Partial trisomy 10q with mild phenotype caused by an unbalanced X;10 translocation


ELECTRONIC LETTER

Partial trisomy 10q has been detected in spontaneous abortions and prenatally. Although there are no reports of duplication of the whole long arm of chromosome 10, duplication of 10q21–qter has been found in a stillborn infant. Trisomy of more proximal 10q is associated with a characteristic syndrome and has been described in many cases which almost always are familial, but patients with trisomy of the proximal or medial segment of 10q have been less often described.

We report on a 4 year old girl with a de novo unbalanced X;10 translocation, karyotype 46,X,der(X)t(X;10)(q21.2;q11.2), who is thus trisomic for almost the whole long arm of chromosome 10. As her clinical phenotype is disproportionally mild in relation to the region of 10q trisomy, we hypothesised that preferential inactivation of the derivative X;10 chromosome with spreading of X inactivation into the 10q segment might account for this discrepancy between phenotype and genotype. We report results of investigations of late replication, a feature of the inactive X, and expression and sequence analysis of genes located on the translocated region of 10q, and discuss our results relative to previous reports of unbalanced X;10 translocations.

CASE REPORT

Clinical findings
The proband was the second child of a healthy 28 year old mother and 40 year old father, born at term after an uneventful pregnancy. Her birth measurements were low but appropriate for gestational age: weight 3230 g (25th centile), length 46.5 cm (3rd centile), and head circumference 33 cm (10th centile). Apgar scores were 9 at one minute and 9 at five minutes. There was no family history of repeated miscarriages, mental retardation, or malformation syndromes.

She was referred for neurological evaluation aged 2 years because of delayed speech development. She had hardly any expressive speech and her ability to understand spoken language was delayed by almost one year. Psychomotor development and neurological status were otherwise regarded as normal. Hearing was intact. She was not strikingly dysmorphic. Height (50th centile) and weight and head circumference (25th centile) were within the normal range. The cardiologist’s evaluation showed an innocent heart murmur. The echocardiogram and renal ultrasound examination were normal. Ophthalmological evaluation did not show any ocular abnormality.

Pertinent dysmorphological findings at the age of 3 years when evaluated at the Department of Clinical Genetics (fig 1) included deep set eyes, epicanthic folds, straight palpebral fissures which were of normal length, normal interpupillary, inner canthal, and outer canthal distances of the eyes, bluish sclerae; flat nasal base, short anteverted nose, short columella; short philtrum with distally deviating pillars; downturned corners of the mouth, slightly high arched palate; small well folded ears with ear length on the 3rd centile and attached lobules bilaterally; appearance of a slightly short neck, normal posterior hairline; broad chest with widely spaced, inverted nipples, mild pectus excavatum; and a sandal gap between the first and second toes.

Key points
- In cases of X;autosome translocation X inactivation can spread into an attached segment of autosomal chromatin in a variable manner.
- We have studied this phenomenon in an infant, karyotype 46,X,der(X)t(X;10)(q21.2;q11.2).
- Studies of late replication, a feature of the inactive X, and expression analysis of two translocated autosomal genes clearly show an extensive spread of X inactivation covering most of the translocated 10q chromatin. These findings explain the disproportionally mild phenotype seen relative to the region of 10q trisomy.
- Comparison of this case with previous reports of unbalanced X;10 translocations provides further insight into the spread of X inactivation in X;autosome rearrangements.

Abbreviations: LINE-1, long interspersed nuclear element-1; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase PCR

Figure 1  Full face and profile of the proband aged 3 years showing deep set eyes, flat nasal base, short, anteverted nose, and downturned corners of the mouth.
between chromosomes X and 10. The abnormal X chromosome comprised a partial deletion of the long arm of the X substituted by most of the long arm of chromosome 10, karyotype 46, X, der(X)(X:10)(q21.2;ql1.2). Parental karyotypes were normal.

Analysis of inactivation of the X chromosome at the AJAX locus was uninformative. Combined detection of late replicating chromatin by exposure of peripheral blood cultures to BrdU for five hours, immunolabelling with monoclonal anti-BrdU, and subsequent in situ hybridisation with whole chromosome 10 paint showed that in each of 27 cells examined the der(X) was late replicating, indicating skewed X inactivation with preferential silencing of the translocated X:10 chromosome. In every cell examined a partial spreading of late replication into the translocated 10q segment was observed, although the extent of this spread varied among cells (fig 2). In most metaphases (17 of 27), BrdU staining extended over two thirds to three quarters of the translocated 10q chromatin. However, although the most proximal 10q bands were strongly labelled, BrdU labelling over the medial segment of translocated 10q was weak, diffuse, and variable.

By contrast, seven of 27 cells showed a strong and continuous spread of BrdU staining over most of the 10q segment. In the remaining three of 27 cells examined, there was a minimal spread of late replication into only the most proximal region of translocated 10q.

Results of allele specific transcription studies are shown in figs 3 and 4. DNA and RNA were extracted from peripheral blood lymphocytes of the proband and her parents by standard protocols, and cDNA was synthesised with M-MLV RTase (Gibco BRL). Polymerase chain reaction (PCR) amplification of a transcribed 5 bp insertion polymorphism within PTEN (located in 10q23.3) and a transcribed pentamer repeat within MXI1 (10q25.2) (http://gdbwww.gdb.org/) was then performed with DNA and cDNA, and the products resolved on an ABI 377 sequencer. For both PTEN and MXI1, results from proband DNA (track 1) show one allele to be roughly double the relative intensity of that in parental DNA (tracks 2 and 3), indicating the inclusion of these loci in the trisomic segment of 10q. However, analysis of proband cDNA (track 4) shows a reduction in the height of one allele relative to that seen in her DNA, indicating transcriptional silencing of these genes. For MXI1, in proband cDNA (track 4) the single 240 bp allele is reduced to about one quarter of the relative intensity of proband DNA (track 1), suggesting that transcription of this gene from the der(X;10) is reduced to some 25% of normal. Similarly for PTEN, the relative allele ratio in proband cDNA (track 4) is similar to that found in both DNA (tracks 2 and 3) and cDNA (track 6) of normal controls, and significantly different from that in the proband DNA (track 1), indicating complete or nearly complete inactivation of this gene on the der(X;10).

Gene sequences of PTEN (covering 102 904 bp) and MXI1 (60 337 bp) were extracted from the Human Genome Browser, April 2002 assembly (http://genome.ucsc.edu/) and were analysed with RepeatMasker (http://ftp.genome.washington.edu/RM/RepeatMasker.html) to determine long interspersed nuclear element-1 (LINE-1) content. LINE-1s comprise of 19.8% PTEN and 11.4% MXI1 intragenic sequence.

DISCUSSION

We report on a female patient with trisomy of 10q11.2–qter and a monosomy of Xq21.2–qter owing to a de novo unbalanced X:10 translocation, associated with speech delay and facial dysmorphism, but no major malformations. Although her phenotypic findings do not conclusively identify with a specific syndrome, similar facial features have been reported in distal 10q trisomy. Other mild dysmorphic signs present in our patient, for example, the mild pectus excavatum and a widened gap between the big toe and second toe, are also associated with trisomy of distal 10q. Although the translocation also results in monosomy for Xq21-qter, she does not have any major stigmata of Turner’s syndrome, except for a short neck and broad chest, although ovarian function is currently unknown because of her present age (4 years).

The phenotype of the patient we describe here is clearly milder than that for partial trisomy of distal 10q. Although her facial dysmorphism resembles distal 10q trisomy, she lacks several characteristic features of the syndrome, for example, flat facies, short, downward slanting palpebral fissures, and ocular abnormalities. Our patient also lacks microcephaly and prenatal and postnatal growth retardation which are present in most patients. About 25% of reported patients with distal 10q trisomy die within the first year of life, mostly resulting from internal malformations and respiratory infection, and most survivors are severely to profoundly mentally retarded.1,4

Our studies provide compelling evidence that the disproportionately mild phenotype of our patient is the result of preferential inactivation of the translocated X, with spreading of X inactivation in cis into the translocated 10q segment. Replication timing studies showed a complex spread of late replication into the autosomal portion of the der(X). Although the most proximal portion of translocated 10q seemed to be late replicating in every cell, late labelling within the medial region (roughly bands 10q23-25) was highly variable and often diffuse. We interpret these variations to indicate either a delayed replication timing in this region, intermediate
between that of the inactive X and normal chromosome 10, or alternatively mosaicism owing to a reduced ability of autosomal chromatin to either transmit or maintain the X inactivation signal in a stable state. The mosaicism hypothesis is supported by recent studies of X;autosome translocations.

Our findings of mild patient phenotype and variation in the spread of late replication were consistent with transcription studies of two genes on the translocated 10q segment, which similarly had reduced or abolished expression. Thus, our finding of the spreading of X inactivation shows close similarities to that in an unbalanced X;21 translocation reported by Couturier et al., who similarly found an intermediate delay in replication timing of the translocated chromosome 21 segment, accompanied by reduced activity of a gene located upon it and an attenuated clinical phenotype.

Sequence analysis of both the X chromosome and X;autosome translocations strongly suggests that LINE-1 repeats act to promote the spread of X inactivation in cis. Although X inactivated genes contain high densities of LINE-1s, they occur at significantly lower density in genes escaping X inactivation. Consistent with their inactivation in this case, both PTEN and MXI1 contain high densities of LINE-1 (19.8% and 11.4% respectively). By comparison, analysis of five X;autosome translocations found the mean LINE-1 density of autosomal genes silenced by the spread of X inactivation to be 8.7%, while autosomal genes which escaped the spread of X inactivation contained a mean of 1.2% LINE-1.

There have been three previous reports of unbalanced X;10 translocations involving similar regions to that seen in our patient. Garcia-Heras et al. reported on a patient trisomic for the segment 10q21–qter, karyotype 46,X,der(X)t(X;10)(q26;q21). Although she had a smaller translocated region of 10q than our case, her phenotype was more marked, with moderate mental retardation, microcephaly, short stature, blepharophimosis, and ptosis. Although there was exclusive silencing of the der(X;10), no spreading of late replication into the translocated 10q segment was noted. Sharp et al. reported a second female patient with trisomy for the region 10q23.3–qter, karyotype 46,X,der(X)t(X;10)(q26.3;q21). Although there was a smaller translocated region of 10q than our case, her phenotype was more marked, with moderate mental retardation, microcephaly, short stature, blepharophimosis, and ptosis. Although there was exclusive silencing of the der(X;10), no spreading of late replication into the translocated 10q segment was noted. Sharp et al. reported a second female patient with trisomy for the region 10q23.3–qter, karyotype 46,X,der(X)t(X;10)(q26.3;q23.3), who completely lacked any features normally associated with trisomy 10q, presenting only with secondary amenorrhoea. Studies in this case also found exclusive inactivation of the der(X;10).
However, despite a complete lack of spreading of late replication, expression studies showed a spread of gene silencing over most of the translocated 10q segment. A third case described only in an abstract, with apparently the same karyotype as our patient, showed short stature, facial dysmorphism including deep set eyes, mild mental retardation, and pulmonary stenosis.

Thus, as indicated by the attenuated phenotypic abnormalities in these patients, X inactivation seems to have a remarkable ability to spread into 10q chromatin. The spread of late replication in these translocations varies, apparently diminishing with increasing distance from the X inactivation centre (Xq13.2). Expression studies in the case reported by Sharp et al. showed that MXI1 was completely inactivated on the der(X;10). However, analysis in our case shows that this same gene retains roughly 25% activity from the der(X;10). Therefore, although sequence specific factors, such as LINE-1 repeats, play a considerable part in dictating the spread of X inactivation, comparison of these cases shows that the relative position of translocation breakpoints also strongly influences the extent of spread of X inactivation in X;autosome rearrangements. These data also suggest that the ability of X inactivation to silence autosomal genes diminishes with increasing distance from cis linked X chromatin.

References


Figure 4 Photomicrograph and ideogram of the der(X;10) showing location and expression status of the two 10q genes assayed by RT-PCR.
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