Gene 502 (2012) 40–45

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short Communication

Complex rearrangement involving 9p deletion and duplication in a syndromic patient: Genotype/phenotype correlation and review of the literature

Maria Paola Recalcati [a,*], Melissa Bellini [b], Lorenzo Norsa [b], Lucia Ballarati [a], Rossella Caselli [a], Silvia Russo [a], Lidia Larizza [a,c], Daniela Giardino [a]

[a] Laboratorio di Citogenetica Medica e Genetica Molecolare, IRCCS Istituto Auxologico Italiano, Milan, Italy
[b] Clinica Pediatrica, A.O. San Paolo, Università di Milano, Milan, Italy
[c] Dipartimento di Medicina, Chirurgia e Odontoiatria, A.O. San Paolo, Università di Milano, Milan, Italy

ARTICLE INFO

Article history:
Accepted 9 April 2012
Available online 17 April 2012

Keywords:
Chromosome 9p complex rearrangement
Array-CGH
FISH
9p deletion syndrome
9p duplication syndrome
Phenotype–genotype correlation

ABSTRACT

We describe a 7-year-old boy with a complex rearrangement involving the whole short arm of chromosome 9 defined by means of molecular cytogenetic techniques. The rearrangement is characterized by a 18.3 Mb terminal deletion associated with the inverted duplication of the adjacent 21,5 Mb region. The patient shows developmental delay, psychomotor retardation, hypotonia. Other typical features of 9p deletion (genital disorders, midface hypoplasia, long philtrum) and of the 9p duplication (brachycephaly, down slanting palpebral fissures and bulbous nasal tip) are present. Interestingly, he does not show trigonocephaly that is the most prominent dysmorphism associated with the deletion of the short arm of chromosome 9. Patient's phenotype and the underlying flanking opposite 9p imbalances are compared with that of reported patients and the proposed critical regions for 9p deletion and 9p duplication syndromes.

1. Introduction

Chromosome 9 short arm monosomy and trisomy are syndromic conditions with peculiar clinical phenotypes, consequent to complete or partial 9p deletions/duplications.

Both 9p deletions and duplications are associated with mental and psychomotor retardation, hypotonia, hypertelorism and skeletal malformations. In addition, 9p deletion carriers show variable genital and/or gonadal disorders if XY patients, trigonocephaly, midface hypoplasia, small and up slanting palpebral fissures, long philtrum (Christ et al., 1999; Kawara et al., 2006; Swinkles et al., 2008). Conversely 9p duplication carriers present with microcephaly/brachycephaly, down slanting palpebral fissures, bulbous nasal tip, short philtrum and short neck (Fujimoto et al., 1998; Jelin et al., 2010; Zou et al., 2009). However, a great clinical heterogeneity is observed depending on the 9p genomic regions involved in the rearrangements. Due to this variability the precise molecular characterization of the unbalanced regions is an important tool to: (1) deepen the correlation between 9p deleted or duplicated genomic regions and phenotypic features, (2) define critical minimum overlap regions for the phenotype to refine or confirm those that have been proposed, (3) provide an "ad hoc" genetic counseling.

We present a 7-year-old male patient with an inverted duplication and a terminal deletion of the short arm of chromosome 9. The rearrangement has been finely characterized by array-based Comparative Genomic Hybridization (array-CGH) and Fluorescent In Situ Hybridization (FISH). Moreover we address the correlation between the patient's clinical manifestations and the regions involved in the rearrangement by comparison to the clinical presentation and the 9p genomic imbalances of other reported cases.

2. Materials and methods

2.1. Clinical description

The patient is a 7 years old Caucasian boy, showing developmental delay and craniofacial anomalies. He is the first child of non-consanguineous parents with an unremarkable family history for genetic disorders. Prenatal ultrasound monitoring revealed macrosomy. Pregnancy and delivery were normal. At birth he presented a duodenal stenosis, surgically corrected. In his first year of life he showed

Abbreviations: Array-CGH, Array based comparative genomic hybridization; FISH, Fluorescent in situ hybridization; OFC, Occipitofrontal circumference; BAC, Bacterial artificial chromosome; dUTP, Deoxyuridine triphosphate; Cy3, Cyanine 3; DEAC, Diethylaminocoumarine; PCR, Polymerase chain reaction; MLPA, Multiple ligation-dependent probe Amplification; UCSC Genome Browser, University of California Santa Cruz Genome Browser; DMRT gene, Doublesex and Mab-3 related transcription factor; DOCK8 gene, Dedicator of cytokinesis 8; KANK1 (ANKRD15) gene, KN motif and ankyrin repeat domains 1; SLC1A1 gene, Solute carrier family 1, member 1; GLDC gene, Glycine dehydrogenase.

* Corresponding author at: Laboratorio di Citogenetica Medica e Genetica Molecolare, IRCCS Istituto Auxologico Italiano, via Zucchi 18, 20095 Cusano Milanino MI, Italy. Tel.: +39 02 619112416; fax: +39 02 619112464.
E-mail address: p.recalcati@auxologico.it (M.P. Recalcati).

0378-1119/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.gene.2012.04.030

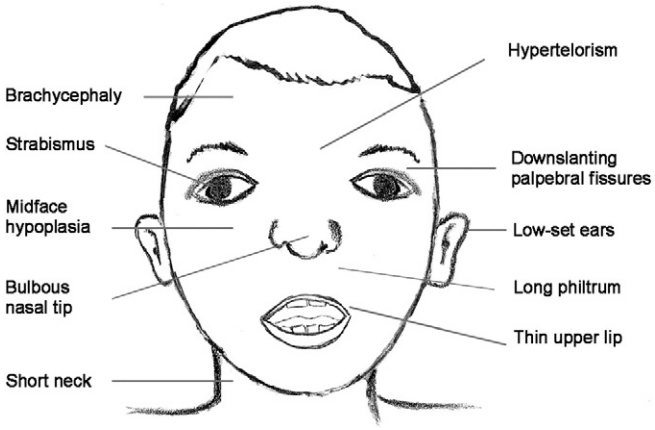

Fig. 1. Diagram showing the patient's main facial dysmorphisms.

laryngomalacia, gastroesophageal reflux, bilateral cryptorchidism, ostium secundum interatrial defect and developmental delay.

Our clinical evaluation at 7 years of age revealed hypotonia and ataxia, brachycephaly, asymmetric, round and flat face with hypoplasic midface, hypertelorism, strabismus, wide nasal bridge and bulbous nose, long and smooth philtrum, thin upper lip, open mouth appearance, high-arched palate and low-set ears (Fig. 1 and Supplementary Fig. 1). Short neck, pectus carinatum, heart murmur, wide-spaced nipples and dorso lumbar scoliosis were also noted; testicles spontaneously descended and no hypospadias was present. Auxological data were the following: weight and length 25th-50th percentile and OFC 75th percentile. Blood analyses for hematochemical parameters, thyroid function and metabolic disorders screening provided normal results. Abdominal ultrasound also showed normal patterns. In order to better characterize the neurological involvement, a specialist examination was performed which evidenced a severe developmental delay. Electroencephalogram was normal while cerebral magnetic resonance showed the presence of hypoplasia of corpus callosum and brain-stem.

2.2. Cytogenetic and Fluorescent In Situ Hybridisation (FISH) Analysis

Cytogenetic analysis was performed on peripheral blood lymphocytes from the patient and his mother (father not available) using QFQ banding techniques on metaphase chromosomes obtained by standard procedures. The karyotype was described in accordance with ISCN 2009 (Shaffer and Slovak, 2009). The BAC probes used in the FISH study were selected according to the University of California, Santa Cruz (UCSC) Genome Browser (release March 2006) and provided by Prof. Mariano Rocchi (University of Bari, Italy). BAC probes were nick translation labelled with biotin-dUTP (La Roche) or Cy3-dUTP (Amersham), and detection of biotin-dUTP labelled probe made by DEAC-streptavidin. The standard FISH protocol was followed with minor modifications (Lichter and Cremer, 1992).

2.3. High resolution array comparative genomic hybridization (array-CGH) analysis

Genomic DNA was purified from peripheral blood mononucleate cells by using the GenElute™ Blood Genomic DNA kit (Sigma-Aldrich) according to the supplier's instructions. Array-CGH was performed by using the 244 K Human Genome CGH Microarray Kit (Agilent, Santa Clara, CA) with a mean resolution of ~50 kb. Protocol provided by Agilent has been followed with no modifications. The arrays were analyzed with the Agilent Scanner Control (v 7.0) and the Feature Extraction software (v 9.5.1). Graphical overviews were obtained using the CGH Analytic software (v4.0.81). Nucleotide designations were assigned according to the hg18 build of the human genome.

2.4. Microsatellites analysis

Segregation analysis of polymorphic loci was performed on patient and his mother (father not available) using microsatellites mostly spanning the chromosome 9 deleted and duplicated regions. The following polymorphic markers were used: D9S1813, D9S286, D9S157, D9S169, D9S1817, D9S1791, D9S1799, D9S167, D9S1872. Primers sequences and positions are available on UCSC Genome Browser (release March 2006; http://genome.ucsc.edu/cgi-bin/hgGateway).

Polymerase chain reaction (PCR) assays were developed and optimized to amplify each fragment containing a marker of interest in a 15-μl volume using TaqGold 0.15 u (Biorad, Hercules, CA) and GeneAmp PCR Gold Buffer 10× (Biorad, Hercules, CA) with 50–100 ng DNA and 0.1 μM each primer. Final products were prepared for injection on the ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA), using deionized formamide, 0.5 μl GS

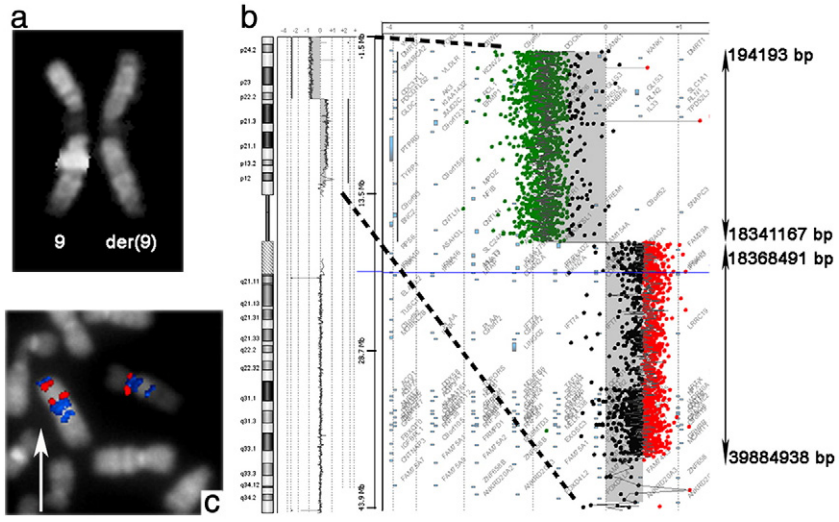

Fig. 2. Cytogenetic characterization of rearranged 9p. (a) Q-banded partial karyotype of the propositus, showing the derivative chromosome 9 on the right; b) Chromosome 9p ideogram (left) and magnification of the anomalous array-CGH profile (right): green dots represent deletion and red dots duplication. Breakpoints are indicated; c) Dual-colour FISH with probes RP11-3J10 (red signal) and RP11-108C23 (blue signal). The hybridization pattern on derivative chromosome 9 (arrowed) indicates that the duplication is inverted. The co-hybridization signals given by RP11-108C23 BAC probe are visible on the 9q pericentromeric region of both chromosomes 9.

Table 1
Segregation pattern of polymorphic loci analysed for patient and his mother (father alleles are deduced). Bolding indicates informative loci.

Locus	Chromosome band	Position	Father	Patient	Mother
D9S1813	9p24.2	4,023,584–4,223,960	?/?	-/A1	A1- A2
D9S286	9p24.1	7,943,378–8,143,709	?/?	-/A1	A1- A2
D9S157	9p22.2	17,518,219–17,718,591	?/?	-/A2	A2- A1
D9S169	9p21.2	27,128,617–27,329,008	**?/A2**	**A2-A2/A1**	**A1- A3**
D9S1817	9p13.3	33,749,593–33,949,887	**?/A1**	**A1-A1/A2**	**A2- A2**
D9S1791	9p13.3-13.2	36,283,375–36,483,713	**?/A1**	**A1-A1/A3**	**A3- A2**
D9S1799	9q21.1	72,456,672–72,657,036	?/A3	A3- A2	A2- A1
D9S167	9q21.32	84,873,828–85,074,162	?/A2	A2- A1	A1- A3
D9S1872	9q33.1	120,729,316–120,929,460	?/A1	A1- A2	A2- A3

ROX500 size standard (Applied Biosystems, Foster City, CA) and 1.0 μl PCR products. Products were separated by POP4 and analyzed by GeneScan.

3. Results

The QFQ-banding analysis revealed the presence of one chromosome 9 abnormal in the short arm (Fig. 2a); to exclude any low rate mosaicism the analysis has been extended to 100 mitoses. Array-CGH analysis identified an 18.3 Mb 9p terminal deletion (breakpoint at 9p22.2) and a 21.5 Mb duplication of the adjacent region with telomeric breakpoint at 9p22.2 and centromeric breakpoint at 9p13.1 (Fig. 2b). Double colour FISH with BAC probes RP11-3J10 (located at 9p13.2) and RP11-108C23 (located at 9p11.2 and co-hybridizing to the pericentromeric region of chromosome 9q) allowed us to establish that the duplication also encompasses the 9p11.2 band and is an inverted duplication (Fig. 2c). The proband's karyotype could thus be defined as 46,XY, der(9)del(9)(p22)dup(9)(p22p11.2).ish dup(9)(p13.2p11.2)(RP11-3J10++,RP11-108C23++).arr 9p24.3p22.2(194,193-18,341,167)x1, 9p22.2p13.1(18,368,491-39,884,938)x3. The cytogenetic and array-CGH analyses of the proband's mother gave normal results, while the father was not available.

Microsatellites analysis was carried on DNAs from the patient and his mother using markers located into the deleted and duplicated regions. Informative markers allowed us to deduce the paternal origin of the rearrangement: unbalanced ratio between areas of paternal and maternal allele peaks was indicative of a double contribute from the father in the duplicated region previously identified by array-CGH analysis. Table 1 shows the observed segregation pattern.

4. Discussion

Here we present a male patient carrying an abnormal short arm of chromosome 9 identified by QFQ banding and subsequently refined by array-CGH and FISH as a complex rearrangement with a 9p24.3p22.2 terminal deletion and an adjacent 9p22.2p11.2 inverted duplication. Microsatellites analysis allowed us to deduce that rearrangement in the patient occurred on chromosome 9 inherited from the father.

In Fig. 3 our patient's unbalanced regions are compared to previously reported cases of 9p duplications with associated deletions, 9p

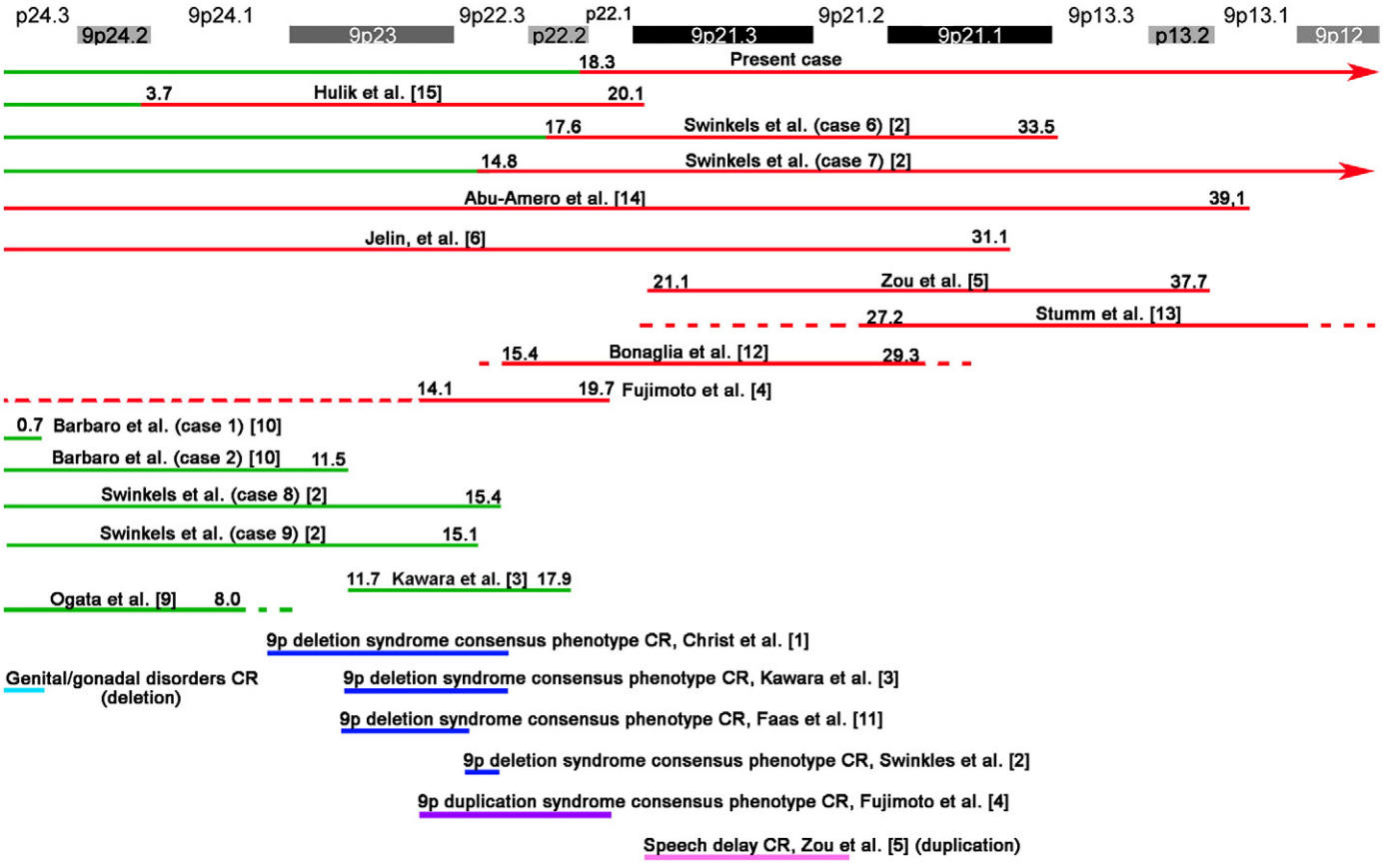

Fig. 3. 9p24.3p12 map showing regions involved in our patient's rearrangement, compared to molecularly characterized 9p deletions with associated duplications, 9p isolated partial duplications, 9p isolated partial deletions and a mosaic supernumerary 9p chromosome reported in the literature. Deleted and duplicated regions are represented respectively by green and red bars: distance (Mb) from the 9p telomere is indicated. Dotted lines represent undefined deletions/duplications end regions. Light blue bar refers to the critical region for genital/gonadal disorders in the context of 9p deletion; blue and violet bars illustrate the critical regions for the consensus phenotypes of 9p deletion syndrome and 9p duplication syndrome, respectively. The proposed critical region for speech delay associated with 9p duplication is represented by the pink bar. CR: critical region.

Table 2
Presence (+), absence (−) or mild manifestation (+/−) of 9p deletion and duplication syndromes recurrent features in the present case and in cases from the literature (nk, not known).

	Deletion and duplication				Isolated duplications/marker					Isolated deletions				
	Our patient (XY)	Hulik [15] (XX)	Swinkles Case 6 [2] (XX)	Swinkles Case 7 [2] (XX)	Abu-Amero [14]	Jelin [6]	Zou [5]	Bonaglia [12]	Fujimoto [4]	Barbaro Case 2 [10] (XY)	Swinkles Case 8 [2] (XY)	Swinkles Case 9 [2] (XX)	Kawara [3] (XY)	Ogata [9] (XY)
9p deleted region	9p24.3p22.2	9p24.3p24.2	9p24.3p22.2	9p24.3p22.3						9p24.3p23	9p24.3p22.3	9p24.3p22.3	9p23p22.2	9p24.3p?24.1
9p duplicated region	9p22.2p12	9p24.2p21.3	9p22.2p13.3	9p22.3p12	9p24.3p13.1	9p24.3p21.1	9p21.3p13.2	9p22.39p21.1	9p?23p22.1					
9p deletion/duplication features														
Developmental delay	+	+	+	+	+	+	+	−	+	+	+	+	+	−
Psychomotor retardation	+	+	+	+	+	+	+	−	+	+	+	+	+	−
Hypotonia	+	+	+	+	−	−	−	−	nk	+	−	+	nk	−
Hypertelorism	+	+	−	−	−	−	−	−	−	−	−	−	+	−
Low-set and posteriorly angulated ears	+	+	+	+	−	+	−	−	+	+	+	+	+	+
Skeletal malformations	+	−	+	−	−	+	+	−	−	−	+/−	+/−	−	+
9p deletion features														
Trigonocephaly	−	−	+	+						−	+	−	+	−
Midface hypoplasia	+	+	+	+/−						−	+	+	+	−
Up slanting palpebral fissures	−	−	−	+						−	+	−	+	−
Short palpebral fissures	−	−	+	+						−	+/−	+	+	−
Anteverted nostrils	−	−	+	+						−	−	+	+	+
Long philtrum	+	+	+	+/−						+	+	−	+	−
Thin upper lip	+	+	+	+						−	+	+	+	−
Micrognathia	−	+	+	+						−	+	−	−	+
Short/broad neck	+	−	+	−						+	+	+	nk	−
Cardiac defects	+	−	+	+						−	−	−	+	−
Genital/gonadal disorders	+	−	−	−						+	−	−	+	+
Inguinal hernia	+	−	−	−						−	+	+	−	−
Omphalocele	−	−	+	−						−	−	−	−	−
9p duplication features														
Speech/language delay	+	nk	+	+	+	+	+	+	+					
Growth retardation/ short stature	−	+	+	+	+	nk	+	−	+					
Microcephaly/ Brachycephaly	+	−	−	−	+	+	−	−	+					
Deep and wide-set eyes	−	+	−	−	+	−	−	−	−					
Down slanting palpebral fissures	+	−	−	−	−	−	−	−	+					
Bulbous nasal tip	+	+	+	+	−	+	+	+	+					
Short philtrum	−	−	−	−	−	+	+	+	−					
Downturned corners of the mouth	−	+	−	−	−	−	−	−	+					
Highly arched palate	+	−	+	+	−	−	−	+	+					
Cleft palate/lip	−	+	−	−	−	+	−	−	−					
Toes with short/ distrophyc nails	−	+	−	−	−	nk	nk	−	−					
Clinodactily	−	+	−	−	+	+	+	−	−					

partial duplications and 9p partial deletions which have been finely characterized by array-CGH, FISH, Multiple Ligation-Dependent Probe Amplification (MLPA) or microsatellites analysis. The phenotypes of the patients at comparison, each identified by his/her 9p rearrangement, are summarized in Table 2.

With regard to 9p deletion syndrome a critical region involved in gonadal dysgenesis in XY patients has been proposed to reside at 9p24.3, from 9p telomere to the *DMRT* genes cluster (Barbaro et al., 2009; Ogata et al., 1997). The phenotype of XY patients with terminal 9p deletions varies from complete sex reversal to milder phenotypes. Genes belonging to *DMRT1, 2* and *3* cluster have been proposed as candidates, since they are involved in the vertebrate sex-determining pathway and exhibit a gonad-specific expression pattern. This 9p24.3 critical region is included in the deletion of our patient, who only shows bilateral cryptorchidism, a mild genital/gonadal phenotype.

Different critical regions have been suggested for the consensus phenotype associated to 9p deletion syndrome (Christ et al., 1999; Faas et al., 2007; Kawara et al., 2006; Swinkles et al., 2008). The first, proposed in 1999 (Christ et al., 1999) is associated with developmental delay/mental retardation, trigonocephaly, midface hypoplasia and long philtrum. Subsequently, efforts to narrow down the critical region have been attempted. Swinkles et al. (2008) proposed a 300 kb long critical region in 9p22.3, while Faas et al. (2007) and Kawara et al. (2006) proposed wider and more distally extending regions in 9p23p22.3 (Fig. 3). Typical features of 9p monosomy syndrome such as midface hypoplasia, hypertelorism, long philtrum, anomalous auricles and broad neck are present in our patient, but not micrognathia and up slanting palpebral fissures. Cardiac defects, inguinal hernia and scoliosis, all present in our case, have been rarely observed (Swinkles et al., 2008). Trigonocephaly is considered the most prominent feature of 9p deletion syndrome consensus phenotype. This anomaly is not present in our patient, although his deletion overlaps all critical regions proposed for the 9p deletion syndrome consensus phenotype. We speculate that his duplicated region influenced the cranial features more than the flanking deletion. Indeed, in addition to the terminal deletion, our patient carries an adjacent duplication involving the 9p22.2p11.2 segment. The 9p22 band has been proposed as the candidate region for the consensus phenotype of the 9p duplication syndrome (Fujimoto et al., 1998). Described patients had developmental delay/mental retardation, small stature, microcephaly/brachycephaly, down slanting palpebral fissures, deep-set eyes, hypertelorism, low-set ears, bulbous/prominent nose, downturned mouth and limb anomalies (Fujimoto et al., 1998). Recently, Jelin et al. (2010) characterized a 31.1 Mb duplication from 9p telomere to 9p21.1 in a female patient showing in addition short philtrum, orofacial clefting and thoracic kyphosis. Duplications in 9p21.3p13.2 and in 9p22.3p21.1 in patients with milder dysmorphic features, growth retardation and speech/language delay have been also reported (Bonaglia et al., 2002; Zou et al., 2009). Interestingly, Stumm et al. (2002) described a phenotypically normal male carrying an interstitial duplication of 9p21p12, indicating in 9p21 band the distal boundary of the critical region for 9p duplication syndrome. A mosaic supernumerary marker chromosome involving part of the short arm of chromosome 9 has been described in a patient showing a subset of the 9p duplication features, likely due to the mosaic nature of the marker (Abu-Amero et al., 2010). Our patient manifests brachycephaly, down slanting palpebral fissures, hypertelorism, low-set ears, bulbous/prominent nose and skeletal malformation. Moreover, it is important to notice that cleft palate or other palate malformations are described in all reviewed patients with 9p duplication except in the patients described by Zou et al. (2009) and Abu-Amero et al. (2010), suggesting that a palate malformation predisposing region may resides in 9p22.2p22.1 if duplicated.

The coexistence of partial 9p monosomy and trisomy has been described in other cases discussed in the present paper (Fig. 3 and Table 2) (Al Achkar et al., 2010; Hulik et al., 2009; Swinkles et al., 2008). All show features shared by 9p deletion and 9p duplication syndromes, such as developmental delay, psychomotor retardation, hypotonia and low-set ears, but the manifestation of syndrome-specific features is variable and depends on the length of the different genomic regions involved. Among the 9p deletion dysmorphic features, these cases share midface hypoplasia, thin upper lip, long philtrum and micrognatia and their deleted regions overlap about 3.7 Mb of the 9p24.3p24.2 interval. Among the 9p duplication features they share only bulbous nasal tip, and their duplications overlap about 1.8 Mb in 9p22.2p22.1 (Fig. 3 and Table 2).

Based on the UCSC database there are about 53 genes annotated in the region deleted in our patient. Loss or mutation of a few genes such as *DOCK8*, *KANK1*(*ANKRD15*), *SLC1A1* and *GLDC*, has been already associated with mental, motor retardation and/or other neurological symptoms (Bailey et al., 2011; Griggs et al., 2008; Lerer et al., 2005; Meyer et al., 2010), making their deletion likely responsible for the severe mental and motor delay of our patient. At least 120 genes are located in the duplicated regions of our patient and some may be dosage-sensitive thus contributing to the observed phenotype.

Further studies providing for these patients a refined molecular cytogenetic characterization such as that performed in this study are needed to appoint dosage sensitive genes of chromosome 9p and assign the genes responsible for the developmental delay and craniofacial dysmorphisms of our and previously reported patients. Genetic counselling aimed at assuring the best follow-up of the patients would greatly benefit of the increased understanding of the genotype/phenotype correlations in such patients.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.gene.2012.04.030.

References

Abu-Amero, K.K., et al., 2010. A de novo marker chromosome derived from 9p in a patient with 9p partial duplication syndrome and autism features: genotype–phenotype correlation. BMC Med. Genet. 11, 135.

Al Achkar, W., Wafa, A., Moassass, F., Liehr, T., 2010. Partial trisomy 9p22 to 9p24.2 in combination with partial monosomy 9pter in a Syrian girl. Mol. Cytogenet. 3, 18.

Bailey, C.G., et al., 2011. Loss-of-function mutations in the glutamate transporter *SLC1A1* cause human dicarboxylic aminoaciduria. J. Clin. Invest. 121, 446–453.

Barbaro, M., et al., 2009. Characterization of deletions at 9p affecting the candidate regions for sex reversal and deletion 9p syndrome by MLPA. Eur. J. Hum. Genet. 17, 1439–1447.

Bonaglia, M.C., et al., 2002. 20 Mb duplication of chromosome 9p in a girl with minimal physical findings and normal IQ: narrowing of the 9p duplication critical region to 6 Mb. Am. J. Med. Genet. 112, 154–159.

Christ, L.A., Crowe, C.A., Micale, M.A., Conroy, J.M., Schwartz, S., 1999. Chromosome breakage hotspots delineation of the critical region for the 9p-deletion syndrome. Am. J. Hum. Genet. 65, 1387–1395.

Faas, B.H.W., de Leeuw, N., Mieloo, H., Bruinenberg, J., de Vries, B.B.A., 2007. Further refinement of the candidate region for monosomy 9p syndrome. Am. J. Med. Genet. A 143, 2353–2356.

Fujimoto, A., Lin, M.S., Schwartz, S., 1998. Direct duplication of 9p22-p24 in a child with duplication 9p syndrome. Am. J. Med. Genet. 77, 268–271.

Griggs, B.L., Ladd, S., Saul, R.A., DuPont, B.R., Srivastava, A.K., 2008. Dedicator of cytokinesis 8 is disrupted in two patients with mental retardation and developmental disabilities. Genomics 91, 195–202.

Hulik, P.J., et al., 2009. Cytogenetic and array-CGH characterization of a complex de novo rearrangement involving duplication and deletion of 9p and clinical findings in a 4-month-old female. Cytogenet. Genome Res. 126, 305–312.

Jelin, A., Perry, H., Hogue, J., Oberoi, S., Cotter, P.D., Klein, O.D., 2010. Clefting in trisomy 9p patients: genotype–phenotype correlation using microarray comparative genomic hybridization. J. Craniofac. Surg. 21, 1376–1379.

Kawara, H., et al., 2006. Narrowing candidate region for monosomy 9p syndrome to 4.7 Mb segment at 9p22.2-p23. Am. J. Med. Genet. A 140, 373–377.

Lerer, I., Sagi, M., Meiner, V., Cohen, T., Zlotogora, J., Abeliovich, D., 2005. Deletion of the *ANKRD15* gene at 9p24.3 causes parent-of-origin-dependent inheritance of familial cerebral palsy. Hum. Mol. Genet. 14, 3911–3920.

Lichter, P., Cremer, T., 1992. Chromosome analysis by non-isotopic in situ hybridization. In: Rooney, D.E., Czipolkowski, B.H. (Eds.), Human Cytogen—A Practical Approach. Oxford University Press, Oxford, pp. 157–192.

Meyer, S., Acquaviva, C., Shamdeen, M.G., Haas, D., Vianey-Saban, C., 2010. A novel missense mutation in a neonate with nonketotic hyperglycinemia. Pediatr. Neurol. 43, 363–367.
Ogata, T., Muroya, K., Matsuo, N., Hata, J., Fukushima, Y., Suzuki, Y., 1997. Impaired male sex development in an infant with molecularly defined partial 9p monosomy: implication for a testis forming gene(s) on 9p. J. Med. Genet. 34, 331–334.
Shaffer, L.G., Slovak, M.L., 2009. ISCN 2009: An International System for Human Cytogenetic Nomenclature. S. Karger AG, Switzerland.
Stumm, M., et al., 2002. Partial trisomy 9p12p21.3 with a normal phenotype. J. Med. Genet. 39, 141–144.
Swinkles, M.E.M., et al., 2008. Clinical and cytogenetic characterization of 13 dutch patients with deletion 9p syndrome: delineation of the critical region for a consensus phenotype. Am. J. Med. Genet. A 146, 1430–1438.
Zou, Y.S., Huang, X., Ito, M., Newton, S., Milunsky, J.M., 2009. Further delineation of the critical region for the 9p-duplication syndrome. Am. J. Med. Genet. A 149, 272–276.