggests offering subtelomeric analysis to a wide spectrum of mental retardation.

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

Mental retardation affects 1-3% of the general population. The etiology of mental retardation is heterogeneous, including both environmental and genetically determined factors. Chromosomal abnormalities are responsible in 4-34.1% of patients, the proportion being higher among the severely retarded and lower among the mildly retarded[1].

Cryptic subtelomeric rearrangements, which are undetectable by routine chromosomal studies due to submicroscopic size or indistinguishable banding patterns, have been recognized as important underlying causes in mental retardation since 1993[2]. Subtelomeric rearrangements account for 0.5-1.1% of patients with mild mental retardation and for 6.8-7.4% of patients with moderate-severe mental retardation[3]. The frequency of subtelomeric rearrangements has not been previously investigated in large groups of Turkish patients.

Based on the commonly observed features in a series of patients, de Vries et al.[4] proposed a five-item checklist designed to facilitate preselection of patients for subtelomere testing. The checklist includes family history of mental retardation, prenatal onset of growth retardation, postnatal abnormalities of growth, facial dysmorphic features, and non-facial dysmorphic features and/or congenital abnormalities. A score of at least 3 was suggested as the cut-off for subtelomeric testing, which provided correct exclusion of approximately 20% of patients from unnecessary testing[4].

Testing for subtelomeric abnormalities in mental retardation is possible using a number of different techniques. Being an easy-to-perform and sensitive method, multiprobe subtelomeric fluorescence *in situ* hybridization (FISH) has been the most widely used technique. The experience of the Clinical Genetics Unit in the Department of Pediatrics at Hacettepe University Faculty of Medicine is herein reported. Descriptions of three patients with subtelomeric rearrangements, in a series of 130 mentally retarded Turkish children, are provided.

Material and Methods

Patients

A total of 130 patients with unexplained mental retardation, referred to the Clinical Genetics Unit in Hacettepe University İhsan Doğramacı Children's Hospital, were included in the study. The majority of the patients had mental retardation and/or developmental delay with/without dysmorphic features. The range of disabilities included speech delay, behavioral disorder and growth retardation. All patients were previously examined by pediatricians and pediatric neurologists for other relevant causes of mental retardation. Mental development was analyzed with tests including Bayley Scale of Infant Development, Wechsler Intelligence Scale for Children and Stanford-Binet Intelligence Scale. The checklist proposed by de Vries et al.[4] was applied to all patients. To exclude patients with cytogenetically visible abnormalities and fragile X syndrome, chromosome analysis and fragile X molecular analysis were performed.

Cytogenetic Analysis

Cytogenetic analyses were performed on GTG-banded metaphase spreads prepared from phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes after standard culture and chromosome preparation techniques. Chromosome analyses were performed at a resolution of 550 bands.

Fluorescence In Situ Hybridization (FISH)

Fluorescence *in situ* hybridization (FISH) was performed and commercial probe kit, consisting of 41 telomere probes for subtelomeric screening, was used following the manufacturer's instructions (ToTelVysionTM Multicolor DNA Probe, Vysis®, Abbott Laboratories). All analyses were carried out using the Vysis ToTelVysion probe panel following the instructions. One hundred metaphase cells were analyzed for each hybridization area and interphase nuclei were analyzed for deletion, duplication and mosaicism. Identified abnormalities were confirmed with single-probe FISH. Parental FISH analyses of probands with subtelomeric rearrangements were performed to determine whether the abnormality was inherited or *de novo*.

Fragile X Mutation Analysis

Molecular diagnosis of the *FMR1* gene mutations was based on two methods: radioactive polymerase chain reaction (PCR)[5] and Southern blot[6]. PCR was used as first screening to rule out normals and premutations and Southern blotting was performed to examine those cases where PCR did not provide an amplification signal. Southern blot analysis was performed using *Hind III/Nru I* double digests and probing with the StB12.3 probe[7].

Results

The patient group included 76 male and 54 female pediatric patients with mental retardation. Thirty-two of the patients had "mild mental retardation", 31 had "moderate" and 16 had "severe mental retardation". Three with IQ scores between 70-85 were grouped as "borderline intelligence". The remaining 48 patients who were younger than three years of age were classified as "developmental delay", as intelligence scale could not be performed. The clinical checklist suggested by de Vries et al.[4] was applied to all patients and 113 patients scored at least 3. Thirteen patients scored 2 and 4 patients scored 1 in the checklist.

Subtelomeric rearrangements were detected in 3 patients (2.3%) (Table I), including one with subtelomeric deletion (Patient 2) and two submicroscopic unbalanced rearrangements (Patients 1 and 3). In Patient 1, unbalanced chromosomal abnormality was due to maternally inherited cryptic translocation, whereas in the other two patients the rearrangements were *de novo*. These three patients are described below in detail.

Case Reports

Patient 1

A four-year-old male patient was referred for developmental delay, malformations and dysmorphic features. He was born at term as the only child of his healthy consanguineous parents (3rd-degree cousins), with a birth weight of 3770 g (75th-90th centiles). No prenatal or natal problems were encountered. A daughter of a maternal aunt, who was reported not to have similar phenotypic features, also had mental retardation of unknown cause.

He was operated for omphalocele and gastric volvulus, and underwent cranioplasty for correction of trigonocephaly. He also had orchiopexy operation for bilateral undescended testes. He required special education for mild mental retardation. His body weight was

Table I. Description of Three Patients with Subtelomeric Rearrangements

Patient	Age	Rearrangement	Chromosome Imbalance	Inheritance	Mental Status	Clinical Features	Score*
1	4 years	46,XY,der(9)t(4;9)(qter;pter)	9p monosomy 4q trisomy	mat	Mild mental retardation	MR, DD, hypotonia, microcephaly, trigonocephaly, long face, high and narrow forehead, arched and sparse eyebrows, hypertelorism, bilateral epicanthic folds, prominent nasal bridge, flat and bulbous nasal tip, long philtrum, small mouth, high palate, small chin, speech delay, behavioral problems, omphalocele, undescended testes	5
2	4.5 years	46,XY,del(22)(qter)	22q monosomy	de novo	Borderline intelligence	Speech delay, prominent antihelices and tragi, prominent nasal bridge, long philtrum, retrognathia, cutaneous syndactyly between 2nd-3rd toes	3
3	6.5 years	46,XY,der(4)t(4;8)(pter;pter)	4p monosomy 8p trisomy	de novo	Severe mental retardation	MR, DD, hypotonia, short stature, rounded face, synophrys, left-sided epibulbar dermoid, wide and flat nasal bridge, bilateral helix anomaly, speech delay, epilepsy, hypospadias, cryptorchidism, metacarpophalangeal hyperlaxity, postaxial polydactyly of the left foot, dystrophic nails	10

MR: Mental retardation. DD: Developmental delay. mat: maternal.
*Clinical checklist score by de Vries et al.[4].

13 kg (3rd-10th centiles), height 102 cm (25th-50th centiles) and head circumference 47 cm (below 3rd centile). He had microcephaly, trigonocephaly with a prominent metopic suture, long face with a wide and tall forehead, bitemporal narrowing, arched and sparse eyebrows, hypertelorism with a prominent nasal bridge, bilateral epicanthic folds, flat and bulbous nasal tip, hypoplastic columella, long philtrum, small and round mouth, high palate, pointed chin, and bilateral pes planus (Fig. 1A). He could communicate with two-word sentences, could understand simple orders, and could walk with support. At 3.5 years of age, his mental development was appropriate for 13 months. The patient had spontaneously corrected atrial septal defect of secundum type. Abdominal and renal ultrasonography, cranial magnetic resonance imaging, and visual and auditory examinations were normal. He scored 5 points on the checklist.

Chromosome analysis from peripheral blood revealed 46,XY. Subtelomeric FISH analysis further clarified the karyotype as 46,XY,der(9)t(4;9)(qter;pter), leading to subtelomeric trisomy 4q and subtelomeric monosomy 9p (Fig. 1B and 1C). Parental subtelomeric FISH revealed a maternal balanced submicroscopic translocation: 46,XX,t(4;9)(qter;pter). No samples from the daughter of the maternal aunt were available for further genetic testing.

Patient 2

A 4.5-year-old male patient was referred for speech delay. He was born at term as the third child of healthy unrelated parents, with a birth weight of 3150 g (25th-50th centiles). He had two healthy elder sisters. There was no other history of mental retardation in the family. On admission he weighed 15.5 kg (25th-50th centiles), his height was 106 cm (25th-50th centiles) and head circumference was 49.5 cm (25th percentile). He had no significant dysmorphic features except for prominent antihelices and tragi, a prominent nasal bridge, long philtrum, retrognathia, and bilateral syndactyly between second and third toes (Fig. 1D and 1E). The patient had a borderline IQ with predominant delay in speech. He communicated with two-word sentences and could understand simple orders. Abdominal and renal ultrasonography, echocardiography,

cranial magnetic resonance imaging, and visual and auditory examination were all normal. His clinical checklist score was 3 points.

Karyotype as revealed by routine cytogenetic analysis was 46,XY. However, FISH analysis revealed 46,XY,del(22)(qter) (Fig. 1F). Parental analyses showed that the deletion occurred *de novo*.

Patient 3

This 6.5-year-old male patient was referred for severe mental retardation and dysmorphic features. He was born as the second child of healthy unrelated parents at the 42nd week of gestation by cesarean section with a birth weight of 1800 g (below 10th centile). Prenatally there was a history of threatened abortion. He had a healthy elder brother and his mother had seven previous miscarriages. One paternal cousin and one paternal uncle had mental retardation of unknown cause. Five maternal uncles died due to an unknown reason at six months of age, one had polydactyly.

On admission, the patient weighed 9600 g and his height was 88 cm (both below the 3rd centile). His head circumference was 44 cm, which was below -3SD. The patient had severe mental retardation with delay in both mental and motor functions. Dysmorphic features, shown in Figure 1G, included synophrys, epibulbar dermoid on the left, subconjunctival scleral pigmentation on the right, wide and depressed nasal bridge, bilateral anomalous helices, increased anteroposterior diameter of the thorax, hypospadias and an abdominal scar due to inguinal hernia operation. He

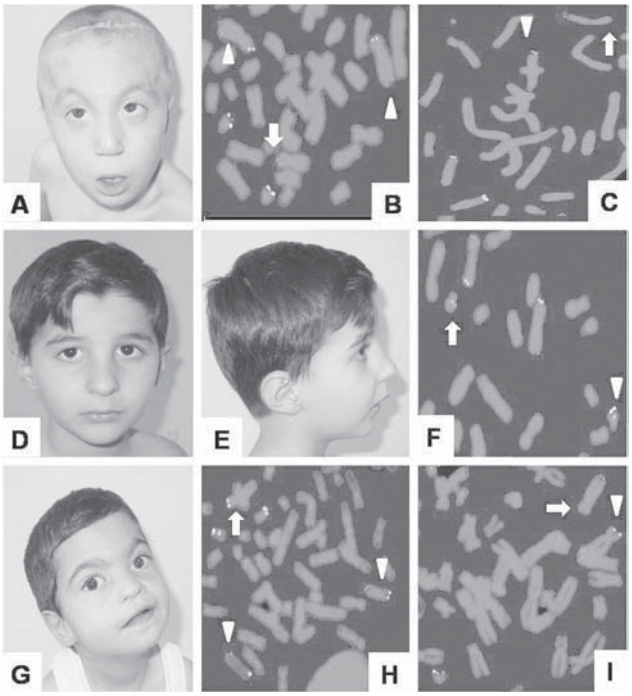

Fig. 1. Facial features and FISH views of the patients with subtelomeric rearrangements.

Facial features of Patient 1 are seen in Fig. 1A. Note the microtrigonocephaly, long face, high and narrow forehead, arched and sparse eyebrows, hypertelorism, bilateral epicanthic folds, prominent nasal bridge, flat and bulbous nasal tip, long philtrum, small mouth and small chin. Subtelomeric FISH reveals three red signals (trisomy 4q) (Fig. 1B). Arrowheads show normal chromosomes 4 and the arrow shows derivative chromosome 9 with a red signal from the third copy of 4q. In Fig. 1C, arrowhead shows normal chromosome 9 and arrow shows the derivative chromosome 9 with no green signal on 9p (monosomy 9p).

Facial features of Patient 2 are seen in Fig. 1D and Fig. 1E. Note the prominent antihelices and tragi, prominent nasal bridge, long philtrum and retrognathia. Subtelomeric FISH reveals a yellow signal only on one of chromosomes 22 (monosomy 22q) (shown by the arrow) (Fig. 1F). The arrowhead shows the normal chromosome 22.

Facial features of Patient 3 are seen in Fig. 1G. Note the rounded face, synophrys, left-sided epibulbar dermoid, wide and flat nasal bridge, and helix anomaly. Arrowheads in Fig. 1H show normal chromosomes 8 and the arrow shows derivative chromosome 4 with a green signal from the third copy of 8p (trisomy 8p). Arrowhead in Fig. 1I shows normal chromosome 4 and arrow shows derivative chromosome 4 (monosomy 4p).

also had epilepsy, hypotonia, laxity of the metacarpophalangeal joints, dystrophic nails, postaxial polydactyly on the left foot and bilateral cryptorchidism. He had no speech or social eye contact. Abdominal and renal ultrasonography, echocardiography, and visual and auditory examinations were normal. Cranial magnetic resonance imaging showed atrophy on the posterior region and splenium of the corpus callosum, and decreased white matter volume. He scored 10 points in the checklist.

Karyotype analysis revealed 46,XY, whereas further analyses for subtelomeric rearrangements revealed 46,XY,der(4)t(4;8)(pter;pter) (Fig. 1H and 1I). Parental karyotypes were normal.

Discussion

Rearrangements of gene-rich subtelomeric regions of chromosomes constitute a significant subgroup among patients with unexplained mental retardation[3,8], ranging between 0-29.4%[1]. The severity of mental retardation significantly affects the yield of analyses for subtelomeric rearrangements. Such rearrangements were detected in 0.5-1.1% of patients with mild mental retardation and in 6.8-7.4% of patients with moderate-severe mental retardation, with an overall frequency of 5.1%[3]. Two recent studies on 11,688 and 7,000 patients with unexplained mental retardation revealed overall frequencies of 2.6%[9] and 2.4%[10], respectively. In the present study, subtelomeric rearrangements were detected in 2.3% of patients with mental retardation of unknown cause. If the group had included more patients with moderate-severe mental retardation, a higher ratio of subtelomeric rearrangements could have been expected.

Studies on subtelomeric rearrangements focus mainly on two topics. The first is determining the inclusion criteria for testing, which aims at increasing the diagnostic yield of testing without missing any cases. The second issue is detection and description of new clinical entities resulting from rearrangements of subtelomeric regions of chromosomes, which requires accumulation of data from case reports. Data accumulated until now revealed that the most frequently detected rearrangements include deletions of 1p, 22q, 4p, 9q, 8p, 2q and 20p[9]. Genotype/phenotype correlations have already been established in some of the conditions[9,12].

Widely accepted checklists or scoring systems for screening subtelomeric rearrangements are as yet unavailable. Clinical checklists are designed to determine inclusion criteria for subtelomeric screening. The selection criteria are mostly based on the severity of the mental retardation, prenatal/postnatal growth retardation, the presence of facial/nonfacial dysmorphism with or without congenital anomalies and family history. One such checklist by de Vries et al.[4] that offers a score of at least 3 as a cut-off for subtelomere screening was reported to have a sensitivity of 100% and a specificity of 27%. A cut-off of 9 points yielded a sensitivity of 11% and a specificity of 99%[4]. Novelli et al.[11] reported that yield may be as high as 16.3% in appropriate groups included using appropriate selection criteria.

Patients included in the present study were scored according to the clinical checklist suggested by de Vries et al.[4]. Subtelomeric rearrangements were detected in three patients with checklist scores of 5, 3 and 10, who had borderline intelligence, mild mental retardation and severe mental retardation, respectively (Table I). Since none of our patients who scored less than 3 had subtelomeric rearrangements, we consider a cut-off at 3 points appropriate for testing; however, statistical confirmation of this cut-off value in collectively larger groups of mentally retarded patients is mandatory. Furthermore, our results also indicate that detection of subtelomeric rearrangements is possible even when the level of mental retardation is not severe.

To date, more than 50 patients with 9p subtelomeric deletions have been reported[12]. Consistent findings include dysmorphic facial features (trigonocephaly, upward slanting palpebral fissures, midface hypoplasia and a long philtrum) and mental retardation[12,13]. Hypertelorism, epicanthic folds, small palpebral fissures, flat nasal bridge, anteverted nares, low-set malformed posteriorly angulated ears, microstomia, micrognathia, short neck, widely spaced nipples, squared convex nails, dolichomesophalangy, and hypotonia were frequently reported. Rare findings include cardiac defects, hernias, omphaloceles, choanal atresia, abnormal genitalia, and scoliosis[14-17].

In some of the reported patients, correct delineation of the clinical features is difficult as a result of complex subtelomeric rearrangements.

Pure deletions of 9p exhibit a more clearly delineated phenotype of the submicroscopic aberration. Trisomy of subtelomere 4q in our Patient 1 may as well be expected to have confounded the phenotype caused by 9p deletion. Fryns et al.[18] reported dup(4)(q34→qter) in a two-month-old female patient who had a birth weight of 3960 g, large tongue and omphalocele. She had hypertonia and microcephaly, widely spaced hypoplastic nipples and hypoplastic labia majora[18]. However, no consistent phenotype of 4q duplications has been described. Instead, duplications/triplication 4q was reported as a neutral genomic polymorphism by Hengstschlager et al.[19] in a seven-year-old mentally retarded boy. Interestingly, along with other clinical features, this boy also presented with omphalocele, a prominent forehead, hypertelorism, epicanthal folds, low-set ears and cryptorchidism.

Patients with del(22)(q13.3) were reported even before the development of techniques detecting submicroscopic rearrangements as a cytogenetically visible aberration. Since the development of subtelomeric screening methods, more than 10 cases with a submicroscopic or cryptic deletion of 22q13.3 region have been reported[12,20]. Phelan et al.[20] reviewed 37 individuals with deletions of 22q13, mostly detected by conventional chromosome analysis. The most consistent clinical features are developmental delay, hypotonia, severe expressive language delay leading to absence of speech, pervasive behavior, normal to advanced growth, and subtle facial dysmorphism[4,12,20-22]. Facial features do not have a characteristic pattern, although the majority of the patients have dolichocephaly, ptosis, epicanthic folds and dysplastic ears[20]; facial features may be more subtle and variable[12,20]. Other frequently reported minor anomalies caused by del(22)(q13.3) include long fingers, nail dysplasia, seizures and ataxia[21-23]. Syndactyly between toes 2-3 were found in 28-38% of patients with del(22)(q13.3)[20]. Manning et al.[24] reported autistic features in 6 of the 11 patients and Anderlid et al.[22] reported an adult female with autistic features.

Clinical features of our second patient consistent with 22q13.3 deletion were speech delay, ear anomalies including prominent antihelix and tragus, subtle facial features, 2-3 syndactyly of the toes and mild mental retardation. He scored 3 in the de Vries checklist, and the patient reported by Baker et al.[21] scored 2 in the same checklist. Considering that most of the patients with del(22)(q13.3) have borderline or mildly low IQ, it is appropriate to investigate del(22)(q13.3) in patients with mild retardation with predominant speech problems and with minor dysmorphic features, even if they score 3 or lower from the checklist.

Terminal deletions of 4p produce a characteristic and well-known phenotype of Wolf-Hirschhorn syndrome, which includes microcephaly, hypertelorism and a prominent glabella with a broad nasal bridge, epicanthic folds, down-turned corners of the mouth, short philtrum and micrognathia along with developmental delay, prenatal growth deficiency and hypotonia. Submicroscopic deletions of subtelomere 4p produce a less severe phenotype with a subset of the described features, which includes growth retardation, microcephaly, mental retardation, seizures, and distinctive facial features[12,22]. Intrauterine growth retardation, hypotonia, hypospadias and atrial septal defect have been described in a patient with submicroscopic 4p deletion[25].

To what extent 8p subtelomeric trisomy contributes to the clinical picture in our Patient 3 is not as easy to identify as it is for subtelomeric 4p monosomy. Duplication (8)(pter→p22), being a long segment of the terminal 8p, was reported to produce mild mental retardation without dysmorphic features[26]. Developmental delay, hypotonia, growth retardation, rounded face, wide and flat nasal bridge, speech delay, and epilepsy are well-known features of subtelomeric del(4p), and hypospadias has been described as a feature[25]. However, epibulbar dermoids, synophrys, undescended testes, anomalies of the ear helix, umbilical hernia, dystrophic changes of the nails, metacarpophalangeal hyperlaxity, and postaxial polydactyly were not described before in the 4p microdeletion cases and these findings may be related to 8p trisomy.

In two of our three patients, the subtelomeric rearrangements occurred *de novo*, which was consistent with the previous reports stating that *de novo* rearrangements represent almost half of the patients in the literature[27].

Interpreting the results of subtelomere testing can be complicated by the fact that in addition to subtelomere rearrangements that are most

likely the cause of the phenotype, there are also deletions or duplications of the subtelomere regions that appear to be benign familial variants, where an affected proband has an imbalance that is subsequently identified in one of the phenotypically normal parents. There have been apparent subtelomeric deletions detected by FISH techniques that have been proven to be benign familial "variations" and not the cause of the child's developmental delay/mental retardation. The most common benign telomeric polymorphisms involve 2q, 4q and 10q[28]. These findings underline the importance of follow-up parental analysis when a subtelomeric abnormality is identified in an affected proband to determine the clinical significance of the results.

The number of reported cases with subtelomeric rearrangements is still inadequate. Therefore, genotype-phenotype correlations are yet to be established in many of the subtelomeric microdeletions. Most subtelomeric abnormalities detected by FISH lead to rarely encountered mental retardation syndromes that have not been fully delineated. Establishing the genotype-phenotype correlations in complex submicroscopic chromosomal aberrations may be even more difficult, as these are usually formed due to unbalanced inheritance of derivative chromosomes in balanced parental rearrangements, leading to coexistent segmental monosomies and trisomies. Thus, recognition and selection of patients for such testing is clinically challenging, and counseling families regarding the natural history of the diagnosis may be difficult.

Testing for subtelomeric rearrangements is now an essential step in the flowcharts for clinical genetic evaluation of mental retardation, following the initial steps of routine chromosome analysis and fragile X testing, the latter being the most common cause of inherited mental retardation. Among the many testing techniques for subtelomeric rearrangements are FISH, array-based comparative genomic hybridization (aCGH) and multiplex ligation-dependent probe analysis (MLPA), the latter two being advantageous in providing higher resolutions. aCGH utilizes newer technology and is more expensive than the others, and is yet unavailable in many Turkish centers. In our opinion, subtelomeric FISH analysis may be considered more appropriate as the initial technique in our country until higher technology is available for routine diagnostics, particularly if clinical evaluation leads to suspicion of a specific chromosomal rearrangement. Furthermore, 44% of the rearrangements were shown to be larger than 5 Mb[10], which renders inappropriate skipping the easier and cheaper steps of the laboratory work-up.

We conclude that analysis for subtelomeric rearrangements should be performed in all patients with unexplained mental retardation, dysmorphic features and normal karyotype, after exclusion of other possible causes suggested by the pattern of the clinical features. One remarkable result from our study is that borderline level of intelligence should not be an exclusion criterion for further subtelomeric screening.

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