A novel case of unilateral blepharophimosis syndrome and mental retardation associated with de novo trisomy for chromosome 3q

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Abstract

We have evaluated a 3 2/12 year old girl who presented with unilateral blepharophimosis, ptosis of the eyelid, and mental retardation. Additional dysmorphic features include microcephaly, high, narrow forehead, short stubby fingers, and adduction of the right first toe. Cytogenetic analysis showed an unbalanced karyotype consisting of 46,XX,add(7)(q+) that was de novo in origin. Fluorescence in situ hybridisation (FISH) using microdissected library probe pools from chromosomes 1, 2, 3, 7, and 3q26-qter showed that the additional material on 7q was derived from the distal end of the long arm of chromosome 3. Our results indicate that the patient had an unbalanced translocation, 46,XX,der(7)t(3;7)(q26-qter;q+) which resulted in trisomy for distal 3q. All currently reported cases of BPES (blepharophimosis-ptosis-epicanthus inversus syndrome) with associated cytogenetic abnormalities show interstitial deletions or balanced translocations involving 3q22-q23 or 3p25.3. Our patient shares similar features to BPES, except for the unilateral ptosis and absence of epicanthus inversus. It is possible that our patient has a contiguous gene defect including at least one locus for a type of blepharophimosis, further suggesting that multiple loci exist for eyelid development. (*J Med Genet* 1997;34:772-776)

Keywords: blepharophimosis; ptosis; mental retardation; 3q26-qter trisomy

Blepharophimosis or shortening of the horizontal orbital fissure is a congenital eyelid malformation that is inherited in an autosomal dominant fashion. There are now more than 150 cases described with the syndrome BPES (MIM 110100¹) showing combined features of blepharophimosis, ptosis, and epicanthus inversus (fold curving in the mediolateral direction, inferior to the inner canthus), low nasal bridge, and ptosis of the eyelids leading to narrowing, both vertically and horizontally, of the palpebral fissures. Thus, subjects with BPES have smaller than normal eyelid openings. The ptosis is usually bilateral and symmetrical. Additional dysmorphic features of the eye include nystagmus, microphthalmos, microcornea, and stenosis of the lateral canal-

iculi. Other pleiotropic features of BPES are mental retardation, notably seen in sporadic cases, and female infertility. The association with female infertility distinguishes two types of BPES, type I and type II, where in the latter type affected females are fertile, so transmission occurs through both sexes.³⁻⁴

Earlier findings of cytogenetic abnormalities that included balanced translocations⁵⁻⁹ and interstitial deletions¹⁰⁻¹⁶ in association with BPES suggested a chromosomal location at 3q22-q23. Subsequent linkage studies have confirmed the map location for both types of BPES to the 3q22-q23 interval,¹⁷⁻²² indicating the possibility that the two types of BPES are allelic or that BPES represents a contiguous gene syndrome.

We report here a 3 2/12 year old, mentally retarded girl with blepharophimosis and unilateral ptosis in addition to multiple other anomalies. Cytogenetic analysis indicated an unbalanced 7q+ chromosome arising from trisomy of the 3q26-qter region.

Case report

The proband was the first child of a healthy couple and there were no other sibs nor any significant family history of the disorder (fig 1). Birth weight and length were reported to be normal but no records were found. The mother and father were 25 and 27 years old, respectively, at the birth of the child. The parents are of Chinese Han descent and are phenotypically normal. However, the paternal grandparents of the patient are first cousins. The pregnancy was uncomplicated except that the mother had an episode of unconsciousness lasting for one minute during the 12th week of pregnancy. The mother had no known contact with any teratogenic agent before or during pregnancy. The child had mild hypoxia lasting for a short time at birth.

The patient was first evaluated at 13 months of age when mild mental retardation and slight

Figure 1 Pedigree of family 3673 with BPES.

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Figure 2 Anterior view of the proband aged 3 years. Note the distinctive facial features showing blepharophimosis, ptosis of the right eye, high forehead, and microcephaly. (Photograph reproduced with permission.)

ptosis of the right eyelid were noted. However, no ophthalmological examination was done at that time. She could sit unaided, but was unable to crawl. The child showed slow responses to surrounding changes despite a normal audiology screen. She also had simple vocalisation. Physical examination showed that the lungs, heart, and abdomen were normal. No limb abnormalities were found and the fontanelles have fully closed. Thirteen teeth had erupted and bone x rays showed normal bone development typical of a 13 month old child.

The child was re-examined at 38 months of age. Mental retardation was quite evident and the ptosis of the right eyelid had become obvious. Vocalisation consisted of a single word. On examination her length at 93.5 cm and weight at 14 kg were normal. A length and weight of 94.2 cm and 13.44 kg is average for a 3 year old Chinese Han girl. The occipitofrontal circumference (OFC) of 46 cm was much smaller than normal (<1st centile and comparable to the mean OFC (46.2 cm) for Chinese children at 18 months of age).²³ In addition the right temporal bone was smaller than the left, the occiput was flat, and the forehead was narrow (fig 2). The patient also showed blepharophimosis and ptosis of the right eyelid but there was no epicanthus inversus. The inner canthal distance (ICD) was 3.5 cm (>6th centile with a mean ICD (3.284 cm) age of a female adult) and the outer canthal distance (OCD) was 8.6

cm (<1st centile with a mean OCD (8.672 cm) age of a female adult). The palpebral fissure length was normal at 2.5 cm and the maximum vertical palpebral opening for the left eye was 0.6 cm compared to 0.4 cm for the right eye.

The proband also showed a dull face, gelasmus, hypotrichosis with a low posterior hairline, a flat nasal bridge, high but narrow palate, redundant skin on the neck, and low set and posteriorly rotated ears. Chest circumference was normal at 52.5 cm and the distance between the two nipples was also normal. The circumference of the abdomen was also normal at 53 cm, and the liver and spleen were of normal size. The finger to finger distance was normal at 91 cm. The hands were broad and the fingers were short and stubby. The second toe on the right foot overrode the third toe and adduction of the first toe was evident. Her gait was immature and clumsy. Examination of the vulva was normal. Tests for muscular tone showed the child has mild generalised hypotonia. No abnormal pathological reflexes were found.

CYTOGENETICS

Peripheral blood was set up in 72 hour cultures and the metaphase spreads were prepared for G banding and high resolution staining using standard techniques. Chromosomal analysis showed an unbalanced karyotype with additional material on the terminal end of the long arm of chromosome 7, 46,XX,7q+ (fig 3A, B). The karyotype of both parents was normal. No other cytogenetic abnormality was detected in the child's chromosomes. The banding patterns indicated that no chromosome 7 material was lost during the translocation although loss of a small region at the tip of 7q is possible.

FISH

Fluorescent in situ hybridisation (FISH) with chromosome specific paint probes was performed using standard procedures. Whole chromosome microdissection probe pools^{24 25} from chromosomes 1, 2, 3, 7, and 21 were used. The chromosome 7 library probe indicated that one chromosome 7 did not have the signal extending completely to its long arm terminal end confirming the extra chromosome 7 material (results not shown). Closer examination also indicated that there was no visible reciprocal translocation of chromosome material from chromosome 7 to other chromosomes. Chromosome 21 microdissection probe pool was next used for chromosome painting because the patient's mental retardation is similar to that of trisomy 21. However, the results (data not shown) indicated that the extra chromosomal material on 7q was not derived from chromosome 21. Similarly, chromosome painting using whole chromosomes 1 and 2 library pools painted only chromosomes 1 and 2, respectively (data not shown). However, three signals were obtained when whole chromosome 3 library pool probe was used where both chromosomes 3 were fully painted and an additional signal was present on the terminal der(7q) (results not shown).

Figure 3 (A) Routine G banded karyotype of the patient. The two chromosomes 7 are indicated by arrows. (B) Partial chromosome 7 karyotype is shown with the arrows indicating where the breakpoints in chromosomes 3 and 7 occurred.

Figure 4 FISH with chromosome 3q26-qter specific probe. In addition to the signals from the normal chromosomes 3, an additional signal was obtained at the terminal end of chromosome 7q (indicated by an arrow) using the 3q26-qter microdissection probe pools.

The results of G banding (fig 3B) and FISH using chromosome 3 probe indicated that only the distal part (3q26-qter) of chromosome 3 may be involved in the duplication. Further FISH analysis was performed using microdissected chromosome band specific probe pool from 3q26-qter. The results confirmed that the additional material on 7q was derived from the region of 3q26-qter (fig 4). Since no extra chromosome painting signal was obtained with chromosome 7 library pool probe (see above), the additional 3q26-qter material on chromosome 7q was the result of an unbalanced translocation leading to trisomy 3q26-qter. The patient's karyotype was designated 46,XX,der(7)t(3;7)(q26-qter;7q+) de novo.

Discussion

The cumulative cytogenetic data for BPES cases have suggested overlapping chromosomal abnormalities in the 3q22-q23 region (reviewed recently in Jewett *et al*¹⁴). However blepharophimosis and ptosis have also been associated with the loss of 3p25,^{26, 28} suggesting genetic heterogeneity in patients with BPES.²⁹ Recently, BPES in a large Indian pedigree was linked to chromosome 7p13-p21.³⁰ Table 1 presents a summary of the spectrum of clinical features of BPES in association with known cytogenetic abnormalities compared to the features seen in our patient with trisomy 3q26-qter. With the exception of unilateral ptosis and

absence of epicanthus inversus, the physical features of the patient presented in this study show similarities to that of BPES patients. Other cases of BPES without epicanthus inversus have previously been reported.^{30, 31}

To our knowledge this is the first description of a partial trisomy for chromosome 3q26-qter that leads to blepharophimosis, ptosis, and mental retardation. Other reported cases of partial trisomy of the long arm of chromosome 3 are presented in table 2 and compared to our case. It is interesting that in two of these cases,^{32, 33} unilateral anomalies of the right eye, similar to those described here, are associated with partial trisomy for 3q. Additional pleiotropic features in BPES consisting of microcephaly, developmental retardation, primary amenorrhoea, premature ovarian failure, cryptorchidism, cleft palate, micrognathia, dental anomalies, pectus excavatum, brachycamptodactyly, and polythelia^{4, 6, 10, 11, 13, 14, 16, 34, 46} indicate the possibility of a contiguous gene syndrome. It is reasonable to suspect that reported cases of BPES with multiple anomalies associated with cytogenetic abnormalities are the result of a contiguous gene syndrome, whereas isolated cases of BPES with no cytogenetic rearrangements may be the result of a single gene defect.²⁰ In our patient the region of trisomy which is distal to 3q22-q23 further suggests that BPES is genetically heterogeneous and the clinical features may indicate a contiguous gene syndrome encompassing at least one locus for eyelid development⁴⁷ in chromosome 3q. It is possible that a small undetectable chromosomal loss from the distal tip of chromosome 7q may have contributed to the clinical features of the patient described here. However, cases involving partial deletion or monosomy for chromosome 7q34-qter show clinical features of Smith-Lemli-Opitz (SLO, MIM 270400¹) syndrome.⁴⁸ SLO syndrome predominantly shows genitourinary abnormalities, cleft palate, and polydactyly. These features are not apparent in our patient though the microcephaly and mental retardation overlap in both diseases.

It is of interest that a number of candidate genes of significance to eye development have been mapped to the distal long arm of chromosome 3. The retinol binding proteins RBP1 and RBP2⁴⁹ have been mapped to 3q21-q22 and 3q21-q25, respectively. Mouse mutants that are homozygous null in the RXRa retinoic acid receptor gene have smaller palpebral fissures than the wild type,⁵⁰ indicating that

Table 1 Summary of BPES associated phenotype involving chromosome deletions and balanced translocations

Chromosome aberration	del(3p)	del(3q)	del (7p)	del(7q)	t(2;3)	t(3;4)	t(3;7)	t(3;8)	t(3;11)	This study
Chromosomal breakpoints	3qter-3p25.3	3q22-3q23	7p13-7p15	7pter-7q34	3q23; 2pter-2q22	3q23; 4p15	3q23; 7q23	3q23; 8p21	3q21; 11q23	Trisomy 3q26-qter
Blepharophimosis	+	+	+	+	+	+	+	+	+	+
Ptosis	+	+	-	+	+	+	+	+	+	+
Epicanthus inversus	+	+	+	+	+	+	+	+	+	-
Microcephaly	+	+	+	+	NR	-	-	+	-	+
Malformed ears	+	+	+	+	+	-	-	+	-	+
Malformed palate	NR	+	-	+	NR	-	NR	+	NR	+
Mental retardation	+	+	NR	+	+	-	-	+	-	+
Growth delay	+	+	+	+	+	-	-	+	-	+
Syndactyly of toes 2-3	NR	+	+	NR	+	-	NR	NR	NR	+
Adduction of toe 1	NR	+	+	NR	+	-	NR	NR	NR	+
References	29	11-16, 29	59	29	29	60	8	7	6	

+ present; - absent; NR not reported; (R) observed only on the right side of the body.

Table 2 Summary of clinical features associated with partial trisomy of 3q

Chromosomal breakpoints	3q21-qter	3q21-qter	3q22.1-q24	3q26	3q25-q28	3q26.2-qter	This study
Blepharophimosis	-	NR	-	-	+	-	+ (R)
Ptois	-	NR	-	-	NR	-	+ (R)
Epicanthus inversus	-	-	-	-	-	-	-
Anophthalmia	-	+ (R)	-	-	-	-	-
Microcephaly	+	NR	-	NR	NR	NR	+
Malformed ear	NR	+	-	+	+	+	+
Malformed palate	NR	+	-	NR	+	+	+
Syndactyly of toes 2-3	-	NR	-	-	NR	NR	+ (R)
Adduction of toe 1	-	NR	-	NR	NR	NR	+ (R)
Talipes equinovarus	NR	+	-	NR	+	NR	-
Clinodactyly of 5th finger	+	+	+	NR	+	NR	-
Mental retardation	NR	+	+	NR	+	+	+
Growth delay	NR	+	-	+	+	NR	+
Short, webbed neck	+	+	-	+	NR	+	+
Hirsutism	NR	+	-	+	+	-	-
Cataract	NR	NR	NR	+	NR	+	-
Glaucoma	NR	NR	NR	+	NR	NR	-
Coloboma of iris of eyes	+ (R)	NR	NR	NR	NR	NR	-
References	32	33	35	61	62	63	

+ present; - absent; NR not reported; (R) observed only on the right side of the body.

retinoic acid signalling may play an important role in eyelid development. In addition, the ceruloplasmin (CP) gene has been mapped to 3q23 and mutations in this gene give rise to excessive iron accumulation resulting in neurodegeneration of the retina and basal ganglia.^{51 52} Another likely candidate is the HRV gene that has been mapped to 3q28-q29⁵³ and is the human homologue of the hairy gene in *Drosophila*. The protein product of the hairy gene is a participant in the Notch signalling pathway and is involved in segmentation and neural development during early *Drosophila* embryogenesis.^{54 55} The murine and rat homologues of this gene have been established to be important in eye development and morphogenesis.⁵⁶⁻⁵⁸ Additional studies will be necessary to determine the potential role(s) of these candidate genes in BPES.

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