European Journal of Medical Genetics 52 (2009) 31–36

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Original article

Unusual 8p inverted duplication deletion with telomere capture from 8q

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ARTICLE INFO

Article history:
Received 14 July 2008
Accepted 28 October 2008
Available online 17 November 2008

Keywords:
Inv dup del (8p)
Telomere capture
Oligo array CGH

ABSTRACT

Inverted 8p duplication deletions are recurrent chromosomal rearrangements that are mediated through non-allelic homologous recombination (NAHR) between olfactory receptor (OR) gene clusters at 8p23.1. These rearrangements result in a proximal inverted duplication of various extent, a single copy region between the OR gene clusters and a terminal 8p deletion. The terminal deletions are stabilized by direct addition of telomeric repeats, so called telomere healing. Here, we report a patient with an unusual inverted duplication deletion of 8p. Stabilization of the broken chromosome end was achieved by telomere capture instead of telomere healing, resulting in an additional duplication of 8q24.13→qter on the short arm of chromosome 8. Moreover, the inverted duplication was only 3.4 Mb in size (restricted to band 8p22) and thus cytogenetically undetectable. To the best of our knowledge this is the smallest inverted duplication reported hitherto. We describe the molecular characterization by FISH and array CGH of this unusual inv dup del (8p) and a previously reported patient with a similar 8q duplication and review the literature on cases associated with telomere capture.

1. Introduction

Structural features of particular genomic regions can trigger the formation of recurrent chromosome rearrangements. One class of sequences frequently associated with regions of chromosomal instability is segmental duplications [6]. Duplicated blocks may be substrates for non-allelic homologous recombination (NAHR) resulting in large structural polymorphisms and chromosomal rearrangements that directly lead to genomic disorders [16].

In recent years, several studies have shown that a particular subset of segmental duplications, namely olfactory receptor (OR) gene clusters, is substrate for recurrent rearrangements involving the short arm of chromosome 8 [9–11,25]. Giglio et al. [10] demonstrated that the presence of a paracentric inversion polymorphism in 8p23.1 may trigger meiotic misalignment and NAHR between the inverted OR gene repeats. This mechanism generates a dicentric intermediate which breaks during anaphase, leading to the formation of an 8p inverted duplication of various extent (ranging from ~12 to 30 Mb) associated with deletion of the 8p telomere (8p23.2-pter) and a single copy region at 8p23.1 [9,10].

Terminal deletions include loss of telomeric sequences that, if not properly repaired, can be damaging for the cell and result in severe genomic instability [17]. Therefore, broken chromosome ends must acquire a new telomeric cap in order to be structurally stable. Telomeric sequences can be acquired *de novo* by direct addition of telomeric repeats ("telomere healing") [26], or by "telomere capture" in which broken chromosomes obtain the telomeric end of another chromosome [1–3]. Alternatively stabilization can occur through circularization of the inv dup del chromosome, leading to the formation of a ring chromosome [13,20].

We describe the characterization by array CGH, FISH and microsatellite analysis of an inverted duplication deletion of 8p capped with distal 8q material and the re-evaluation of a previously described rearrangement [7]. Unlike previously described 8p terminal inverted duplications, the duplication was only 3.4 Mb in size and restricted to band 8p22. Moreover, an additional duplication of 8q24.13→qter was detected on the short arm of chromosome 8. This observation indicates that after the formation of the inv dup del (8p), the broken chromosome end has been stabilized by telomere capture through an additional rearrangement with distal 8q material.

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doi:10.1016/j.ejmg.2008.10.007

Table 1
Fluorescent *in situ* hybridization (FISH) results.

Probe name	Accession number	UCSC March 2006 [hg18]	Chromosome band	FISH
DJ580L5	D8S2333	8ptel (max. 250 kb from telomere)	8p23.3	Deleted
RP11-29A2	AC007718	chr8: 5,106,141–5,256,105	8p23.2	Deleted
bK2629I16	AF233439	chr8: 6,604,702–6,835,984	8p23.1	Deleted
RP11-5E15	BES	chr8: 6,719,131–6,880,128	8p23.1	Deleted
RP11-912D6	BES	chr8: 6,869,169–7,022,807	8p23.1	Single copy
RP11-42L14	BES	chr8: 6,928,849–7,093,755	8p23.1	Single copy
RP11-257J3	BES	chr8: 7,160,933–7,339,593	8p23.1	Single copy
RP11-623J22	BES	chr8: 7,562,108–7,735,433	8p23.1	Single copy
RP11-834N9	BES	chr8: 7,777,309–7,936,168	8p23.1	Single copy
RP11-399J23	BES	chr8: 8,156,720–8,327,336	8p23.1	Single copy
G248P81184C8	FES	chr8: 8,239,111–8,282,168	8p23.1	Single copy
RP11-177H2	BES	chr8: 10,634,275–10,796,495	8p23.1	Single copy
G248P89650H6	FES	chr8: 11,286,496–11,330,297	8p23.1	Single copy
RP11-589N15	BES	chr8: 11,627,389–11,803,111	8p23.1	Single copy
RP11-247B12	BES	chr8: 11,819,908–11,980,152	8p23.1	Single copy
RP11-483N3	AC092766	chr8: 12,359,608–12,511,876	8p23.1	Single copy
RP11-303G3	AC068587	chr8: 12,437,502–12,611,672	8p23.1	Single copy
RP11-252C15	BES	chr8: 12,586,955–12,762,845	8p23.1-p22	Duplicated
RP11-148E1	BES	chr8: 12,761,281–12,937,684	8p22	Duplicated
RP11-60C8	AC091559	chr8: 15,279,356–15,445,712	8p22	Duplicated
RP11-545M21	AC023396	chr8: 15,939,816–16,105,557	8p22	Duplicated
RP11-447G11	AC087360	chr8: 16,091,520–16,188,212	8p22	Duplicated
RP11-771E22	BES	chr8: 16,150,757–16,348,466	8p22	Duplicated
RP11-255E13	AC091162	chr8: 16,323,058–16,472,753	8p22	Single copy
RP11-19N21	BES	chr8: 16,444,062–16,618,564	8p22	Single copy
RP11-174I12	AF267170	chr8: 124,550,516–124,718,432	8q24.13	Single copy
RP11-102L9	BES	chr8: 124,672,556–124,847,951	8q24.13	Single copy
RP11-788I22	BES	chr8: 124,806,936–124,964,478	8q24.13	Single copy
RP11-1112G17	BES	chr8: 124,933,507–125,082,012	8q24.13	Single copy
RP11-293H22	AF216672	chr8: 124,859,258–125,033,119	8q24.13	Single copy
RP11-166E20	AF252827	chr8: 125,030,797–125,196,119	8q24.13	Duplicated
RP11-37N22	AC090921	chr8: 125,171,337–125,353,348	8q24.13	Duplicated
RP11-383J24	AC090192	chr8: 125,347,935–125,546,833	8q24.13	Duplicated
RP11-158K1	BES	chr8: 125,497,283–125,691,169	8q24.13	Duplicated
489D14	D8S1925	8qtel (max. 170 kb from telomere)	8q24.3	Duplicated

BES: BAC end sequence; FES: fosmid end sequence.

2. Materials and methods

2.1. Cytogenetic analysis

Analysis of G-banded metaphase chromosomes was performed on short-term lymphocyte cultures using standard procedures. Fluorescence *in situ* hybridization (FISH) was performed as described [23].

2.2. Array CGH analysis

DNA was isolated from total blood using the Puregene Genomic DNA Purification Kit (Gentra Systems), according to the manufacturer's instructions. DNA was hybridized on the Agilent Human Genome CGH Microarray 44K (AMADID#014950), according to the manufacturer's instructions with minor modifications. In brief, 500 ng of genomic DNA was labeled with Cy3 (patient) or Cy5 (control) (BioPrime Array CGH Genomic Labeling System, Invitrogen). After clean up of the labeled fragments using Microcon YM-3 filter units (Millipore), patient and control samples were pooled together with Cot-1 DNA, Agilent 10X Blocking Agent and Agilent 2X Hybridization Buffer. This hybridization mixture was hybridized on the microarrays for 24 h at 65 °C. After washing, the slides were scanned using a Tecan LS reloaded scanner. The scan images were processed with ArrayPro software and further analysed with our in-house developed and freely available software tool arrayCGHbase (http://medgen.ugent.be/arraycghbase/) [18]. Profiles were also evaluated by circular binary segmentation (CBS) to detect regions with aberrant copy-number [19].

2.3. Microsatellite analysis

Polymorphic CA repeats were selected from the Marshfield map. Genotyping of these microsatellite markers was performed on an ABI 3130xl Genetic Analyzer followed by analysis with GeneMapper v3.7 software.

2.4. Clinical report

The proband was born after an uncomplicated pregnancy of 38 weeks. Birth weight was 3150 g (P50), length 49 cm (P90) and head circumference 32 cm (<P10). A heart murmur was detected at birth and echocardiography showed a supravalvular pulmonary stenosis. Physical examination at the age of 3 months revealed the baby in good general condition. Craniofacial inspection showed hypertelorism, intermittent strabismus of the left eye, heterochromia iridis of the right eye, upslanting palpebral fissures, blue sclerae and slight retrognathia. The ears were posteriorly rotated with a preauricular tag on the left side. A bilateral simian crease was present. There was an intergluteal hairy dimple. Additional ophthalmological examinations revealed bilateral decreased vision with astigmatism and hypermetropia. Hearing screening test and ultrasound of the kidneys was normal. At the age of 5 months, growth parameters were normal with weight 7.45 kg (P50–P75), height 66 cm (P75) and head circumference 42 cm (P50). Last clinical evaluation at 13 months confirmed normal growth but showed developmental delay. A Bailey developmental scale demonstrated a developmental age of 7.5 months for a calendar age of 13 months. Supravalvular pulmonary stenosis was found stable.

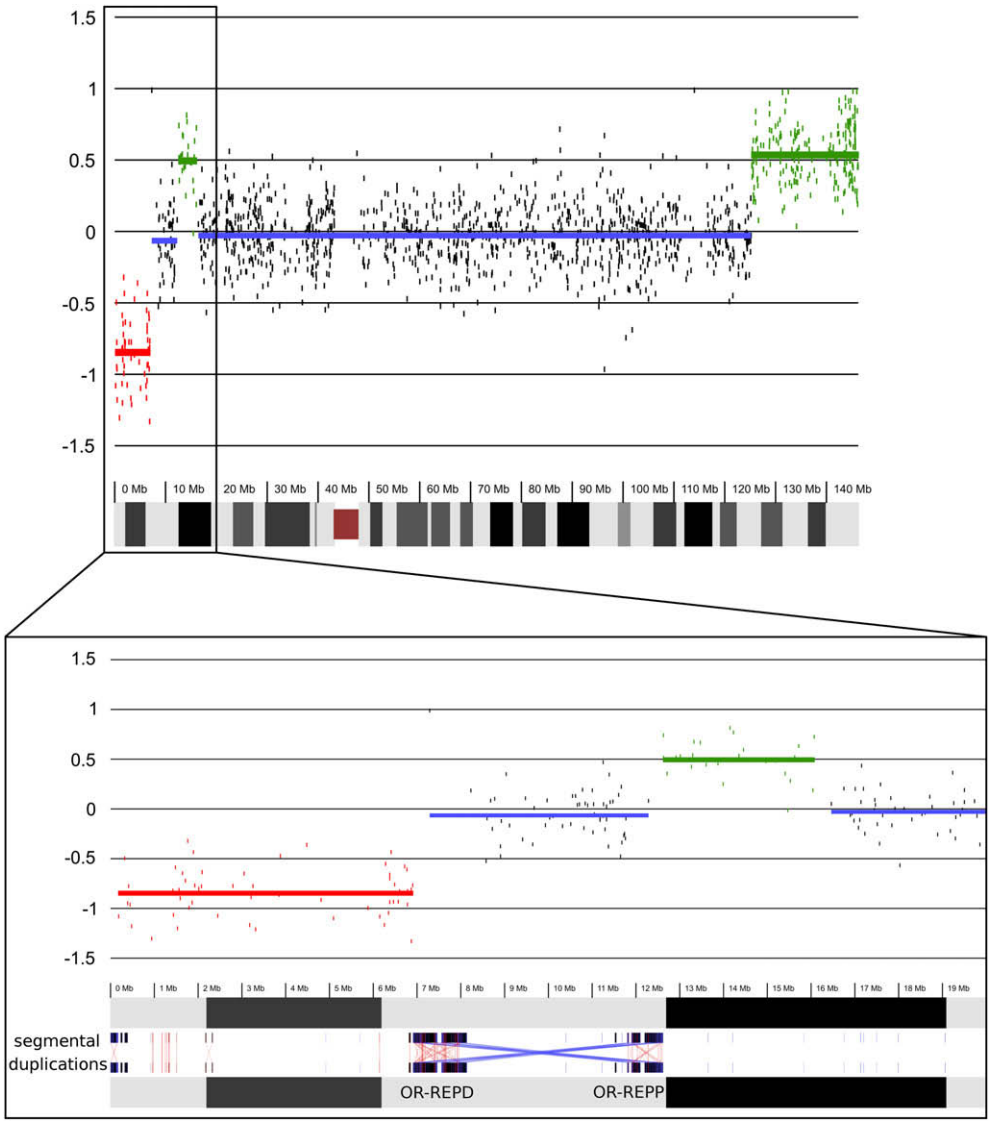

Fig. 1. Array CGH profile for chromosome 8 showing a 6.9 Mb deletion at 8pter, a 3.4 Mb duplication at 8p22 (12.63–16.07 Mb [hg18]) and a 20.9 Mb duplication at 8qter (125.34–146.25 Mb [hg18]). Dots represent $\log_2$-ratios of individual oligonucleotides. Colored (red for deleted, blue for normal, green for duplicated) horizontal bars indicate regions of equal copy-number as determined by CBS (circular binary segmentation). The black box zooms in on the distal 20 Mb of the short arm of chromosome 8. The positions of the OR-gene clusters are indicated. The karyotype is described as 46,XX,der(8)(qter→q24.13::p22→p23.1::p23.1→qter). arr cgh 8pterp23.1(A14_P202169→A_14_P116446)x1, 8p23.1-p22(A_14_P200822→A_14_P116183)x3, 8q24.13qter(A_14_P103407→A_14_P132395)x3. (For interpretation of colors in the figure legend, the reader is referred to the web version of the article.)

3. Results

G-banding analysis revealed an abnormal chromosome 8 with additional material on the short arm. The chromosome 8 origin of the extra material on the short arm was confirmed by FISH using a chromosome 8 painting probe. FISH analysis with 8p and 8q subtelomeric probes (Table 1) showed no signal for the 8p-probe on the short arm of the derivative chromosome 8 whereas the 8q-probe hybridized to the subtelomeric regions of both the p and q arm of this chromosome. The rearrangement was initially interpreted as a recombinant deletion–duplication chromosome resulting from a balanced pericentric inversion in one of the parents. However, high resolution array CGH analysis revealed an additional duplication of 3.4 Mb of the 8p22 region (12.63–16.07 Mb [hg18]). This cytogenetically undetectable duplication was separated from the 8pter deletion by a ~5 Mb single copy region flanked by OR gene clusters (Fig. 1). The finding of a distal deletion followed by a single copy region and a subsequent duplication was reminiscent of the 8p inverted duplication deletions as described by Floridia et al. [9]. Further FISH experiments confirmed the presence of an inverted duplication deletion with classical breakpoints within the OR gene clusters (Fig. 2A, Table 1). In contrast to the published cases, the inverted duplication in our proband is only 3.4 Mb in size and capped with 20.9 Mb of distal 8q material (8q24.13→qter). Microsatellite analysis showed the maternal origin of the rearrangement (Table 2).

FISH experiments with fosmid probes, allowing visualization of the polymorphic 8p23.1 paracentric inversion, showed that the proband was carrier of the inversion on the short arm of the normal chromosome 8 (Fig. 2B). Karyotype analysis of both parents was normal. FISH analysis showed that each parent was a heterozygous carrier of the polymorphic 8p23.1 inversion (Fig. 2C and D).

In silico analysis of the proximal 8p and 8q duplication breakpoints using the UCSC genome browser did not reveal any segmental duplications that could have mediated the 8q rearrangement through NAHR.

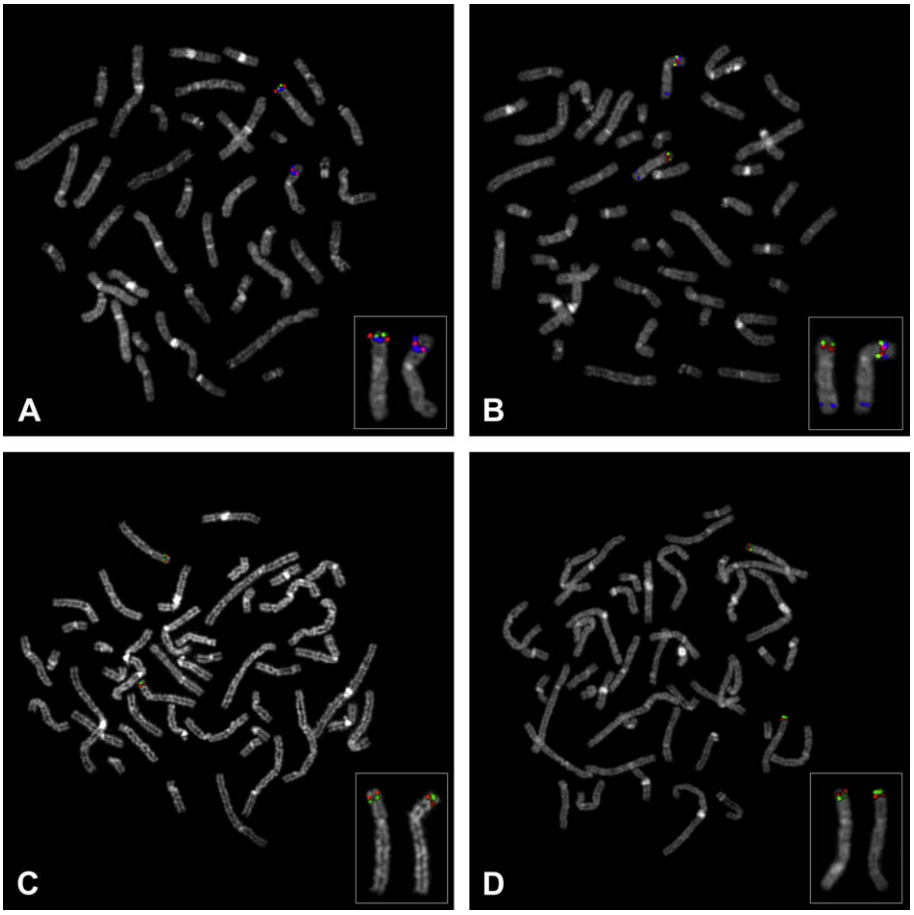

Fig. 2. (A) Cohybridization of G248P81184C8 (red, 8,239,119–8,282,168 bp), RP11-29A2 (green, 5,106,141–5,256,105 bp) and RP11-447G11 (blue, 16,091,520–16,188,212 bp) shows the 8p deletion (green) and the single copy region (red) in between the inverted duplication (blue). (B) Cohybridization of G248P81184C8 (red, 8,239,119–8,282,168 bp), G248P89650H6 (green, 11,286,497–11,330,302 bp) and RP11-158K1 (blue, 125,497,283–125,691,169 bp) shows the inversion polymorphism in the normal chromosome 8 (left) and duplication of the 8q arm on top of the derivative chromosome (right). (C and D) Cohybridization of G248P81184C8 (red, 8,239,119–828,2168 bp) and G248P89650H6 (green, 11,286,497–11,330,302 bp) in the mother (C) and father (D) shows that they are both carriers of the polymorphic 8p23.1 inversion. (For interpretation of colors in the figure legend, the reader is referred to the web version of the article.)

An inverted 8p duplication with a similar additional duplication of region 8q24.13→qter attached to the short arm was described previously by Fan and Siu [7]. They performed a molecular characterization by high resolution G-banding, spectral karyotyping and FISH. The karyotype was described as 46,XY,der(8)(qter→q24.13::p21.3→p23.3::p23.3→qter) without deletion of distal 8p. Because of the resemblance to the aberration in our proband, we decided to retrospectively analyse this case by array CGH. Surprisingly, our analysis revealed a 3.9 Mb deletion of 8pter→p23.2. In contrast to classical inv dup del (8p)s, the inverted duplication immediately flanked the deletion, extending from 8p23.2 to p21.2 (4.48–24.31 Mb [hg18]). The 8q duplication was 28.3 Mb in size (117.93–146.25 Mb [hg18]) with the breakpoint at 8q24.11 (Fig. 3). A schematic representation comparing both chromosomes 8 for the two patients is given in Fig. 4.

Table 2
Results of the microsatellite analysis in the proband and her parents.

Marker	Band	Position (Mb, hg18)	Proband	Mother	Father	Status
D8S504	8p23.3	1005	B	AB	B	U
D8S1781	8p23.2	3565	A	BC	AB	del(M)
D8S1788	8p23.2	3624	A	AB	A	U
D8S277	8p23.1	6504	B	A	AB	del(M)
D8S1819	8p23.1	6737	C	AD	BC	del(M)
D8S552	8p22	12,786	ACD	AC	BD	dup(M)
D8S1790	8p22	13,111	A*B	AB	A	U
D8S1731	8p22	15,283	C	BC	AC	U
D8S1774	8q24.21	127,492	A*B	A	A	U
D8S1813	8q24.21	127,751	AB*	B	AB	U
D8S1717	8q24.3	141,632	AD*	BD	AC	dup(M)
D8S1836	8q24.3	143,747	A*C	A	BC	dup(M)

A, B, C, D: polymorphic alleles of increasing length.
*Alleles with increased fluorescence intensity, indicative of duplicated status.
U: uninformative; del(M), dup(M): deletion or duplication of maternal origin.

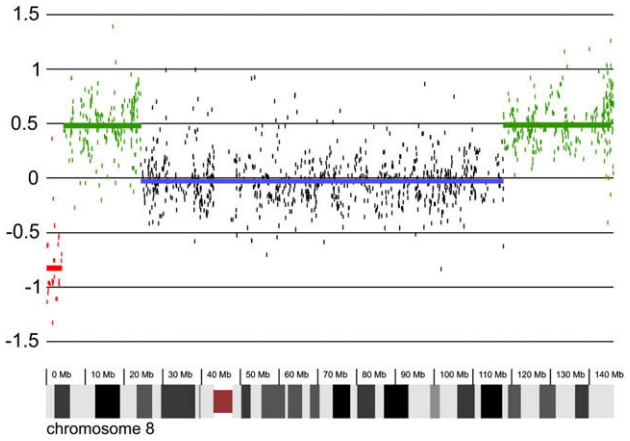

Fig. 3. Array CGH profile for chromosome 8 for the patient previously described by Fan and Siu [7]. The karyotype is described as 46,XY,der(8)(qter→q24.11::p21.2→p23.2::p23.2→qter). arr cgh 8pterp23.2(A_14_P119514→A_14_P137209)x1, 8p23.2p21.2(A_14_P106068→A_14_P124873)x3, 8q24.11qter(A_14_P104491→A_14_P132395)x3.

4. Discussion

We describe the molecular and cytogenetic findings in an unusual case with an inverted duplication deletion of 8p and the re-evaluation of a previously described patient with a rearrangement that seems to be stabilized by a similar mechanism [7]. By high resolution oligo array CGH, we detected the smallest inverted duplication of 8p reported thus far, with additional duplication of 8q24.13→qter on the short arm of the abnormal chromosome 8 (Figs. 1 and 2A and B). FISH, array CGH and microsatellite findings are in keeping with the classical formation of an inv dup del (8p) mediated through NAHR between homologous OR gene repeats at maternal meiosis as previously described by Floridia et al. [9] and Giglio et al. [10].

In contrast to classical inv dup del (8p) cases in which telomere healing seems to be the predominant mechanism involved in the stabilization of the broken 8p end [9,10], telomere capture from 8q occurred in the proband in order to reconstitute the broken end of the short arm. At least four models have been proposed to explain the molecular basis of telomere capture (reviewed by Ballif et al. [2]). Our data are in favour of break-induced replication (BIR), a double-strand break repair model in which the broken chromosome end only needs a site of microhomology to invade another template and replicate sequences from there on [15].

We could only find two additional reports [7,14] which describe an identifiable telomeric region on an inverted duplication of 8p. Fan and Siu report an inverted duplication of 8p with an additional duplication of 8q24.13→qter on 8p [7]. The deletion breakpoint being ~3 Mb away from the distal OR gene cluster (OR-REPD) and the absence of a single copy region at 8p23.1 exclude the

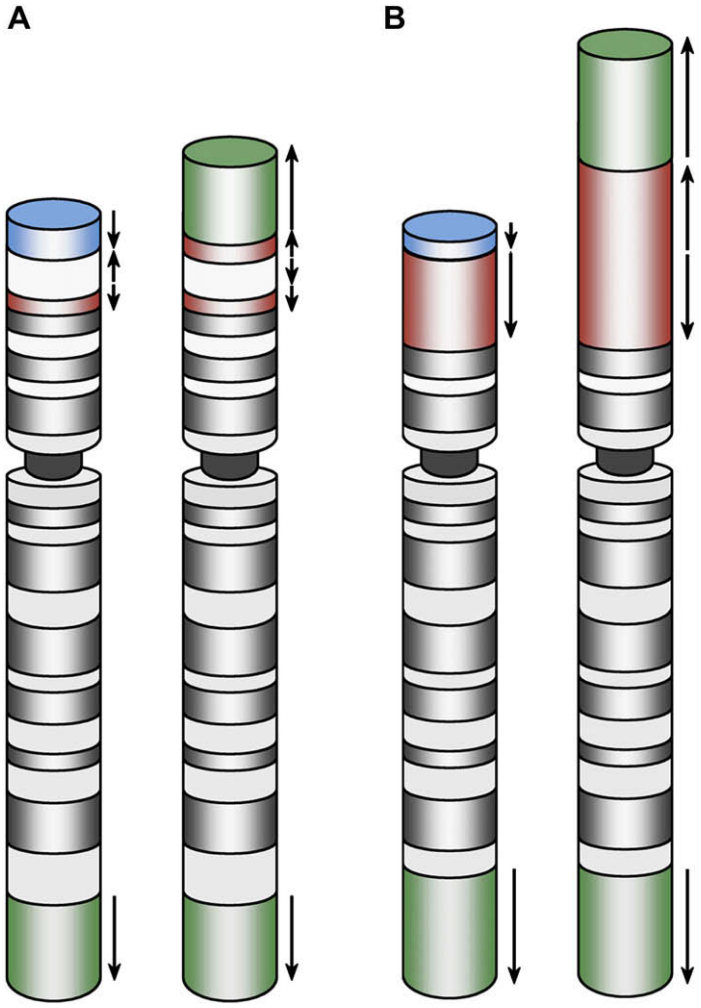

Fig. 4. Schematic overview of both chromosomes 8 in (A) the proband and (B) the patient previously described by Fan and Siu [7]. The arrows show the orientation of the blocks. The blue, red and green blocks respectively refer to the regions of 8pter deletion, 8p duplication and 8qter duplication on the derivative chromosome 8. (For interpretation of colors in the figure legend, the reader is referred to the web version of the article.)

involvement of OR gene clusters in this rearrangement. The aberration might be the result of a U-type exchange as proposed by Weleber et al. [24] and Dill et al. [5] followed by telomere capture in accordance with the BIR model. The second report, by Kostiner et al., describes a classical inv dup del (8p) stabilized by telomere capture of distal 18q [14]. Taken together, telomere capture seems to be a rare mechanism for stabilization of inv dup del (8p)s.

Patients with inverted duplication deletions of 8p have a common phenotype characterized by severe mental retardation, minor facial anomalies, agenesis of the corpus callosum, congenital heart disease and orthopedic abnormalities [4,8,12,21]. Patients with distal trisomy 8q (q24→qter) show a milder phenotype with congenital malformations being rare, although heart defects have been reported. There is growth retardation, several facial anomalies including hypertelorism and dysplastic low-set and small ears, clino- and camptodactyly and sandal gap of the toes [21]. Except for the heart defect and some craniofacial dysmorphic features, our proband's phenotype does not seem to resemble that of other inv dup del (8p) patients. This might be due to the fact that the inverted duplication in our proband is very small (3.4 Mb compared to 12–30 Mb), since the phenotypical features have been mostly ascribed to the inverted duplication and to a lesser extent to the subtelomeric deletion. The 8pter deletion might however be causal for the heterochromia iridis in our patient as it affects the WS2C locus for type II Waardenburg syndrome [22]. High resolution molecular analysis of additional patients with small(er) inverted duplications will enable more detailed phenotype–genotype correlation studies.

Without the duplication of 8q, the rearrangement would have remained cytogenetically undetectable, stressing the necessity to perform high resolution whole genome analysis in patients with idiopathic mental retardation and/or congenital anomalies. Re-evaluation of recombinant deletion–duplication chromosomes would be of interest to reveal additional 'hidden' inv dup del (8p)s and to determine the incidence of telomere capture.

Acknowledgements

We are grateful to the patients and their family for their cooperation. This work was made possible by grants G.0200.03 from the FWO and GOA-grant 12051203 from Ghent University.

Karen Buysse and Bert Callewaert are research assistants and Bart Loeys is a senior clinical investigator of the Research Foundation – Flanders (FWO – Vlaanderen). This study is supported, in part, by the Fund for Scientific Research, Flanders, with a mandate fundamental clinical research to Geert Mortier.

This text presents research results of the Belgian program of Interuniversity Poles of attraction initiated by the Belgian State, Prime Minister's Office, Science Policy Programming (IUAP).

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