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ORIGINAL ARTICLE

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Characterisation of a non-recurrent familial translocation t(7;9)(q11.23;p24.3) points to a recurrent involvement of the Williams–Beuren syndrome region in chromosomal rearrangements

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Abstract Recurrent and non-recurrent chromosomal rearrangements seem to reflect susceptibility to DNA rearrangements due to the presence of recombinogenic motifs in at least one partner chromosomal region. While specific genomic motifs such as AT-rich repeats, fragile sites and Alu repeats are often found in recurrent translocations, the molecular mechanisms underlying non-recurrent chromosomal rearrangements remain largely unknown. Here, we map the breakpoint region of a non-recurrent translocation, t(7;9)(q11.23;p24.3), present in a healthy woman who inherited the apparently balanced translocation from her mother and transmitted the same rearrangement to two sons —respectively healthy and aborted. Characterisation by a two-step FISH analysis, first with BAC clones and then with small locus-specific probes, restricted the breakpoint intervals to 8–10 kb. Both regions contained specific Alu sequences, which, together with the flanking low copy repeat block Ac in 7q11.23, might stimulate the translocation. We noted that, although the translocation is non-recurrent, 7q11.23 is recurrently involved in different chromosomal rearrangements, supporting the hypothesis that the 7q11.23 genomic structure is prone to recombination events.

Key words t(7;9)(q11.23;p24.3) · 7q11.23 · Williams–Beuren region · Recurrent breakpoint · Alu sequences

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Introduction

Structural chromosomal rearrangements are defined as recurrent or non-recurrent on the basis of their frequency in the human population and the involvement of the same cytogenetic band. Their occurrence is likely to be related to architectural features of specific genomic regions (Stankiewicz and Lupski 2002). It is well known that recurrent deletions, duplications and inversions are caused mainly by non-allelic homologous recombination (NAHR), mediated by low copy repeats (LCRs) (Lupski 1998; Stankiewicz and Lupski 2002), while AT-rich repeats (Kurahashi et al. 2003), fragile sites (Stankiewicz and Lupski 2002) and specific Alu repeats (Hill et al. 2000) are often involved in recurrent translocations. Other than these features, the molecular mechanisms underlying non-recurrent chromosomal rearrangements are often unknown or are simply called "mediated by random events", even if some of them seem to reflect susceptibility to DNA rearrangements stimulated by genomic architecture (Inoue et al. 2002; Stankiewicz et al. 2003). Evidence for the involvement of LCR-rich regions in both recurrent segmental aneusomies and recurrent or non-recurrent translocations has been reported for chromosomal regions 17p11.2-p12, 22q11 and 7q11.23 (Stankiewicz et al. 2003; Hill et al. 2000; Morris et al. 1993; von Dadelszen et al. 2000; Duba et al. 2002). It is worth noting that 17p11.2-p12 LCRs are implicated in the deletion causing Smith-Magenis [SMS (MIM 182290)] and hereditary neuropathy with liability to pressure palsies [HNPP (MIM 162500)] (Chen et al. 1997; Reiter et al. 1996), and in the duplication of the same region causing Charcot-Marie-Tooth type 1A (CMT1A [MIM 118220]) and dup(17)(p11.2p11.2) syndrome (Chance et al. 1994; Potocki et al. 2000). 22q11 LCRs have a role in deletions giving rise to DiGeorge syndrome [DGS (MIM 188400)] (Shaikh et al. 2000), velocardiofacial syndrome [VCFS (MIM 192430)] (Shaikh et al.

2000) and conotruncal anomaly face syndrome [CAFS (MIM 217095)] (Shaikh et al. 2001), while LCRs in 7q11.23 are implicated in the deletion causing Williams–Beuren syndrome [WBS (MIM 194050)] (Valero et al. 2000). The same 22q11 region was found to be involved in the recurrent translocations t(11;22) and t(17;22), which leads to normal and neurofibromatosis type 1 [NF1 (MIM 162200)] phenotypes, respectively (Hill et al. 2000; Kehrer-Sawatzki et al. 1997). The 17p11.2 and 7q11.23 regions are involved in non-recurrent translocations and, depending on the localization of breakpoints on both partner chromosomes, they may cause either a normal or a pathological phenotype. Here, we describe a non-recurrent translocation, t(7;9)(q11.23;p24.3), identified in a woman showing a normal phenotype. The breakpoint of chromosome 7 maps at WBS region, which is characterised by the presence of three large LCRs named A, B and C, flanking WBS deletions (Valero et al. 2000).

We precisely mapped the breakpoints of t(7;9)(q11.23;p24.3) by FISH with BAC clones and small locus-specific probes. Following restriction of the breakpoint intervals and bioinformatic analysis, we found specific genomic motifs possibly stimulating the translocation in the 7q11.23 region, recurrently involved in different chromosomal rearrangements.

Materials and methods

Subject

The index case was a healthy woman, first identified as a carrier of a balanced translocation t(7;9)(q11.23;p24.3) in the genetics laboratory of the Medical Genetics Department, University of Turin, Italy. She experienced six early spontaneous pregnancy interruptions and had only one living child (13 years old) showing the same translocation. She had inherited the chromosomal rearrangement from the mother, who did not show reproductive failure and had another child with normal karyotype. At ongoing further pregnancy, the index case requested prenatal diagnosis, and amniocentesis was performed at the 16th week of gestation. The karyotype from amniocytes, performed in our prenatal diagnosis lab, evidenced apparently the same translocation. At the 30th week of gestation, the woman delivered a stillborn male due to a *Candida albicans* infection.

Cell cultures, chromosome and interphase nuclei preparations

A lymphoblastoid cell line from the index case was established from peripheral blood using Epstein–Barr virus (EBV) according to standard procedures, by means of a service provided by the Biochemical and Genetics Lab of Neurological Institute C. Besta in Milan. Cell culture was performed using standard protocols. Chromosome preparations were obtained using a standard technique.

Clone preparations

Some BAC clones (RP11-10G22, RP11-143M15, RP11-147I11, RP11-148M21) were supplied by the DIBIT-HSR Resource Centre in Milan, Italy, and other from RES-GEN (Invitrogen, Carlsbad, CA; RP11-622P13, RP11-731K22, CTB-23I15, CTA-325H1). DNA was obtained starting from a single colony grown in 4 ml LB medium supplemented with 20 μg/ml chloramphenicol (Sigma, St. Louis, MO) following standard procedures.

Locus-specific probe preparation

The method previously described (Riva et al. 1999) is based on two consecutive reactions using BAC clones containing the loci of interest. The primers used to generate the eight locus-specific probes are listed in Table 1.

FISH

BAC clones and locus-specific probes were labelled with digoxigenin-dUTP (Roche Diagnostic, Mannheim, Germany) using a nick translation kit (Roche Diagnostic). The FISH experiments were performed according to standard procedures (Lichter et al. 1992).

In silico sequence analysis

In silico sequence analysis was performed using the following databases and bioinformatic tools: Entrez Nucleotides Database (build 35.1), http://www.ncbi.nlm.nih.gov/Entrez/ query.fcgi?db=nucleotide; NCBI BLAST, http://www.ncbi.nlm.nih.gov/Blast/; Ensembl Human Genome Browser (release 26.35.1), http://www.ensembl.org/Homo_sapiens; Duplication in Human Genome (Assembly: July 2003), http://tcag.ca/index.

Table 1 Sequences of primers used for locus-specific probe generation

Primer	Sequence 5′–3′
23-LS 22 F	GAAGCCGAAGAAGCCCTG
23-LS 22 R	CACCTTGGAGCACTATGAC
23-LS 60 F	CCAGTTTAGAGGAGGAGCC
23-LS 60 R	CAAAAAGGAGCCAGTGATG
23-LS 80 F	ACCTGATGCATGCAGTGAAA
23-LS 80 R	GCTATCCTCACGCCTGACTT
143-LS 23 F	GTTCTGGCTCTCTTCTTCCT
143-LS 23 R	CTTCCTGCTTTCTTTGGTGCT
143-LS 80 F	CAGAGAGGTAGCAGAAGTGT
143-LS 80 R	GGCAGTGGGAAAACGAGAG
143-LS 90 F	CATCCCCCAGCATTTTCAC
143-LS 90 R	TCTCATTCTCTAAGTTCTCTA
143-LS 130 F	GTTAGTTGTGGAGGTAGATT
143-LS 130 R	GAGAGAAGAGATGATTGCTG
143-LS 170 F	CTTCCTCTTCATCACATCCTT
143-LS 170 R	TCCTCCCACCCCCATCATC

php?pagename=tcagDatabases.php; Palindrome, http://bioweb.pasteur.fr/seqanal/rna/intro-uk.html; PipMaker, http://pipmaker.bx.psu.edu/pipmaker/

Results

Localisation of breakpoint regions

Conventional cytogenetic analysis of the translocation t(7;9)(q11.23;p24), following Q banding, confirmed that the 7q breakpoint was localized in the Williams–Beuren critical region. We thus performed FISH analysis using the commercial Elastin (ELN) probe giving fluorescent signals only on der 9. As reported in the 7q11.23 physical map, three different D7S489 markers are present in this region: D7S489A (excluded from the breakpoint region by ELN FISH analysis), D7S489B and D7S489C (Valero et al. 2000). From the published physical map we selected 6 BACs proximal to the ELN gene (Fig. 1a). Following FISH analysis we observed that clone 23I15, specific for the B allele proximal to the ELN gene, showed fluorescent signals on both der 7 and der 9. FISH with the remaining four clones covering the region between the ELN gene and allele B, and one clone specific for allele C, produced specific signals only on der 9 and der 7, respectively, confirming that 23I15 contains the translocation breakpoint on chromosome 7 (Fig. 1a). We matched the clone 23I15 sequence with the complete genome using BLAST software (http://www.ncbi.nlm.nih.gov/Blast/), allowing identification of the 9p24-specific clone 143M15, which shows significant stretches of similarity with CTB-23I15, with a mean identity of 85–91% and a maximum size of 600 bp. Comprehensive similarity analysis of 23I15 with RP11-143M15 and reciprocal matching allowed us to establish and visualize the distribution of all regions of similarity between the two clones (Fig. 2). The analysis showed that the percentage of the two clones displaying >75% similarity is 32% for 143M15 and 60% for 23I15. The presence of multiple lines sharing similarity indicates the repetitive nature of these sequences. We performed FISH with 143M15, which was shared by the two derivatives and thus contains the 9p breakpoint, and with two further clones, 147I11 and 130C19 (Fig. 1b), showing signals on der 7 and der 9, respectively (data not shown). On the basis of the above findings, the 7q and 9p breakpoints were mapped to genomic intervals sized 107 and 179 kb, respectively. In order to restrict the critical breakpoint regions, we generated, from the two clones encompassing the breakpoints, eight locus-specific probes, three for 7q and five for 9p, most of them centred on the major points of similarity between the two clones (Fig. 3).

Following FISH analysis we observed that the 7q probes LS20, LS80 and LS60, generated from 23I15, were localized on der 9, der 7 and on both derivative chromosomes, respectively. Regarding the 9p probes generated from 143M15, only LS170 was observed on both

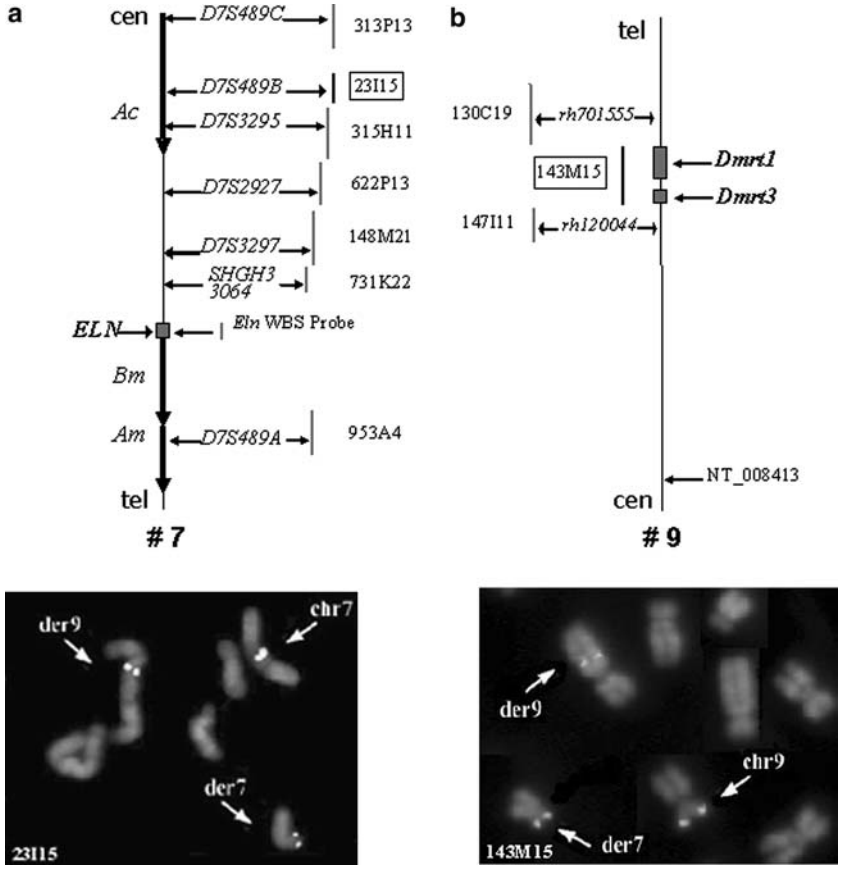

Fig. 1 **a** Schematic representation of the 7q11.23 genomic region. All clones and the commercial probe specific for ELN–WBS (Elastin–Williams–Beuren syndrome) gene used for FISH experiments are indicated on the *right*. The *boxed* clone 23I15 identified the breakpoint region on chromosome 7. *Lower panel* Partial metaphase plate after FISH with 23I15 probe. *Arrows* Normal chromosome 7 and derivatives, all showing specific hybridisation signals. **b** Schematic representation of the 9p24.3 genomic region. Clones used for FISH experiments are indicated on the *left*. The *boxed* clone 143M15 identified the breakpoint region on chromosome 9. *Lower panel* Partial metaphase plate after FISH with 143M15 probe. *Arrows* Normal chromosome 9 and derivatives, all showing specific hybridisation signals

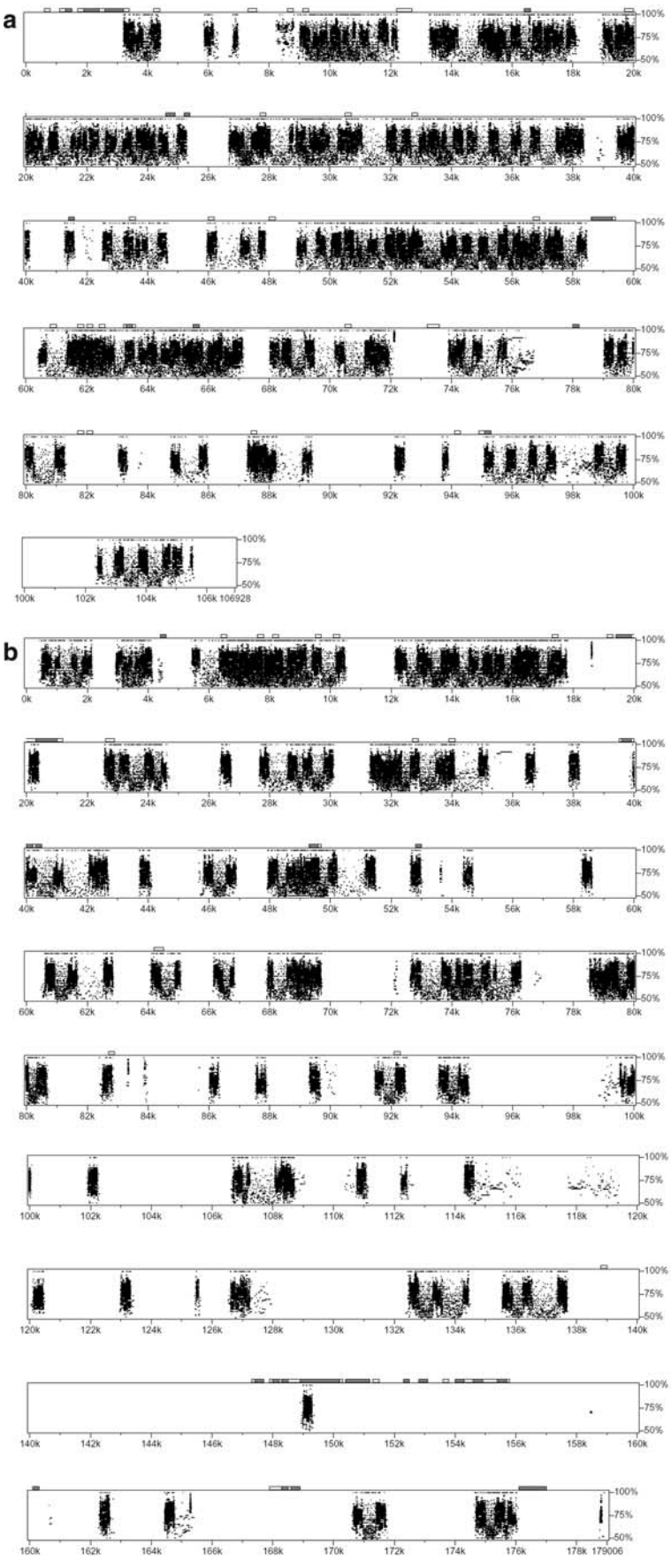

Fig. 2 Identity plot of the alignment between the sequences of clones RP11-143M15 and CTB-23I15, relative to RP11-143M15 sequence position (**a**) and CTB-23I15 sequence position (**b**). The percentage of nucleotide identity is indicated by the position of the *black lines* along the ordinate axis. *White* and *grey boxes* indicate frequency of CpG/GpC higher than 0.60 and 0.75, respectively. The plot was generated by the PipMaker Web Server (http://pipmaker.bx.psu.edu/pipmaker/)

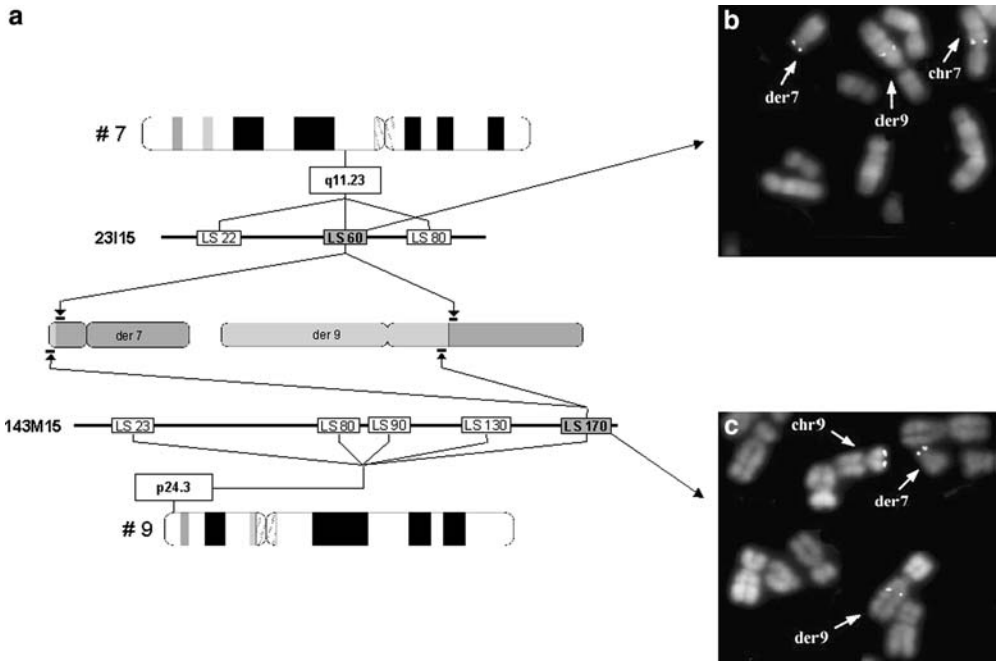

Fig. 3a–c Identification of translocation breakpoints. **a** Schematic representation of mapping of locus-specific probes on clones covering the breakpoints of both derivatives. The locus-specific probes mapping the breakpoints are *boxed in grey*. **b** Partial metaphase plate of the proband after FISH with probe LS60. *Arrows* Hybridisation signals on normal chromosome 7 and on both derivatives. **c** Partial metaphase plate of the proband after FISH with probe LS170. *Arrows* Hybridization signals on normal chromosome 9 and on both derivatives

derivatives, while the remaining five were localised on der 7 (Fig. 3). These findings allowed us to restrict the 7q and 9p breakpoint regions within 8 kb and to observe that the breakage on chromosome 7 falls inside the predicted gene GENSCAN00000067131 (Fig. 4), while the breakpoint on 9p maps inside, or very close to, the Dsx and Mab-3 domain transcription factor 3 (*DMRT3*) gene (Fig. 4). With the aim of identifying genomic intervals of similarity between the regions covered by the two locus-specific probes, we compared their sequences, finding a similarity of 86% in a stretch of 239 bp, between an Alu-Jb within LS170 and an Alu-Sx within LS60.

Bioinformatic analysis of breakpoint regions

In order to verify the presence of specific motif(s) possibly implicated in the rearrangement, we performed a bioinformatic analysis of the genomic clones containing the breakpoint region of both derivative chromosomes. We established the distribution of DNA polymerase α and β consensus sequences, GC-rich regions, repeats such as fragile X breakpoint cluster repeats and Alu sequences, and LCRs, all of which have been found to be associated with translocations (Abeysinghe et al. 2003) (Fig. 4).

Analysis of clone 23I15, mapping on chromosome 7, revealed a high density distribution of Alu sequences and transposon type I (LINEs) in the breakpoint interval restricted to 10 kb (Fig. 4a). This region is also flanked by two duplicons contained in LCR block Ac (Bayes et al. 2003) (http://tcag.ca/index.php?pagename=tcagDatabases.php) (Figs. 1a, 3a). The bioinformatic analysis performed on clone 143M15, mapping on chromosome 9, revealed no high density occurrences of the above sequence motifs (Fig. 4b).

Discussion

We have characterised, by conventional cytogenetic analysis and FISH, an apparently balanced translocation t(7;9)(q11.23;p24) in a healthy woman with repeated reproductive failure. Conventional cytogenetic analysis allowed us to map the chromosome 7 breakpoint to the WBS region, but FISH with an ELN probe excluded the involvement of this gene, because of the normal phenotype of the woman and because in the only reported WBS translocated case the breakpoint was mapped to the ELN gene (Duba et al. 2002). FISH analysis with a further six BAC clones allowed us to map the chromosome 7 breakpoint to the region covered by clone 23I15.

A search for similarities with the 23I15 sequence in the 9p24 region, performed using BLAST (http://www.ncbi.nlm.nih.gov/Blast/) allowed us to select BAC 143M15, which was demonstrated by FISH analysis to contain the chromosome 9 breakpoint.

The high-resolution FISH analysis of translocation t(7;9)(q11.23;p24.3) allowed us to restrict the breakpoint intervals on both derivatives to within 8–10 kb (Riva et al. 1999). On the basis of the sequence analysis of this region, only the breakage of 9p might have interrupted the *DMRT3* gene, or map very close to it, possibly affecting *DMRT3* expression by a position effect. *DMRT3*, which is required for sexual differentiation and is more highly expressed in males, encodes a DM domain transcription factor (Kim et al. 2003), but it is likely that the repeated reproductive failures of the proband are more consistent with an anomalous segregation in meiosis rather than the hypothetical functional alteration to the *DMRT3* gene. The translocation does not affect the function of known genes mapping at

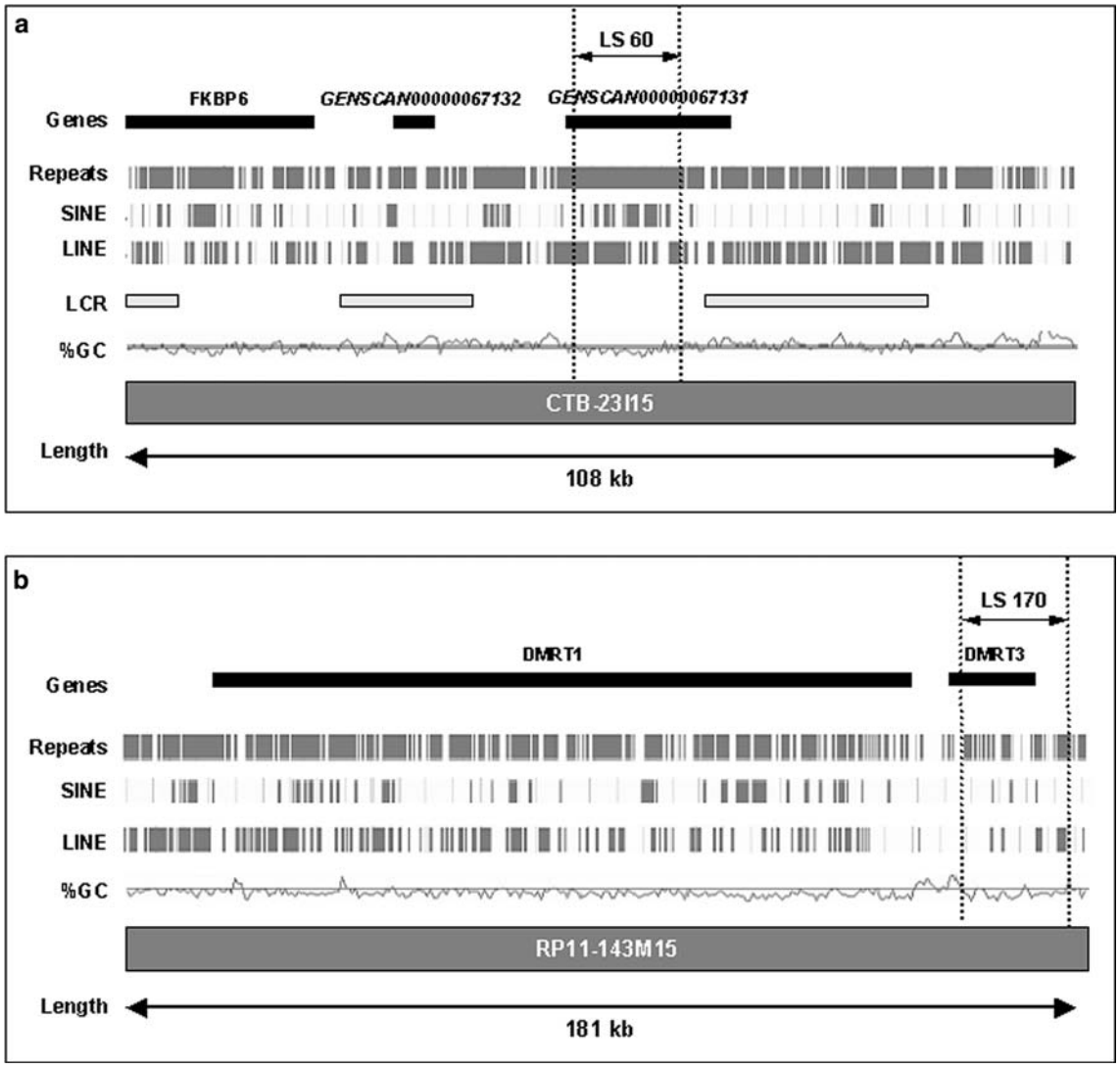

Fig. 4 The genomic physical map of the 7q11.2 (**a**) and 9p24.3 (**b**) regions according to Ensembl Human Genome browser release 26.35.1. Besides known genes, predicted genes, repeats and GC%, low copy repeats (LCRs) have been added according to the Duplication in Human Genome browser (assembly July 2003; http://tcag.ca/index.php?pagename=tcagDatabases.php). The *dotted lines* in both **a** and **b** delimit the genomic intervals covering the breakpoint regions on chromosomes 7 and 9, respectively

7q11.23; in particular, no WBS phenotype was detected, indicating the lack of position effect of this rearrangement. The sequence analysis of the two clones covering the breakpoint regions on both chromosomes 7 and 9 revealed the presence of genomic motifs associated with translocations only for chromosome 7. According to the data reported for clone 23I15 (Ensembl release 26.35.1), there is a high density of repeated sequences in the identified 10 kb region containing the breakpoint. In particular, Alu repeats and LINEs have been found, together with two duplicated sub-blocks (DC1866 and DC1867) contained within LCR block Ac, flanking the breakpoint (Bayes et al. 2003). Alu sequences have been hypothesised to promote non-homologous recombination in translocations occurring between sites of minimal sequence homology (Abeysinghe et al. 2003), although the involvement of Alu repeats in the molecular mechanisms leading to translocation has been debated. The hypothesis implicating an Alu–Alu event in t(11;22) (Hill et al. 2000) was refuted by evidence that palindromic AT-rich repeats rather than Alu sequences were involved in mediating translocation (Kurahashi et al. 2000). This mechanism might mediate recurrent and non-recurrent translocations involving 22q11 (Kehrer-Sawatzki et al. 1997; Edelman et al. 2001; Kurahashi and Emanuel 2001; Kurahashi et al. 2003; Nimmakayalu et al. 2003; Gotter et al. 2004). The lack of AT-rich palindromic motifs in our critical region seems to exclude the involvement of such sequences at the origin of the translocation presented here.

The occurrence of a breakpoint within an LCR, such as we observed in t(7;9)(q11.23;p24.3) reported here, is a finding observed in most translocations involving 22q11.2 (Debeer et al. 2002; Kurahashi et al. 2003; Nimmakayalu et al. 2003; Gotter et al. 2004), while in t(10;17) the breakpoint was localised at the centromeric

end of the distal SMS-REP on chromosome 17 (Stankiewicz et al. 2003). The involvement of LCRs in the origin of common and uncommon deletions/duplications has been demonstrated for several regions and a role for LCRs in stimulating recurrent and non-recurrent translocation has been suggested (Stankiewicz et al. 2003).

Additional evidence that the 7q11.2 region is prone to rearrangements has been provided by its involvement in several rearrangements such as deletions causing WBS and non-recurrent constitutional translocations, t(6;7)(p21.1;q11.23) and t(6;7)(p27;q11.23) causing SVAS [MIM 185500], t(7;16)(q11.23;q13) causing WBS by disrupting the Elastin gene (Morris et al. 1993; von Dadelszen et al. 2000; Duba et al. 2002). The t(7;9)(q11.23;p24) translocation presented here does not disrupt the Elastin gene in a subject showing a normal phenotype. All the translocation breakpoints are contained within LCRs mapping to 7q11.23, which might act synergistically together with other recombinogenic motifs to cause chromosomal rearrangements. Conversely, the only reported constitutional chromosomal aberration involving 9p24 is a complex rearrangement with a 7;9 (q22;p24) translocation and 8q insertion (Cai et al. 2001).

Although sequence analysis of the chromosome 9 breakpoint region did not reveal either specific sequence motifs associated with translocation mechanisms or LCRs, or a high density of repeated sequences, the recombination of 9p24 with 7q11.2 might be promoted by the significant similarity between the sequences mapping to the 7 and 9 breakpoint regions. In addition, the detection of a somatic t(7;9)(q11.23;p24) in a malignant peripheral nerve sheath tumour (MPST; Velagaleti et al. 2004) should reinforce the hypothesis that specific regions of chromosomes 7 and 9 are prone to recombination, although the hypothesis still requires support by further evidence.

Our findings, together with those reported for other constitutional non-recurrent translocations, reveal a predisposition to breakage leading to different rearrangements in a region recurrently involved in breakages of one of the two partner chromosomes. Comparative molecular characterisation of breakpoints of non-recurrent translocations sharing one chromosome partner might address studies aimed at verifying the presence of specific genomic motifs predisposing this chromosomal rearrangement, leading to elucidation of the molecular mechanisms.

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