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Kaposi sarcoma, oral malformations, mitral dysplasia, and scoliosis associated with 7q34-q36.3 heterozygous terminal deletion

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Abstract

Chromosome 7 germline macrodeletions have been implicated in human congenital malformations and developmental delays. We herein report a novel heterozygous macrodeletion of 7q34-q36.3 in a 16-year-old girl originally from West Indies. Similar to previously reported cases of germline chromosome 7q terminal deletions, our patient has dental malposition, and developmental (growth and intellectual) delay. Novel phenotypic features include endemic Kaposi sarcoma, furrowed tongue, thoracolumbar scoliosis, and mild mitral valve dysplasia. The occurrence of human herpes virus 8-driven Kaposi sarcoma, in a child otherwise normally resistant to other infectious agents and without any other tumoral lesion, points to a very selective immunodeficiency. While defects in organogenesis have been described with such macrodeletions, this is the first report of immunodeficiency and cancer predisposition.

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Keywords

Kaposi sarcoma; human herpes virus-8; chromosome 7 deletion

INTRODUCTION

The meiotic pathway is conserved in humans and chromosomal crossover errors during meiosis can cause chromosomal deletions [Hassold and Hunt 2001]. Chromosomal macrodeletions, usually visible microscopically on karyotyping, span at least five megabases (Mb), whereas microdeletions are submicroscopic deletions. Chromosomal macrodeletions and microdeletions leading to human phenotypes have been described affecting a wide range of syndromes [He et al., 2014] including developmental anomalies and cancer predisposition. For example, WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) (OMIM #194072) is a rare congenital heterozygous deletion at chromosome 11p13, which illustrates how a continuous gene deletion syndrome can lead to both detrimental organogenesis and neoplasms [Riccardi et al., 1978].

Terminal deletions in the long arm of chromosome 7 have been reported in the literature with phenotypic heterogeneity. To date, there are 23 reported cases of isolated heterozygous chromosome 7q terminal deletion (Table I) between 7q32 and 7q36.3 [Ayub et al., 2016; Beleza-Meireles et al., 2013; Benzacken et al., 1997; Frints et al., 1998; Horn et al., 2004; Masuno et al., 1990; Rodriguez et al., 2002; Roessler et al., 1997; Su et al., 2008]. All except two patients had microcephaly and/or holoprosencephaly (HPE). There is variable penetrance or expressivity in developmental (growth, psychomotor, intellectual) delay, cranial-facial anomalies, dental abnormalities, and organogenesis defect (lung, kidney, skeletal, and limbs).

We herein describe a heterozygous macrodeletion in 7q34-q36.3 in a French girl of Haitian and Guadalupe descent, presenting with psychomotor and growth delay, oral malformations (furrowed tongue), mitral dysplasia, scoliosis and endemic Kaposi sarcoma (KS). To our knowledge, this is the first reported case of a chromosome 7q terminal macrodeletion with solid tumor cancer predisposition and cardiac organogenesis defect. Furthermore, we extend the phenotype of cranial-facial and skeletal malformations at this region to include furrowed tongue and thoracolumbar scoliosis.

CLINICAL REPORT

The patient is a 16-year-old French female of maternal Haitian descent and paternal Guadalupe descent with 3 half maternal siblings (Figure 1A). Family history is significant for an older maternal half-sister who has polycystic kidney disease, hypothyroidism, and sleep apnea, and a younger maternal half-brother with speech delay. Her parents and another maternal half-brother are alive and healthy.

She was born in Haiti and emigrated to France at the age of 12 years. She was born premature at 36 weeks of gestation with birth weight of 2,090 grams (10th centile) and head circumference of 30.5 cm (10th centile) (Figure 1B). During the postnatal period, she

developed progressive psychomotor delay and a furrowed tongue was noted (Figure 1C). During childhood she displayed further progressive global developmental delay and intellectual disability; with social disinhibition, emotional disinhibition, perseverating behavior, difficulty in comprehension of simple commands, inability to form coherent short sentences, inability to write or draw, apraxia, gait instability and pyramidal hypertonia. No formal neuropsychological assessment of intelligence quotient has yet been performed. In addition, she also has dental malposition, thoracolumbar scoliosis, and mild mitral dysplasia (Figure 1D). The remainder of the physical exam is normal.

At age 12 years, she presented with a right 5th finger lateral dark purple cutaneous lesion that was biopsied and pathology was consistent with possible epithelioid angiosarcoma with definitive resection of the lesion. At age 13 years, the lesion recurred in her right 5th finger and spread to the right foot (Figure 2A). Pathology showed spindle cells with high vascularity, hyaline globs, and positive human herpesvirus-8 (HHV-8) nuclear staining (Figure 2B–2D). Plasma samples were tested for HHV-8-specific Immunoglobulin (Ig) G, in an immunofluorescence assay [Cassar et al., 2007]. Immunoglobulin G antibodies directed against HHV-8 latency-associated nuclear antigen were detected, with typical punctuate nuclear staining, in the patient and her mother at dilution 1/5,1020 and 1/2,560, respectively. The HHV-8 K1 gene was detected in patient's whole blood deoxyribonucleic acid (DNA) by a specific nested-polymerase chain reaction (PCR) that amplifies a 737 base pair fragment. Comparative sequence analysis showed that the HHV-8 viral strain belongs to the Sub-Saharan African B subtype, and clustered with strains previously characterized from Cameroon and Uganda. Overall, the clinical presentation, pathology, and HHV-8 serology and genotype are consistent with endemic Kaposi sarcoma.

She had no other significant infectious history in childhood other than intermittent viral upper respiratory tract infections and varicella zoster. At the time of endemic KS diagnosis, PCR testing for various infectious diseases were performed and negative for: human immunodeficiency virus (HIV)-1/2, human simplex virus-1/2, human herpes virus-6, hepatitis B virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus. Serology was negative for HIV-1/2, human T-lymphotropic virus-1/2, hepatitis A virus, and hepatitis C virus; with positive IgG to CMV, EBV, and varicella zoster virus indicative of a history of primary infection. She received vaccines including Bacillus Calmette-Guerin, hepatitis B, measles, rubella, mumps, and diphtheria vaccines without adverse reactions and with normal vaccine responses. She has normal T, B and natural killer lymphocyte immunophenotyping profile other than persistently elevated CD19+ B lymphocyte population (Table II) with normal IgG, IgA, and IgM.

METHODS AND RESULTS

We collected blood samples from the patient and her mother after obtaining informed consent and approval from the institution's ethical board. Patient's father is not available for clinical follow-up. Comparative genomic hybridization (CGH) array of DNA extracted from lymphocytes in the patient performed on an Agilent 60K oligonucleotide microarray platform was significant for 7q34-q36.3 macrodeletion of 16 megabase pairs (Mbp). The deletion was confirmed by fluorescence in situ hybridization (FISH) analysis using a set of

7q subtelomeric specific probes. FISH analysis was normal in the mother. In order to investigate the mode of inheritance of the heterozygous deletion, Affymetrix Genome-Wide Human SNP (single nucleotide polymorphism) Array 6.0 was performed in the patient and her mother, and data were analyzed using PennCNV Software. Genotyping was highly successful with call rates of 96.8% and 98.1% in the patient and mother, respectively. SNP Array 6.0 confirmed heterozygous deletion in chromosome 7, in position 142,883,341–159,127,004 (Reference genome: b37/hg19) in the patient. The contralateral chromosome non-deleted in the 7q34-q36.3 region in the patient shares more than 5,000 SNPs with only 3 Mendelian errors with the mother; confirming the heterozygous deletion is not inherited from the mother and is either inherited from the father (possibly from a non-reciprocal balanced translocation), or more likely, *de novo* given that both parents are healthy and without any of the child's clinical manifestations (Figure 3). There are 136 genes in the deleted region: 108 protein coding, 19 RNA coding, 8 pseudogenes (Table III).

DISCUSSION

We report a heterozygous 16 Mbp macrodeletion of 7q34-q36.3 (position 142,883,341–159,127,004 in reference genome b37/hg19) in a 16-year-old girl of Haitian and Guadalupe descent with endemic Kaposi sarcoma, oral malformations, mitral valve dysplasia, and scoliosis. This case extends the phenotype of terminal chromosome 7q deletions, and is the first germline immunodeficiency and cancer predisposition attributable to this deleted 7q34-36.3 locus. Similar to previously published reports, our patient has global developmental and growth (including microcephaly) delay, cranial-facial anomalies and skeletal organogenesis defect although furrowed tongue with thoracolumbar scoliosis has not been previously reported (Table I). In contrast to previously described patients, our patient has mild mitral dysplasia, extending the phenotype of organogenesis to include cardiac development. Interestingly, our patient does not have HPE.

This is the first case suggesting a cancer predisposition of endemic Kaposi sarcoma linked to the 7q34-36.3 region. Kaposi sarcoma is an inflammatory neoplasm of endothelial cell origin first described by Moritz Kaposi in 1872 [Kaposi 1872]. Human herpes virus-8 (HHV-8), also designated as KS-associated herpes virus (KSHV), is the causative agent for all epidemiological forms of KS [Chang et al., 1994]. It is currently classified under four epidemiologic forms and represents an inborn or acquired immunodeficiency to oncogenic HHV-8 [Jackson et al., 2016]. Classic KS primarily affects elderly men between the ages of 60–70 years of Eastern European and Mediterranean origin, typically presenting with indolent and chronic cutaneous plaques and nodules. It is exceedingly rare in children. In contrast, endemic KS in Sub-Saharan Africa affects the young population, including children, with typically a more rapidly progressive lymphadenopathic course. Epidemic KS in HIV infected and acquired immunodeficiency syndrome (AIDS) patients and iatrogenic KS in medically immunosuppressed (e.g. transplanted) patients, typically follow a rapidly progressive course, affecting the skin, mucosae, lymphatic system, and visceral organs.

There is evidence that inborn errors of immunity underlie the development of Kaposi sarcoma of childhood [Casanova 2015a; Casanova 2015b]. Recent studies have shown that classic KS of childhood can result from rare single-gene lesions, with mutations in *WAS*,

IFNGR1, *STIM1*, and *TNFRSF4* [Byun et al., 2010; Byun et al., 2013; Camcioglu et al., 2004; Picard et al., 2006]. In line with these previous observations, we conclude there is one or more KS predisposition gene(s) within the 7q34-q36.3 region deleted in the patient. The prevalence of oncovirus HHV-8 varies globally, with high-level of more than 40% seropositivity in parts of Africa and South America, intermediate level of 30–40% seropositivity in the Mediterranean, and low levels of up to 20% seropositivity in non-endemic areas such as North America, Northern Europe, and most of Asia [Mesri et al., 2010]. Prior to emigrating to France, our patient resided for 12 years in Haiti and Guadelupe, both HHV-8 endemic regions, and infected with a Sub-Saharan African HHV-8 strain found in Sub-Saharan Africans or persons of such origin living outside of Africa. There exists some major HHV-8 genotypes, many of which are geographically restricted, with little evidence to support whether any genotype is more virulent or more associated with KS [Dittmer and Damania 2013; Hosseinipour et al., 2014; Meng et al., 1999; Tornesello et al., 2010; Zhang et al., 2001]. Hence, why this patient developed KS but not others with terminal 7q deletions may be secondary to 1) the region deleted, 2) previously reported patients with terminal 7q deletion were not infected by HHV-8, or 3) incomplete penetrance of KS at the age of their last follow-up.

To date, there are 23 published reports of isolated chromosome 7 terminal deletions. The comparison of specific phenotypes to the boundaries of deletions, which are not easily distinguishable among previously published reports due to both method of detection and varying phenotypes, is not easy. Twenty cases (Table I) have utilized FISH, GTG banding, and CGH array, and hence while the general region and deletion size are described, the chromosomal positions are not delineated. Only one report (Figures 3–4, Patient 7) utilized an oligoarray CGH analysis describing a large 7q36.2-qter deletion encompassing position 153,206,357–156,133,135 in reference genome b37/hg19 [Beleza-Meireles et al., 2013]. One case (Figure 4, Patient 20) has a deleted region encompassing the same boundaries as our patient, although the lower and upper bounds of the chromosome positions are not known. This patient has microcephaly and dysmorphia [Roessler et al., 1997].

Patients with terminal 7q deletions have varying phenotypes including HPE, microcephaly, developmental delay, cranial-facial anomalies, coloboma and other eye morbidities, axial and appendicular skeletal malformations, and organogenesis defects (renal and pulmonary). Microcephaly and developmental delay (intellectual, growth, or psychomotor) are the predominant phenotypes in terminal 7q deletion, reported to affect 17 out of the 24 patients. Some of these phenotypes can be explained by haploinsufficiency of the *SHH* and *HLXB9* gene, which our patient harbors. The *SHH* gene localized on 7q36.3 encodes the sonic hedgehog protein, with haploinsufficiency responsible for microcephaly, holoprosencephaly, central incisor defects, colobomas, and other ocular disorders albeit with incomplete penetrance [Garavelli et al., 2004; Nanni et al., 1999; Pineda-Alvarez et al., 2011; Roessler et al., 1996; Schimmenti et al., 2003]. Heterozygous mutation in *HLXB9* homeobox gene located on 7q36.3 has been associated with sacral agenesis. Currarino syndrome (OMIM #176450), a triad of sacral agenesis, presacral mass, and anorectal malformation, is an autosomal dominant condition caused by mutations in *HLXB9*, and displays reduced penetrance and variable expressivity even in the same kindred [Currarino et al., 1981; Kim et al., 2007; Urioste et al., 2004]. Both *SHH* and *HLXB9* genes map to the same chromosomal

region and are responsible for midline embryonic defects, and hence may be allelic variants or a contiguous gene syndrome [Lynch et al., 1995].

There are developmental phenotype differences in our patient compared with previously published cases of terminal 7q deletion. Indeed, our patient displays phenotypes of midline embryonic defects including microcephaly, dental malposition, and furrowed tongue possibly secondary to *SHH* and *HLXB9* haploinsufficiency; although without HPE, ocular defects or sacral agenesis. This observation is congruent with the reduced penetrance and variable expressivity described to these genes. Cranial-facial anomalies and axial skeletal malformations are commonly described in patients with deleted 7q36-qter, and our patient's furrowed tongue and scoliosis, although not previously reported, may extend the phenotype spectrum of these organ systems due to variable expressivity. Although organogenesis defects have been reported, this is the first reported case of cardiac organogenesis malformation. Renal malformations are reported in 6 cases (Figure 4; P9, P11-14, P19), and all share 7q36.1-qter deletion except P19 with 7q35 deletion, suggesting a genitourinary development putative gene(s) at these regions. There are two reported cases of abnormal pulmonary lobulations sharing 7q36-qter deleted regions, of which both were reported in aborted fetuses and hence the full clinical spectrum of this deletion may not have fully manifested due to intra-uterine gestational age. Given that cardiac valvulopathy has not been reported in any of the 23 cases of 7q terminal deletion syndromes, perhaps the suspected gene for valvulopathy may display reduced penetrance or the valvulopathy is subclinical and not detectable across a larger 7q34-q36.3 region in those patients.

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Figure 1.

(A) Pedigree of the family. The proband is represented by a shaded symbol. (B) Microcephaly, patient's head circumference growth chart. (C) Furrowed tongue, CT head. (D) Thoracolumbar scoliosis, X-ray.

Figure 2.

(A) Kaposi sarcoma, dark purple cutaneous lesion. (B) Spindle cells with high vascularity. (C) Hyaline globs with high vascularity. (D) HHV-8 nuclear staining in spindle shaped cells.

Figure 3.

SNP 6.0 Array confirms heterozygous 7q34-q36.3 (7:142,883,341–159,127,004, reference genome b37/hg19) terminal deletion in patient, either inherited or *de novo* from father. Deoxyribonucleic acid (DNA) from the father is not available.

Figure 4. Boundaries of chromosome 7q terminal deletions. Exact chromosome deletion positions are known for P7 (153,206,357–156,133,135 in reference genome b37/hg19) and P24 (142,883,341–159,127,004 in reference genome b37/hg19).

Table 1

Clinical summary of patients with isolated chromosome 7q terminal deletion

Patient	Deleted region	Sex	Phenotype	Diagnostic modality	Inheritance pattern	Reference
1	7q36-qter	F	Microcephaly, corpus callosum partial hypoplasia	FISH	<i>de novo</i>	Frints et al. 1998
2	7q36.1-qter	M	Microcephaly, growth retardation, truncal obesity, cranial-facial abnormalities, absent maxillary central incisor, HPE	FISH	NA	Frints et al. 1998
3	7q36-qter	F	Microcephaly, intellectual retardation, cranial-facial abnormalities, absent maxillary central incisor, HPE	FISH	<i>de novo</i>	Frints et al. 1998
4	7q36-qter	F	Microcephaly, intellectual retardation, cranial-facial abnormalities, small hands and feet, sacral dysgenesis	GTG banding	<i>de novo</i>	Su et al. 2008
5	7q36.1-qter	M	Microcephaly, growth retardation, cranial-facial abnormalities, ptosis, sacral agenesis, tethered cord	CGH, FISH	<i>de novo</i>	Horn et al. 2004 (Case 1)
6	7q36.3-qter	M	Microcephaly, corpus callosum partial hypoplasia, growth retardation, cranial-facial abnormalities, strabismus, ptosis, maxillary central incisor	FISH	<i>de novo</i>	Horn et al. 2004 (Case 2)
7	7q36.2-qter	M	Microcephaly, growth retardation, cranial-facial abnormalities, multiple ocular congenital anomalies, tapered fingers, proximal implantation of thumbs and short fifth finger, absent maxillary central incisor	Oligoarray CGH analysis, FISH	<i>de novo</i>	Beleza-Meireles et al. 2013
8	7q36.2-qter	F	Microcephaly, psychomotor retardation, developmental delay, cranial-facial abnormalities, webbed shortened neck, skin nevi, partial sacral agenesis, lumbar hyperlordosis, axial hypotonia	CGH	<i>de novo</i>	Ayub et al. 2016 (Case 1)
9	7q35-qter	M	Microcephaly, growth retardation, fetal kidney pyelectasis *	CGH	<i>de novo</i>	Ayub et al. 2016 (Case 2)
10	7q36-qter	M	Microcephaly, mental retardation, cranial-facial abnormalities, coloboma, café au lait spots, sacral agenesis	FISH	NA	Rodriguez et al. 2002
11	7q36.1-qter	NA	Microcephaly, mental retardation, cranial-facial abnormalities, short stature, ectopic kidneys, double renal pelvises, dilated ureters, single maxillary central incisor	NA	NA	Masuno et al. 1990
12	7q36.1-qter	NA	Microcephaly, mental retardation, cranial-facial abnormalities, short stature, hydronephrosis, single maxillary central incisor	NA	NA	Masuno et al. 1990
13	7q36-qter	F	Microcephaly, growth retardation, cranial-facial abnormalities, abnormal pulmonary lobulation, hydronephrosis, HPE *	FISH	NA	Benzacken et al. 1997 (Case 1)
14	7q32-qter	F	Severe cystic brain malformation, growth retardation, cranial-facial abnormalities, cleft lip, club foot, abnormal pulmonary lobulation, renal and adrenal hypoplasia, HPE *	FISH	NA	Benzacken et al. 1997 (Case 3)
15	7q32-qter	M	HPE	FISH	NA	Roessler et al. 1997 (Case 8)
16	7q33-qter	M	HPE	FISH	NA	Roessler et al. 1997 (Case 9)
17	7q36-qter	M	HPE	FISH	NA	Roessler et al. 1997 (Case 10)
18	7q36-qter	M	HPE	FISH	NA	Roessler et al. 1997 (Case 11)

Patient	Deleted region	Sex	Phenotype	Diagnostic modality	Inheritance pattern	Reference
19	7q35	M	Microcephaly, mental retardation, sacral and renal hypoplasia	FISH	NA	Roessler et al. 1997 (Case 28)
20	7q34-qter	M	Microcephaly, dysmorphia	FISH	NA	Roessler et al. 1997 (Case 29)
21	7q36-qter	F	Microcephaly, developmental delay, dysmorphia	FISH	NA	Roessler et al. 1997 (Case 30)
22	7q33	F	Dysmorphia, developmental delay	FISH	NA	Roessler et al. 1997 (Case 31)
23	7q36-qter	M	Short stature	FISH	NA	Roessler et al. 1997 (Case 32)
24	7q34-qter	F	Endemic Kaposi sarcoma, global developmental and growth (including microcephaly) delay, furrowed tongue, dental malposition, mitral dysplasia, thoracolumbar scoliosis	CGH, SNP Array	<i>de novo</i>	This study

* Autopsy of aborted fetus between 22–25 weeks of gestation; HPE, holoprosencephaly; NA, not applicable; FISH, fluorescence in situ hybridization; CGH, comparative genomic hybridization; SNP, single nucleotide polymorphism

Table II

Lymphocyte immunophenotyping profile

	Values	Normal Range
CD3+ (unit/uL)	1984	1000–2200
CD3+ (%)	64	56–84
CD4+ (unit/uL)	1116	530–1300
CD4+ (%)	36	31–52
CD8+ (unit/uL)	651	330–920
CD8+ (%)	21	6–23
CD19+ (unit/uL)	651 *	110–570
CD19+ (%)	21	6–23
CD16+CD56+ (unit/uL)	310	70–480
CD16+CD56+ (%)	10	3–22

* Abnormal

Table III

Genes deleted in 7q34-q36.3 (7:142,883,341–159,127,004, reference genome b37/hg19) region.

Region	Genes
7q34	CASP2, CLCN1, FAM131B, GSTK1, TAS2R40, TMEM139, ZYX, TRBJ@, TRBV@, EPHA1
7q35	ARHGEF5, CTAGE15, CTAGE4, CTAGE6, TCAF1, TCAF2, NOBOX, OR2A1, OR2A12, OR2A14, OR2A2, OR2A25, OR2A5, OR2A7, OR2F1, OR2F2, OR6B1, TAS2R41, TPK1, TAS2R60, CNTNAP2, <i>EPHA1-AS1</i> , <i>MIR548F4</i> , ARHGEF34P*, LOC154761*, OR2A20P*, OR2A9P*
7q36.1	ABCB8, ABCF2, ACTR3B, ACTR3C, AGAP3, AOC1, ASB10, ASIC3, ATG9B, ATP6V0E2, C7ORF33, CDK5, CHPF2, CRYGN, CUL1, EZH2, FASTK, GALNT11, GALNTL5, GBX1, GIMAP1, GIMAP2, GIMAP4, GIMAP5, GIMAP6, GIMAP7, GIMAP8, KCNH2, KMT2C, KRBA1, LR8, LRRC61, NOS3, NUB1, PDIA4, PRKAG2, RARRES2, RHEB, SLC4A2, SMARCD3, SSPO, TMEM176A, TMEM176B, TMUB1, WDR86, XRCC2, ZBED6CL, ZNF212, ZNF282, ZNF398, ZNF425, ZNF467, ZNF746, ZNF775, ZNF777, ZNF783, ZNF786, ZNF862, <i>ATP6V0E2-AS1</i> , <i>LINC01003</i> , <i>PRKAG2-AS1</i> , <i>WDR86-AS1</i> , <i>RYN1</i> , <i>RYN3</i> , <i>RYN4</i> , <i>RYN5</i> , <i>MIR671</i> , FABP5P3*, LOC155060*, LOC728743*, ZNF767*
7q36.2	DPP6, HTR5A, PAXIP1, <i>PAXIP1-AS2</i> , <i>HTR5A-AS1</i>
7q36.3	CNPY1, DNAJB6, EN2, ESYT2, INSIG1, LMBR1, MNX1, NCAPG2, NOM1, PTPRN2, RBM33, RNF32, SHH, UBE3C, VIPR2, WDR60, <i>BLACE</i> , <i>C7ORF13</i> , <i>LINC00244</i> , <i>LINC00689</i> , <i>LOC285889</i> , <i>MIR5707</i>

Regular font, protein coding gene; Italicized font, RNA coding gene;

* pseudogene