Genomic Med. (2007) 1:65–73
DOI 10.1007/s11568-007-9008-3

RESEARCH ARTICLE

Molecular cytogenetic characterization of two independent karyotypic anomalies in a patient with severe mental retardation and juvenile idiopathic arthritis

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Received: 26 March 2007 / Accepted: 14 June 2007 / Published online: 11 July 2007

Abstract We report on a patient with severe mental retardation, dysmorphic features as well as juvenile idiopathic arthritis. G-banding indicated two independent karyotypic anomalies in this patient: an interstitial deletion del(X)(p21p22.3) and a rearrangement involving chromosomes 1 and 7, which represents a direct insertion, ins(7;1)(q36;p13.2p31.2). Non-random inactivation of the paternally derived del(X) chromosome was observed in blood lymphocytes and fibroblasts. High resolution analysis of the rearrangement involving chromosomes 1 and 7 subsequently revealed the additional submicroscopic deletion of at least 5 Mb at the 1p13.2 breakpoint. The deletion occurred on the paternal chromosome and encompasses the *PTPN22* gene, already known to be associated with juvenile idiopathic arthritis. Our findings underline the importance of closely investigating the breakpoint regions of apparently balanced rearrangements in patients with abnormal phenotypes since complex chromosomal rearrangements (CCRs) may turn out to be unbalanced.

Keywords Complex chromosome rearrangement · Xp deletion · 1p13.2 deletion · Juvenile idiopathic arthritis

Electronic supplementary material The online version of this article (doi:10.1007/s11568-007-9008-3) contains supplementary material, which is available to authorized users.

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Introduction

Structural chromosome aberrations are evident in ~0.5% of neonates tested by conventional cytogenetic analysis (Jacobs et al. 1992). In most instances, apparently balanced structural chromosomal abnormalities are not associated with any obvious clinical phenotype. However, unfavorable chromosomal segregation during meiosis would be expected to yield unbalanced gametes that could then lead either to reproductive failure or to the production of phenotypically abnormal offspring. Around 6% of apparently balanced *de novo* chromosome rearrangements identified antenatally are associated with phenotypic abnormalities (Warburton 1991). A subgroup of such cases represents complex chromosomal rearrangements (CCRs) that involve more than two breakpoints and an exchange of genetic material between two or more chromosomes (Pai et al. 1980). *De novo* CCRs are in many instances associated with mental retardation and congenital abnormalities. The clinical phenotype in such cases could be consequent either to the disruption of the structure and/or expression of genes in the vicinity of the breakpoints or to subtle imbalances caused by the loss or gain of specific sequences caused by submicroscopic deletions or duplications at the breakpoint sites. Detailed characterization using molecular cytogenetic techniques or array comparative genomic hybridization (CGH) is therefore necessary to detect such sequence gains and losses since many CCRs appear to be balanced at the level of G-banded chromosomes (Wirth et al. 1999; Vermeulen et al. 2004; Gribble et al. 2005).

Here we report on a female patient with severe developmental and psychomotor retardation suggestive of an unbalanced chromosomal aberration. In addition, the patient suffered from severe juvenile idiopathic arthritis, a

clinical phenotype that is somewhat atypical of a patient with a complex chromosomal rearrangement. Karyotypic analysis indicated the presence of two *de novo* structural chromosome anomalies: an interstitial deletion on Xp and a rearrangement involving chromosomes 1 and 7. Using various molecular cytogenetic techniques as well as polymorphic marker analysis, this rearrangement was shown to be unbalanced, being accompanied by a submicroscopic deletion at the 1p13.2 breakpoint.

Case report

The female patient was born, after an uneventful pregnancy, to a 30 year-old mother and a 31 year-old father both of Caucasian origin. She has two healthy sisters, one 3 years older, the other 2 years younger. The patient presented at the age of 2 years with severe somatic developmental delay [weight: 10.4 kg (10.P); height: 78.5 cm (3.P); fronto-occipital head circumference: 44.3 cm (<3.P)], which persisted, to the age of 15. Her motor and intellectual development was also significantly retarded. Microcephaly and persistent salivation were evident. A kidney duplication on the left side came to clinical attention as a result of sonographic examination consequent to recurring urinary tract infections. No other organ anomalies were observed. A broad chest was noted, one of the stigmata of Turner syndrome; however, cubitus valgus and a short webbed neck with superior hairline were absent.

Owing to epileptic seizures with tonic attacks, therapy with an anticonvulsive agent (Liskantin) was initiated at the age of 3 years and no further seizures occurred. Anomalies of the cranial nerves were not apparent.

At the age of nine, psychomotor retardation was pronounced. She attended a school for handicapped children, was able to speak one or two words and to understand short requests given without gestures. She could not read, write or calculate. The investigation of the musculoskeletal system revealed swelling of the wrists as well as flexion contractures of the elbows and digital joints due to juvenile idiopathic arthritis [rheumatoid factor (RF)-negative, ANA-positive, HLA-27-negative]. The knee joints were thickened and the patient had a conspicuous clumsy gait with double-sided reduced motility of the ankle joints. The polyarthritis was treated with methotrexate.

At the age of 15, her height was 148 cm (<3.P) and weight: 54 kg (>25.P) with a body mass index of 24.6 (50.–60.P). Her fronto-occipital head circumference was 51 cm (<3.P). Although she could only speak a few words, her understanding of spoken language had improved significantly. However, during her daily life, she was completely dependent and needed assistance. Upon investigation, short fourth metacarpals were noted as well as stretch inhibition of the elbows and knee joints. She experienced regular menstruation since the age of 11 but she lacked secondary sexual characteristics. An ovarian cyst was removed at age 14. Several dysmorphic features were noted including hypertelorism, short palpebral fissures, short nasolabial distance, flat philtrum but long nasal septum, deep-set dysplastic backwards rotating large ears, bilateral clinodactyly V, smooth palms with only weakly established creases and wide intermammillary distances.

Material and methods

FISH analyses

Chromosome spreads were prepared from PHA-stimulated blood lymphocytes taken from the patient and her parents. BAC clones were purchased from the BACPAC Resources Center (http://www.bacpac.chori.org/) and DNA was isolated using the Plasmid Midi Kit (Qiagen, Hilden, Germany). FISH probes were prepared by labeling BAC DNA with either biotin-16-dUTP (Roche-Diagnostics, Mannheim, Germany) or digoxygenin-11-dUTP (Roche-Diagnostics, Mannheim, Germany).

Signals of biotinylated FISH probes were detected with FITC-avidin and biotinylated anti-avidin (Vector, Burlingame, USA). Where probes were labeled with digoxygenin-11-dUTP, the signals were detected in a first step with anti-digoxygenin antibodies produced in mouse, then with rabbit anti-mouse antibodies conjugated with Texas-Red, and finally in a third step with anti-rabbit antibodies also conjugated with Texas-Red (Dianova, Hamburg, Germany). In addition, the subtelomeric FISH probes for chromosome 7, TelVysion 7q and 7p (Abbott-Vysis Inc., Downers Grove, USA) were used. Slides were counterstained with diamidinophenylindole (DAPI) and mounted with Vectashield antifade solution (Vector, Burlingame, USA). Whole chromosome painting probes for chromosomes 1, 7 and X (WCP-1, WCP-7, WCP-X) were purchased from Abbott Laboratories (North Chicago, USA).

PCR analysis and determination of the X inactivation pattern

DNA was extracted from peripheral blood and from skin fibroblast cell cultures using the DNAeasy isolation kit (Qiagen, Hilden, Germany). To determine whether the Xp deletion occurred on the maternal or paternal X chromosome, four polymorphic markers (DXS8105, DXS8019, DXS8051 and DXS7108) from within the deleted interval were investigated. The X-inactivation status of the androgen receptor (AR) locus at Xq13 was investigated by analyzing the methylation status of the CpG island adjacent

to the polymorphic CAG repeat in exon 1 of the AR gene using primers ARP1 (5′ TCC AGA ATC TGT TCC AGA GCG TGC 3′) and ARP2 (5′ GCT GTG AAG GTT GCT GTT CCT CAT 3′) labeled with 6FAM. After complete digestion with *Hpa*II, PCR was performed and the resulting products were separated on a 3100 DNA sequencer (Applied Biosystems, Foster City, USA).

Analysis of polymorphic markers on chromosome 1

Polymorphic markers D1S119 and D1S418, labeled with 6FAM, were analyzed by PCR and capillary gel electrophoresis to determine the parental origin of the deletion on chromosome 1 using DNA isolated from blood samples of the patient, her sister and her parents.

Comparative genomic hybridization (CGH)

CGH was performed as described by Kallioniemi et al. (1992). DNA of the patient was labeled with biotin-16-dUTP and the normal reference DNA with digoxigenin-11-dUTP, by means of standard nick translation.

Results

Chromosome analysis by G-banding

Karyotype analyses of the patient performed at the ages of 2 and 15 years revealed a large deletion on Xp as well as a rearrangement involving chromosomes 1 and 7. The latter was interpreted as a direct (as opposed to an inverted) insertion of the segment 1p13.2-31.2 into the long arm of chromosome 7. According to the G-banding pattern, the karyotype was: 46,XX,ins(7;1)(q36;p13.2p31.2), del(X)(p21p22.3) or in rather more detail: 46,XX,ins(7;1)(7pter → 7q36::1p31.2 → 1p13.2::7q36 → 7qter;1pter → 1p31.2::1p13.2 → 1qter), del(X)(pter → p22.3::p21 → qter) (Figs. 1 and 2). Both chromosomal aberrations were observed in all metaphases analyzed ($N = 50$). Parental chromosomes appeared to be structurally normal.

FISH analysis

To confirm the insertion, FISH was performed with whole-chromosome painting probes for chromosomes 1, 7 and X (Fig. 3A–C). This analysis revealed that the insertion into 7q36 involved material from chromosome 1 rather than from the X-chromosome. Using subtelomeric probes that hybridize to distal 7q36, the telomeric region of patient chromosome 7q was shown to be retained (Table 1, Fig. 3D). Thus, the insertion of chromosome 1-derived material into 7q36 occurred proximal to probe RP11-620M21. To demarcate the deletion on the X chromosome more precisely, FISH was performed with the BACs listed in Table 2. The interstitial Xp deletion was found to

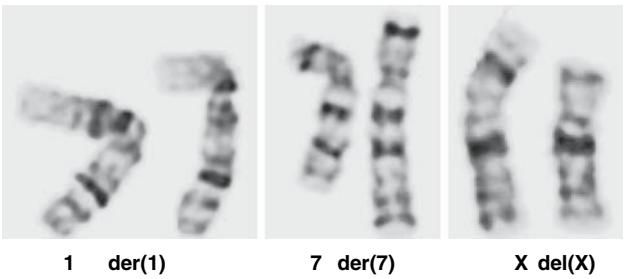

Fig 1 Partial G-band karyotype of the patient. Chromosomal deletions on 1p (der(1)) and Xp, and an insertion on 7q (der(7)) are evident

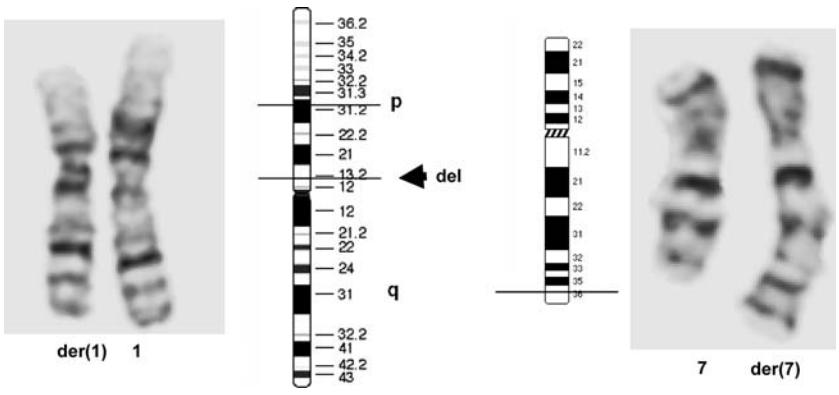

Fig 2 Assignment of the breakpoint regions of the rearrangement involving chromosomes 1 and 7 according to the analysis of G-banded chromosomes. The rearrangement was interpreted as follows: ins(7;1)(q36;p13.2p31.2) or in greater detail: ins(7;1)(7pter → 7q36::1p31.2 → 1p13.2::7q36 → 7qter;1pter → 1p31.2::1p13.2 → 1qter). The arrowhead indicates the position of the submicroscopic deletion in1p13.2

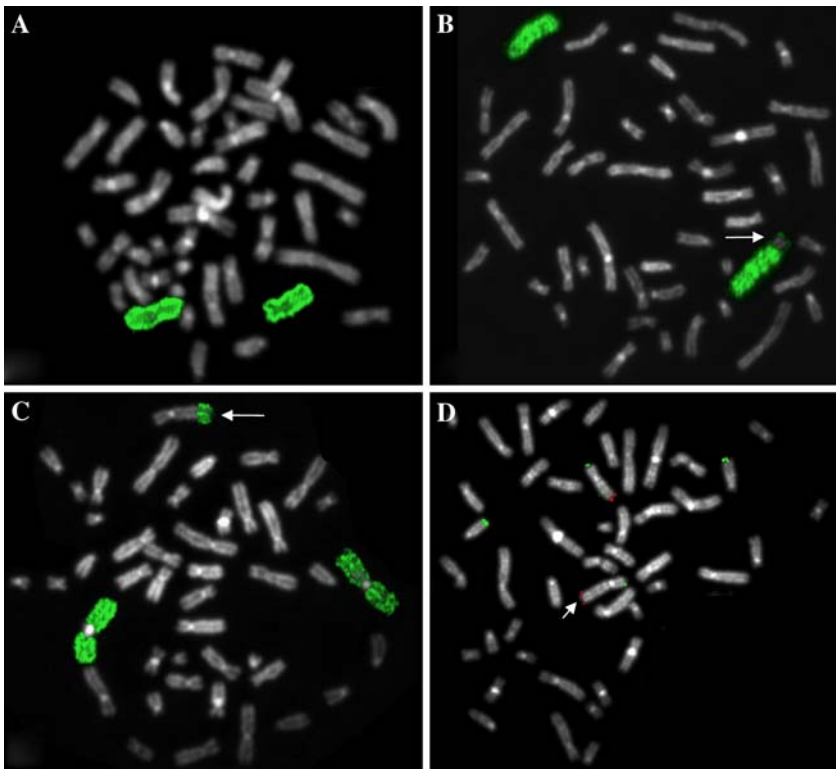

Fig 3 (**A**) FISH analyses with WCP-X on patient chromosomes indicated that the material deleted from one of the X-chromosomes had not been inserted anywhere else in the genome. (**B**) FISH analysis with WCP-7. The insertion on der(7q) is denoted by an arrow. (**C**) FISH analysis with WCP-1. The arrow indicates the der(7) chromosome bearing the inserted material from chromosome 1. (**D**) FISH analysis with subtelomeric probes TelVysion hybridizing to 7q (red) and 7p (green). The subtelomeric region on der(7), identified by an arrow, has been retained despite the insertion of the region 1p13.2-31.2. [The mixed Telvision probe also yields signals within the subtelomeric region of chromosome 15]

Table 1 FISH results with probes hybridizing to the distal 7q36 region

BAC or probe	Accession number/locus (size)	Position on 7q36[a]	FISH pattern[b]
RP13-620M21	AC104594	153436862–153591526	Signal on distal q36 on the der(7)
RP11-331D5	AC006372	156873737–157064382	Signal on distal q36 on the der(7)
TelVysion 7q	VYJyRM2000 STS 2000H	Unknown, but positivefor marker D7S427 from 158595998–158596198	Signal on distal q36 on the der(7)

[a] Nucleotide numbering according to the Ensembl release 43, NCBI build 36

[b] The signal was noted at the very distal end of band q36, distal to the insertion from chromosome 1

encompass at least 22 Mb and hence is predicted to include the 15 disease-associated genes listed in Table 3. Defects in several of these genes are already known to be associated with X-linked mental retardation. The deletion does not encompass the *SHOX* and *ARSE* genes, which are retained and located distal to the deletion. The proximal deletion boundary maps telomeric to the *DMD* gene, which is not itself included within the deletion interval.

According to the G-banding analysis, the 1p13.2-31.2 region became inserted into chromosome 7q36 (Fig. 2). Since the patient suffers from severe juvenile chronic arthritis and the *PTPN22* gene (implicated in susceptibility to rheumatoid arthritis; Michou et al. 2007) maps to 1p13.2, we investigated whether this gene had been affected by the chromosomal rearrangement. FISH analysis demonstrated that the *PTPN22* gene, spanned by clone RP5-1073O3, was heterozygously deleted in the patient since it did not hybridize to either the der(1) or the der(7) chromosomes (data not shown). This finding implied that the rearrangement involving chromosomes 1 and 7 is unbalanced and is associated with a deletion of chromosome 1 at the proximal breakpoint. To determine the size of this deletion, further FISH analysis was performed employing the BAC/PAC clones listed in Table 4. The

Table 2 Results of FISH analyses to investigate the del(X)(p21p22.3)

BAC/PAC or probe	Accession number	Position on Xp[a]	FISH-results
RP13-309C18	BX119906	1507117–1542782	nd
RP11-261P4	AL683870	1541783–1704159	nd
RP13-297E16	AL683807	1745261–1935085	nd
RP11-449L4	AL672040	1933087–2050383	nd
RP11-325D5	AC079176	2311675–2497952	nd
RP11-146D5	AC138085	2714199–2790130	nd
RP11-325L9	AC108682	3014044–3088186	nd
RP11-631N21	AC073493	3793093–4004514	del
RP11-413F15	AC073617	4547336–4698637	del
RP11-615L18	AC095353	5112706–5254705	del
RP11-769N24	AC078989	5554435–5749149	del
RP11-126O22	AC073488	9179481–9249873	del
RP1-108M6	AC003036	9410712–9533914	del
RP1-167A22	AC002349	10388548–10548410	del
RP11-431J24	AC078993	15878386–16092386	del
RP11-421K1	AL732578	18814681–19005998	del
RP11-265D5	AC107612	24841779–24935667	del
RP5-1147O16	AL031542	30896993–33117215	nd

nd, not deleted; del, deleted

[a] Ensembl release 31.35d

Table 3 Genes in Xp21-p22.3 deleted in the patient and included in OMIM morbid map

Gene symbol	Gene description	Associated disease
NLGN4[a]	Neuroligin 4	X-linked mental retardation, autism
VCXA	Variably charged protein X-A	X-linked mental retardation
STS[a]	Steryl-sulfatase precursor	Ichtyosis
VCX	Variably charged protein X-B1	X-linked mental retardation
VCXB	Variably charged protein X-B	X-linked mental retardation
KAL1[a]	Anosmin 1	Kallmann syndrome
TBL1X[b]	Transducin-beta-like-1	Possibly involved in the pathogenesis of ocular albinism with late-onset sensorineural deafness phenotype
GPR143[b]	G protein-coupled receptor 143	Ocular albinism 1
MID1[b]	Midline 1	Opitz/BBB syndrome
OFD1[a]	Orofaciodigital syndrome type I	Orofaciodigital syndrome type I
FANCB[c]	Fanconi anemia complementation group B	Fanconi anemia
NHS [b]	Nance-Horan syndrome	Nance-Horan syndrome (congenital cataracts and dental anomalies)
STK9	Serine/threonine kinase-9	X-linked infantile spasm syndrome
RS1[b]	Retinoschisis	Retinoschisis (X-linked, juvenile) 1
RPS6KA3[c]	Ribosomal protein S6 kinase, 90-KD	X-linked mental retardation, Coffin-Lowry-syndrome
ARX	Aristaless related homeobox	X-linked mental retardation, hydranencephaly and abnormal genitalia
IL1RAPL1	Interleukin 1 receptor accessory protein-like 1	X-linked mental retardation

[a] Escape from X-inactivation according to Carrel and Willard (2005)

[b] Heterogeneity with regard to escape from X-inactivation of this gene has been observed by Carrel and Willard (2005)

[c] The gene is inactivated according to Carrel and Willard (2005)

Table 4 Results of the FISH analysis to determine the extent of the deletion in 1p13.2

BAC	Accession number	Region encompassed by BAC[a]	FISH signals[b] noticed on
RP11-364B6	AC092506.3	104402065–104598344	der(7)
RP11-478L17	AL499605.6	106860590–107048939	der(7)
RP11-552M11	AL390195.10	111745104–111898211	–
RP11-426L16	AL603832.28	112991588–113185191	–
RP11-228G5	AL389921.12	113834485–113903248	–
RP11-473L1	AL390759.10	113903149–113974612	–
RP11-626F04	Not available	113927658–114090547	–
RP5-1073O3	AL137856.24	114408979–114523076	–
RP11-555K17	Not available	114240984–114420320	–
RP11-205J11	Not available	114314370–114488274	–
RP11-372O23	AC023551	114431960–114603500	–
RP11-686O08	Not available	114555843–114706316	–
RP11-735A14	Not available	115582551–115732971	–
RP5-1086K13	AL390066.5	116774543–116878153	–
RP5-871G17	AL359553.14	119719965–119818318	der(1)
RP11-323K8	AL512503.14	120270573–120380184	der(1)

[a] According to Ensembl version 43 (NCBI 36)

[b] In addition to those on the normal chromosome 1

–, These BAC probes did not hybridize to the der(1) and the der(7)

chromosome 1 deletion was found to encompass at least 5.1 Mb but less than 12.7 Mb, as deduced from the positions of the BAC clones investigated. FISH analysis of BAC RP11-478L17 from 1p13.2 yielded signals in the subtelomeric region of the der(7) chromosome indicating that the insertion of 1p13.2-31.2 into 7q36 was a direct insertion (data not shown).

Parental origin of the chromosome 1 deletion

In order to determine the parental origin of the deleted chromosome 1, we analyzed polymorphic markers located within the deleted interval in both the patient and her family. These analyses indicated the loss of the paternal allele due to the deletion. Heterozygosity of the markers was observed in DNA isolated from paternal blood cells indicating that it is unlikely that the father possesses the deletion himself. However, gonosomal mosaicism cannot be unequivocally excluded.

CGH

CGH confirmed the deletion on Xp and was also suggestive of a deletion on 1p13. No loss of genetic material from 7q36 was however detected using this method.

Investigation of the X inactivation pattern

Analysis of polymorphic X chromosome markers demonstrated that the patient's deletion occurred on the paternally inherited chromosome (data not shown). Investigation of the AR gene polymorphism revealed that the X chromosome harboring the deletion had been non-randomly inactivated (more than 95% skewed) in peripheral blood lymphocytes and skin fibroblasts from the patient (data not shown).

Discussion

Two structural chromosome rearrangements were detected in the patient described here: an interstitial deletion del(X)(p21p22.3) and a rearrangement involving chromosomes 1 and 7 (Figs. 1–3). The Xp deletion appears to encompass at least 22 Mb and includes a number of genes known to be associated with mental retardation (listed in Table 3). Women with an Xp deletion may exhibit stigmata of Turner syndrome with mild mental retardation, but the phenotype is highly variable and influenced by the degree of favorable/unfavorable X-inactivation (reviewed in Wandstrat et al. 2000; Chocholska et al. 2006). Phenotypic features of the patient described here that might be

causatively related to the Xp deletion are short stature, a broad chest and a lack of secondary sexual characteristics. However, the patient manifested non-random, favorable inactivation (more than 95% skewed) of the deletion-bearing X chromosome in both blood lymphocytes and skin fibroblasts. We may therefore surmise that additional genomic imbalances could have contributed to the severe phenotype of the patient. The rearrangement involving chromosomes 1 and 7 was therefore further investigated by high resolution FISH. Probes mapping to the proximal breakpoint region on chromosome 1p13.2 identified a deletion of at least 5.1 Mb accompanying the insertion of 1p13.2-p31.2 into 7q36 (Table 4).

The chromosome 1 deletion identified in our patient occurred on the paternal chromosome within a gene-dense region; it spans at least 5.1 Mb but is no larger than 12.7 Mb. The 5.1 Mb segment that is minimally deleted encompasses 46 known genes and further 28 potential genes according to Ensembl (http://www.ensembl.org; Supplementary Table 1). Among the genes deleted in the patient is the haematopoietic-specific protein tyrosine phosphatase gene, *PTPN22*. Intriguingly, the *1858T* allele of the *PTPN22-C1858T* single nucleotide polymorphism, which gives rise to a *R620W* amino acid substitution, has been associated with rheumatoid arthritis in Caucasian populations (Begovich et al. 2004; Bottini et al. 2004; Kyogoku et al. 2004; Carlton et al. 2005; reviewed by Gregersen et al. 2006; Michou et al. 2007). Contradictory results have however been reported regarding the influence of this SNP on juvenile idiopathic arthritis. Whilst no (or very little) influence has been reported by Seldin et al. (2005), a significant effect of *R620W* in juvenile idiopathic arthritis was observed by others (Hinks et al. 2005; Viken et al. 2005; Cinek et al. 2007). One function of PTPN22 is the dephosphorylation of Lck and other mediators of T cell receptor signaling (Hasegawa et al. 2004; Mustelin et al. 2004, 2005; Wu et al. 2006). Further, PTPN22 interacts via its SH3-binding sites with the c-Src tyrosine kinase Csk. In vitro experiments have shown that the W620 variant binds less efficiently to Csk (Begovich et al. 2004; Bottini et al. 2004). This notwithstanding, the R620W substitution increases the enzymatic activity of PTPN22 (Vang et al. 2005) and may therefore be regarded as a gain-of-function mutation which results in the down-regulation of T cell receptor signaling.

No inactivating mutations have so far been identified in the *PTPN22* gene in patients with rheumatoid arthritis (Carlton et al. 2005). There is therefore no compelling evidence that the deletion of *PTPN22* in the patient described here is causatively associated with her juvenile idiopathic arthritis. Moreover, we cannot rule out the possibility that the interchromosomal rearrangement might also be associated with a cryptic microdeletion at 7q36, the site of the insertion. Although we did not detect any loss of chromosome 7 material by CGH, this does not unequivocally exclude the presence of a small deletion in this region.

Constitutional deletions within the proximal short arm of chromosome 1 including band 1p13 are very rare events with only four reports having been published to date (Dockery and Van der Westhuyzen 1991; Tabata et al. 1991; Mattia et al. 1992; Bisgaard et al. 2007). The phenotypic anomalies associated with these deletions are summarized in Table 5. Only the deletion of the patient described by Bisgaard et al. has been investigated by molecular cytogenetic means, thereby enabling a direct comparison with the chromosome 1 deletion identified in the propositus described here. The deletion interval of the patient reported by Bisgaard et al. (2007) overlaps partially with the deletion found in our patient and also includes the *PTPN22* gene. However, the 13 year-old patient was not reported to suffer from juvenile idiopathic arthritis.

Table 5 Summary of the phenotypic features of patients with deletions involving 1p13

Case no	Deletion	Age	Gender	Clinical phenotype
1[a]	del(1)(p22.3 → p13.3)	30 year-old	Female	Twins, growth and mental retardation, microcephaly, deafness, atresia of auditory canals, mild spastic palsy
2[b]	del(1)(p22.3 → p13.3)	7 months	Female	Severe tetralogy of Fallot, multiple congenital anomalies and dysmorphic features, growth and psychomotor retardation, epilepsy
3[c]	del(1)(p22.3 → p13)	22 months	Male	Developmental retardation, minor anomalies like ptosis, kyphoscoliosis, intestinal malrotation, hypotonia
4[d]	del(1)(1p13.1 → p21.1)	13 years	Female	Short stature, developmental delay, mental retardation, epilepsy diplegia, coloboma

[a] Twins described by Dockery and van der Westhuyzen (1991)

[b] Tabata et al. (1991)

[c] Mattia et al. (1992)

[d] Bisgaard et al. (2007)

In order to determine whether segmental duplications might occur within the breakpoint region, potentially involving paralogous sequences in 7q36 and 1p13.1-31.3, we screened the Human Genome Segmental Duplication Database (http://www.projects.tcag.ca/humandup/). However, no such duplications were identified.

Common fragile sites are genomic regions prone to breakage under conditions of replication stress (reviewed by Glover et al. 2005). Currently, 84 common fragile sites are listed in the GDB Human Genome Database (http://www.gdb.org/). Interestingly, common fragile sites were found within two of the three breakpoint regions involved in the ins(7;1) rearrangement, at least at the level of resolution afforded by G-banded chromosomes: FRA7I in 7q36 (aphidicolin-type, GDB:119213) and FRA1C in 1p31.2 (aphidicolin-type, GDB:119170). Precise mapping of the breakpoints would however be needed to determine if these fragile sites had indeed been the target sites of this chromosomal rearrangement.

In conclusion, the rearrangement involving chromosomes 1 and 7 is not simply a balanced insertion of the 1p13.2-31.2 region into 7q36 but is rather a more complex lesion associated with the deletion of ~5–13 Mb at 1p13.2. In addition to position effects affecting the expression of genes in the vicinity of the respective breakpoints, it is likely that sequence loss has contributed to the severe clinical phenotype exhibited by the patient. To our knowledge, this is the first example of a complex chromosomal rearrangement in a patient with severe psychomotor retardation in combination with juvenile idiopathic arthritis and serves to emphasize the importance of high-resolution analysis of the chromosomal breakpoint regions.

Acknowledgement The authors wish to thank Antje Kollak and Helene Spöri for technical support.

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