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CLINICAL REPORT

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Chromosome 9p Deletion Syndrome and Sex Reversal: Novel Findings and Redefinition of the Critically Deleted Regions

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Deletions of the short arm of chromosome 9 are associated with two distinct clinical entities. Small telomeric 9p24.3 deletions cause genital anomalies in male subjects, ranging from disorder of gonadal sex to genital differentiation anomalies, while large terminal or interstitial deletions result in 9p-malformation syndrome phenotype. The critical region for non-syndromic 46,XY sex reversal was assigned to a 1 Mb interval of chromosome 9p, extending from the telomere to the *DMRT* genes cluster. The 9p-syndrome was assigned to bands 9p22.3p24.1, but a phenotypic map has not been established for this condition, probably because of the lack of detailed molecular and/or phenotypic characterization, as well as frequent involvement of additional chromosome rearrangements. Here, we describe a unique patient with a small isolated 9p terminal deletion, characterized by array-CGH and FISH, who shows a complex phenotype with multiple physical anomalies, resembling the 9p-syndrome, disorder of sex development with gonadoblastoma, congenital heart defect and epilepsy. The observed deletion includes the 46,XY sex-reversal critical region, excluding the region so far associated with the 9p-syndrome. Genotype–phenotype correlations are tentatively established comparing our patient to seven other previously reported males with isolated terminal 9p deletions, finely defined at a molecular level. Our observations expand the 9p deletion clinical spectrum, and add significantly to the definition of a 9p-syndrome critical region. © 2012 Wiley Periodicals, Inc.

Key words: chromosome 9p deletion; 9p deletion syndrome; trigonocephaly; congenital heart defect; gonadal dysgenesis; gonadoblastoma; ambiguous genitalia; XY sex reversal; epilepsy

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INTRODUCTION

Since the first report by Alfi et al. [1973] over 180 cases of 9p deletion (9p-) syndrome have been described. This syndrome represents a clinically variable and genetically heterogeneous condition, with a wide spectrum of phenotypic manifestations and variable size of causal deletions.

The main clinical findings are intellectual disability, congenital hypotonia and a range of cranio-facial abnormalities, such as trigonocephaly, prominent forehead, flat occiput, epicanthic folds, small palpebral fissures, arching eyebrows, hypertelorism, midface hypoplasia with short nose, depressed nasal bridge, anteverted nostrils, thin upper lip vermilion, long philtrum, microstomia, micrognathia, malpositioned and missing teeth, short neck with a low posterior hairline, low-set, malformed, and posteriorly angulated ears [Young et al., 1982; Huret et al., 1988; Hou, 2003]. Although less frequently, other anomalies, involving multiple organs, have been observed in patients with 9p deletions [Shashi et al., 1998; Muroya et al., 2000; Hauge et al., 2008], that is, cardiac defects, epilepsy, inguinal hernia, omphalocele, choanal atresia, scoliosis, non-ketotic hypoglycemia.

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Deletions of the terminal portion of 9p are associated in males with genital anomalies which can vary significantly from disorders of gonadal sex (i.e., gonadal dysgenesis or the presence of an ovotestis) to disorders of genital differentiation (i.e., cryptorchidism and/or hypospadias) [Muroya et al., 2000; Ogata et al., 2001; Fujimoto et al., 2004].

The deletion breakpoints cluster in bands 9p22-p24 and in most patients additional rearrangements have been identified involving other chromosomes. No clear-cut genotype–phenotype correlations have been established.

In general, telomeric deletions cause gonadal dysgenesis, while more proximal, interstitial deletions result in the malformation syndrome outlined above. The respective consensus regions (CRs) are reportedly located at 9p24.3, extending from the *DMRT* genes (included) to the telomere, and at 9p22.3-p24.1 [Flejter et al., 1998; Guioli et al., 1998; Christ et al., 1999; Raymond et al., 1999; Calvari et al., 2000; Kawara et al., 2006; Faas et al., 2007; Swinkels et al., 2008].

Except for a single case of sex reversal that was associated to a telomeric deletion not including the *DMRT* genes, in all previously described cases the deletion included the three *DMRT* genes (*DMRT1*, *DMRT3*, and *DMRT2*) [Calvari et al., 2000].

We describe a unique patient where a small terminal 9p deletion is associated with a complex phenotype, consisting of multiple physical anomalies, resembling the 9p-malformation syndrome, disorder of sex development with gonadoblastoma, congenital heart defect, and epilepsy.

CLINICAL REPORT AND GENETIC TESTS

The patient was the fourth child of non-consanguineous parents of Caucasian ethnicity. The older siblings are healthy. Pregnancy and delivery were reportedly uneventful. The child was born at 41 weeks gestation by spontaneous vaginal delivery. Birth weight was 4,500 g (+2.4 Z-score SD), length 56 cm (+2.4 Z-score SD), cranial circumference 38 cm (+2.4 Z-score SD), and Apgar scores were 9 and 10 at 1 and 5 min, respectively. At birth a female sex was assigned, based on the aspect of external genitalia.

In the second day of life a cardiac murmur was detected. ECG and cardiac ultrasound showed patent ductus arteriosus, bicuspid aortic valve, and severe hypoplasia of the aortic arch, which required surgical correction.

At 1 month of age the family pediatrician recognized genital ambiguity, as well as craniofacial anomalies, leading to genetic and hormonal investigations. Chromosomes were apparently normal male (46,XY) and FISH analysis confirmed the presence of the *SRY* gene. Androgen insensitivity and 5alpha-reductase deficiency were ruled out by hormonal tests (basal serum testosterone 2.33 ng/ml and DHEAS 0.48 ng/ml).

At the age of 3 months the baby presented apneic spells and generalized hypertonicity. Brain ultrasound and EEG showed no anomalies, and the pediatric neurologist did not prescribe any therapy. At 8 months, after the occurrence of additional apneic episodes associated with cyanosis and generalized hypertonicity lasting 30–60 sec, the patient was referred to us for further investigations.

The growth was normal for the age, at physical examination, several dysmorphic features were noted: hirsute forehead with prominence of the metopic suture, apparent hypertelorism, epicanthic folds, short and upslanting palpebral fissures, short and bulbous nose, microstomia with a high palate, flat and long philtrum, micrognathia, and short neck. The hands were normal with a mild degree of interdigital webbing. Neurological examination showed normal motor development and mild global developmental delay.

External genitalia showed significant ambiguity. Labio-scrotal swellings were symmetrical; a perineal hypospadias with partial peno-scrotal inversion was present, even though the phallus was well developed, in length and girth (Fig. 1A). A palpable gonad was present in the right inguinal region. A pelvic ultrasound confirmed the presence of a gonad in the right inguinal canal, whereas no gonad was detected on the left side. Hormonal analysis (FSH, LH, 17-OH-progesterone, dehydroepiandrosterone sulphate and

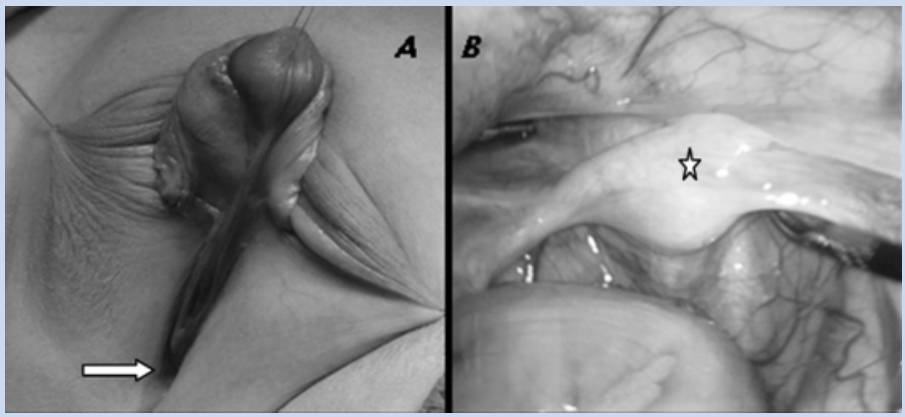

FIG. 1. Genital phenotype and laparoscopic view of the pelvis. A: Perineal hypospadias with partial peno-scrotal inversion. The arrow indicates the tiny vaginal opening, not clearly visible in the picture. B: The small uterus is indicated by an asterisk.

anti-Müllerian hormone) showed normal values. A short hCG test (5,000 UI/m^2 i.m.) was also normal.

Cardiac ultrasound showed good functional correction of the congenital defect.

During hospitalization, the infant presented daily paroxysmal episodes of brief generalized tonic spasms with loss of consciousness and cyanosis, organized in clusters.

Although cerebral ultrasound, awake and sleep EEG and brain MRI were normal, antiepileptic therapy with phenobarbital was started, with prompt seizures control.

Array-CGH performed on genomic DNA using Agilent oligonucleotide array (Human Genome CGH microarray 4 × 44k; Agilent Technologies, Santa Clara, CA) following the manufacturer instructions, showed a small distal deletion of the short arm of chromosome 9 of 6.5 Mb in size, described as: arr 9p24.3p24.1 (204,367-6,582,172)x1 (probe alignments were referred to the human March 2006, hg 18, genomic assembly). This deletion, molecularly ascertained, can be defined cytogenetically as 46,XY, del(9)(p24.1), was confirmed by FISH analysis with a probe specific for 9p telomere on metaphase chromosomes (ToTelVysion™, Vysis, Abbott, IL), which showed a single fluorescent signal on 9p telomere.

Based on these findings, doctors and family decided on a male sex assignment and a correction of abnormal genitalia was planned.

At laparoscopy, a small uterus was found (Fig. 1B). On the left side there was a tiny linear gonad, connected to the uterus by a tubular structure resembling a fallopian tube devoid of fimbriae. On the right side, a round grayish gonad was found with a smooth surface, which was attached to a vas deferens. The uterus, the small vagina and the left gonad were resected en bloc.

The first stage of the urethroplasty was then undertaken by correcting the penile curvature and creating a neo-urethral plate with a graft from the foreskin. Standard orchidopexy and penoscrotal transposition completed the surgical procedure. On histologcal examination, the left mass was constituted by a neoplastic nodule of 11 mm in diameter, developing within a streak gonad. The biopsy of the other gonad showed testicular tissue. The neoplasia was composed by a collection of cellular nests surrounded by connective tissue stroma. The nests were solid, small, of oval or round shape, and contained a mixture of germ cells and sex cord derivates resembling immature Sertoli and granulosa cells, respectively.

The associated gonadal tissue was constituted by fibrous tissue. The histological picture was that of gonadoblastoma developing in a streak gonad, whose nature could not be determined.

DISCUSSION

A host of reported deletions of various sizes map CRs on the short arm of chromosome 9, related to two distinct clinical entities. A non-syndromic form of 46,XY sex reversal maps to band 9p24.3 at the extremity of chromosome 9p. The 9p-malformation syndrome maps more proximally, in an interval corresponding to band 9p22.3p24.1. Genital anomalies ranging from cryptorchidism and/or hypospadias to complete sex reversal can be found in 9p-syndrome males, carriers of large terminal deletions encompassing both CRs [Christ et al., 1999].

The sex reversal CR has been assigned to a 1 Mb interval, extending from the telomere to the *DMRT* genes [Flejter et al., 1998; Guioli et al., 1998; Raymond et al., 1999]. Although all three *DMRT* genes in this region show sequence similarity among themselves and with *Drosophila melanogaster* and *Caenorhabditis elegans* sexual regulators *doublesex* and *mab-3*, respectively, *DMRT1* is the strongest candidate gene for sex reversal [Raymond et al., 1999; Ottolenghi and McElreavey, 2000]. In humans, *DMRT1* is highly expressed in the genital ridge during male sexual differentiation and to the testes in adults. Functional studies in mice showed that *Dmrt1* plays a key role in postnatal testicular differentiation and maintenance [Raymond et al., 2000; Krentz et al., 2009; Matson et al., 2011]. An apparent exception is represented by the case of two 46,XY siblings with sex reversal, carriers of a small 9p terminal deletion, spanning about 700 kb and excluding the *DMRT* gene cluster.

However, the proximal breakpoint was mapped in close proximity of the 5′ end of *DMRT1*, possibly causing a disruption of a regulatory sequence and perturbing its expression [Calvari et al., 2000].

Several attempts were made over the last years to precisely define a CR for the 9p-syndrome. Christ et al. [1999] assigned the CR to a 8 Mb segment between D9S286 and D9S285 markers in 9p22p24, by comparing 24 patients with 9p terminal deletions and one [Wagstaff and Hemann, 1995] with an interstitial deletion, arising from a paternal balanced complex rearrangement between chromosomes 3, 8, and 9. This region was further restricted to a 4.7 Mb interval, spanning from RP11-933C16 to D9S285 in 9p22.3p23, by Kawara et al. [2006] who described a 2-year-old boy with classical 9p-syndrome phenotype, bearing a complex chromosome rearrangement with seven breakpoints involving chromosomes 2 and 9. Subsequently, Faas et al. [2007] narrowed down the extent of this commonly deleted 9p region defining a smallest region of overlap (SRO) of 3.5 Mb, between RP11-33C16 and RP11-725C9 probes, in a patient with a dup/del 9p anomaly.

Finally, genotype–phenotype correlations in 13 deleted patients with and without trigonocephaly, led Swinkels et al. [2008] to further restrict the 9p-syndrome CR to an interval of 300 Kb, falling outside the SRO proposed by Faas et al. [2007] and flanked by RP11-271B19 and RP11-392B02 markers (Fig. 2).

Overall, the proposed regions do not explain a series of reported cases bearing small terminal deletions, whose clinical presentation is compatible with the 9p-malformation syndrome (see below), and complicate genotype–phenotype correlations. Furthermore, the lack of detailed molecular and/or phenotypic characterization of the majority of reported cases, as well as the possible contribution of other chromosomes involved in complex rearrangements, add complexity to the definition of a phenotypic map.

In an attempt to add some clarity to a rather confused issue, we compared our patient with clinical features of sevenreported 46,XY patients, carriers of isolated 9p terminal deletions, finely characterized by MLPA, microsatellite typing, FISH and array-CGH (Fig. 2 and Table I).

Of these seven patients, at least 3 (Cases 1–3 in Fig. 2 and Table I) have deletions that do not correspond to any of the CRs proposed so far, in spite of having some clinical features resembling the 9p-phenotype. One patient had a 1.2 Mb deletion associated with

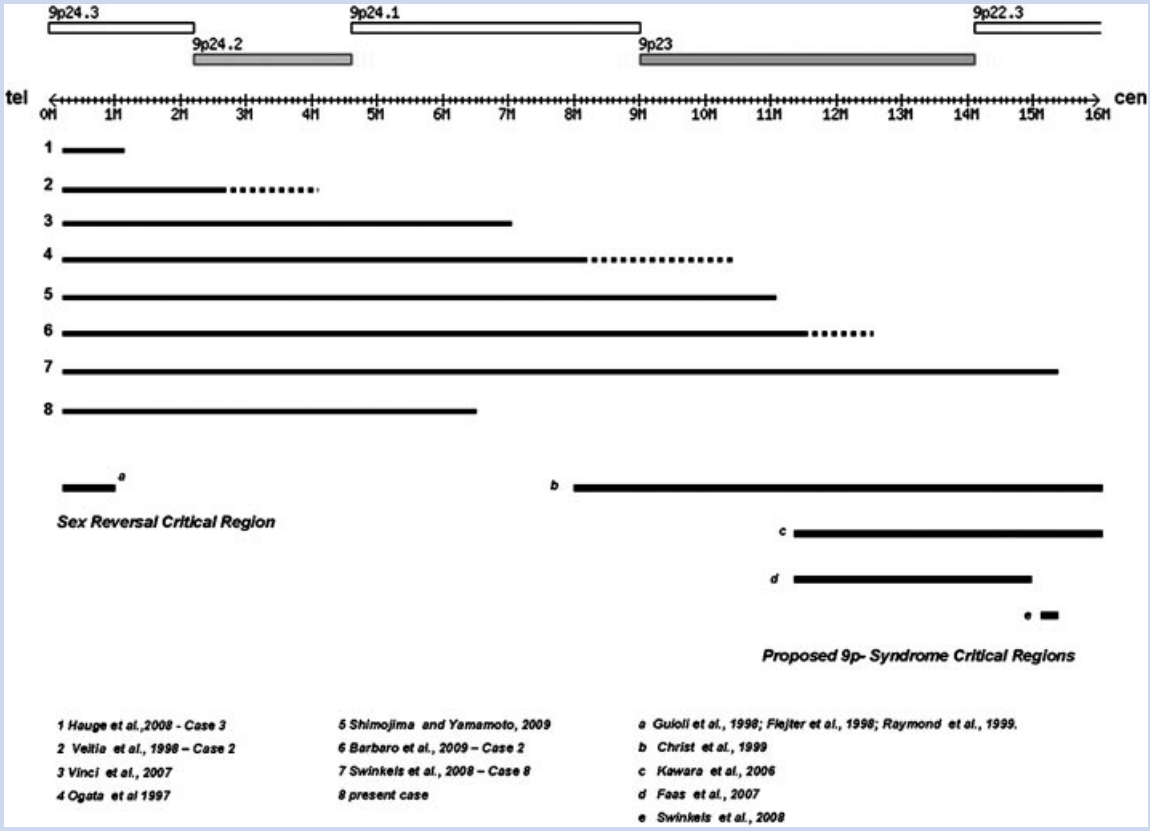

FIG. 2. Schematic representation of the distal 16 Mb of the short arm of chromosome 9 from the telomere to 9p22.3 band. Bars from 1 to 8 indicate molecular defined terminal deletions in seven previously reported patients (1–7) and in present case (8); dotted lines indicate a uncertain proximal breakpoint definition. Bars (a) and (b–d) illustrate the critical region for sex reversal and for 9p-consensus phenotype, respectively.

intellectual disability, distinctive facial appearance, and mild prominence of the metopic suture [Hauge et al., 2008]. Another patient with a 7 Mb terminal deletion presented with intellectual disability, behavior problems, and gonadal dysgenesis [Vinci et al., 2007]. A phenotype with gonadal dysgenesis, learning difficulties and affective disorder was also described in a subject with a small terminal deletion of about 3 Mb [Veitia et al., 1998].

Our patient presented with complex abnormalities of genitalia, including a congenital gonadoblastoma, associated with facial features typical of the 9p-syndrome. He did not have frank trigonocephaly, but rather a prominent forehead, as described in many other cases of this syndrome [Ogata et al., 2001; Barbaro et al., 2009].

There are only a small number of patients with 9p-syndrome in whom gonads have been examined in detail. A gonadoblastoma was reported in only four patients with 9p-syndrome and sex reversal [Huret et al., 1988; Mc Donald et al., 1997; Muroya et al., 2000; Livadas et al., 2003], leading to hypothesize the existence of a gonadoblastoma suppressor gene in the distal portion of chromosome 9p.

The present report is the first description of a 9p deletion in a patient with a complex phenotype, including neurological findings, features of the 9p-malformation syndrome, sex reversal, and gonadal dysgenesis with gonadoblastoma.

The neurological findings consisted of mild developmental delay and epileptic seizures. Almost all previously described cases presented developmental delay of variable severity, particularly behavior problems, language impairment, or learning difficulties. These aspects are difficult to measure precisely in our patient, considering his very young age.

Epilepsy consisted of generalized tonic seizures in clusters. Unfortunately, we could not perform an ictal EEG, so that a focal onset cannot be excluded. Even though we did not find paroxysmal discharges in wakefulness and sleep interictal EEG, seizure semeiology and prompt response to phenobarbital confirmed their epileptic nature. It should be noted that seizure disorder with normal interictal EEG is not uncommon, occurring for instance in benign familial and non-familial infantile seizures [Caraballo et al., 2003].

Epileptic seizures are rarely reported in patients with 9p deletion syndrome. In Case 1 of Hauge et al. [2008] there was a clinical history of suspected seizures, not supported by EEG studies, while Case 8 presented febrile seizure at 2 years followed by a variant of Landau–Kleffner syndrome. The authors suggested that the *DOCK8* gene deletion may play a role in seizures. *DOCK8* is located ~400 kb distal to the *DMRT1* gene. It is involved in the reorganization of the actin filament system and is expressed in many organs, including heart and brain, although at low levels [Vinci et al., 2007].

TABLE I. Phenotype–Genotype Correlations in Eight Patients With Pure Terminal Deletion of Chromosome 9p

	Patients							
Karyotype	**1. Hauge et al. [2008] 46,XY,del 9pter**	**2. Veitia et al. [1998] 46,XY,del 9p24.2pter**	**3. Vinci et al. [2007] 46,XY,del 9p24.1pter**	**4. Ogata et al. [1997] 46,XY,del 9p23?pter**	**5. Shimojima and Yamamoto [2009] 46,XY, del9p23pter**	**6. Barbaro et al. [2009] 46,XY,del 9p23pter**	**7. Swinkels et al. [2008] 46,XY,del 9p22.3pter**	**8. Present case 46,XY,del 9p24.1 pter**
9p deletion extent	**1 Mb**	**2.6–4.1 Mb**	**6.7–7.1 Mb**	**8–10.5 Mb**	**11.1 Mb**	**11.5–12.6 Mb**	**15.2 Mb**	**6.5 Mb**
Head and neck								
Trigonocephaly	−	−	−	−	+	−	+	−
Prominent forehead	+	−	−	+	+	+	−	+
Bitemporal narrowing	−	−	−	−	−	−	+	+
Midface hypoplasia	+	−	−	−	−	−	+	+
Short palp. fissures/Epicanthal fold	+	−	−	−	+	+	−	+
Medial eyebrow flare/arching eyebrows	+	−	−	−	−	−	+	+
Amblyopia/myopia/strasbismus	−	−	−	−	−	−	+	−
Short/broad neck	U	−	−	U	U	+	+	+
Nose								
Small/anterverted nares	+	−	−	+	+	−	−	−
Bulbous nasal tip	+	−	−	−	+	+	+	+
Ears								
Posteriorly angulated	+	−	−	−	+	+	U	+
Low set	−	−	−	+	−	−	+	+
Mouth								
Long/flat philtrum	+	−	−	−		+	+	+
Micro/retrognathia	+	−	−	+		−	+	+
Thin upper lip vermilion	+	−	−	−	U	−	+	+
High/narrow palate	−	−	−	+		+	U	−
Chest								
Funnel/Broad	U	−	−	+	U	+	U	−
Extremities								
Clino-Brachydactyly	+	−	−	+	U	−	−	−
Urogenital								
Ambigous external genitalia	U	+	+	+	U	−	−	+
Dysgenetic gonads		+	+	+		+	−	+
Gastrointestinal								
Inguinal hernia	−	−	−	−	U	−	+	−
Gastroesoph.reflux/hiatal hernia	−	−	−	+		−	−	−
Cardiovascular								
Congenital heart defect	−	−	−	U	U	−	−	+
Neurological								
Developental delay	+	−	+	U	+	+	+	+
Hypotonia	+	−	−		−	+	−	−
Seizures	−	−	−		−	−	−	+
Behavioral problems	+	+	+		−	−	−	+

U, unknown; +, present; −, absent.

Our patient has a congenital heart defect that one could tentatively relate to malfunction of *DOCK8*.

Based on evidence gathered from the study of this patient, we propose that the region associated with the 9p-core phenotype lies between chromosome bands 9p22 and 9p24 as previously suggested [Christ et al., 1999; Kawara et al., 2006; Faas et al., 2007; Swinkels et al., 2008], and that atypical cases, where smaller terminal deletions are associated with 9p-syndrome clinical features, may result from the perturbation of proximally located gene(s), exerted by the deletion of distal regulatory element(s).

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