Molecular Cytogenetics

CASE REPORT

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Interstitial 11q deletion in a patient with Sprengel's deformity: a case report and review of the literature

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Abstract

Background Interstitial chromosome 11 long arm deletions (11q13-q23) represent a rare cytogenetic abnormality characterized by non-specific clinical features including intellectual disability and several malformations without a clear genotype-phenotype correlation. We describe the first case of interstitial 11q deletion identified in a boy with Sprengel's deformity and provide a review of the literature.

Case presentation We report a 9-year-old boy with congenital scapular deformity, iris and chorioretinal coloboma, normal intelligence, and a history of mild motor development delay. The karyotype showed a *de novo* large 11q deletion. Fluorescence *in situ* hybridization (FISH) confirmed that the deletion is interstitial, and array comparative genomic hybridization (aCGH) revealed a loss of 25.8 Mb encompassing the 11q14.1-q22.3 region.

Conclusions The present case and the literature review of 61 previously published cases highlight the clinical heterogeneity and the lack of genotype-phenotype correlation in interstitial 11q deletions. Sprengel's deformity found in our patient might be a new finding in 11q deletions or, more probably, a fortuitous association.

Keywords 11q deletion, Sprengel's deformity, aCGH, coloboma, genotype-phenotype correlation

Background

Interstitial chromosome 11 long arm deletions (11q13-q23) represent a rare cytogenetic abnormality compared to 11q terminal deletions (11q23.3-q25), also known as Jacobsen syndrome. To date, 61 cases have been published [1–47]. In about half of the cases, the deletion was characterized by array Comparative Genomic Hybridization (aCGH). Interstitial 11q deletions are quite heterogeneous in size, ranging from 743 kb [34] to 40.2 Mb [25], with breakpoints located between 11q13.2 and 11q23.3. Clinically, these deletions are associated with non-specific features such as developmental delay, intellectual disability, post-natal growth retardation, dysmorphic features, and in some cases, several malformations involving heart, brain, palate, eyes, bones, and kidneys. Most of the deletions described in the literature are de novo. In 10 cases, the deletion was inherited from one parent [5, 24, 28, 29, 46, 47]. No particular genotype-phenotype correlation has been made so far.

Herein, we report a case of a patient with an interstitial 11q deletion diagnosed with Sprengel's deformity

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(MIM%184400). Although it is a rare malformation, it is the most common congenital shoulder defect. It has been observed in association with a variety of conditions including Klippel-Feil syndrome, scoliosis, rib anomalies, and spinal dysraphism [48, 49]. It has also been described in 3q29 microdeletion [50] but it is still widely considered sporadic due to its unknown etiology and undetermined causal genes [48, 49].

In this report, we describe the first case of interstitial 11q deletion in a patient with Sprengel's deformity. Further, we provide an in-depth review of the literature and discuss the genotype-phenotype correlation.

Case presentation

The proband is a 9-year-old boy who was referred to our department of genetics at the age of six years because of Sprengel's deformity and facial dysmorphism. He is the fourth child of a 38-year-old mother and a 41-year-old father, both healthy and unrelated. His family history was negative for genetic diseases except for a three-year older brother who had autistic behavior.

The child was delivered vaginally following a healthy full-term pregnancy and weighed 4000 g at birth. The neonatal period was uneventful. Early personal history revealed a mild motor development delay: he was able to sit without support at the age of nine months and walked alone at the age of 19 months. However, he had no speech delay or intellectual disability. The patient has been followed up in ophthalmology since the age of nine months for coloboma and myopia, and in pediatric orthopedics since the age of four years because of congenital elevation of the scapula (Sprengel's deformity). He enrolled in primary school at the age of six with apparently normal learning performances except for a slow writing (Fig. 1).

The first examination at the age of six years showed a weight of 23 kg (+1.2 SD), a height of 111 cm (-1 SD), and a head circumference of 52 cm (average). The patient had mild facial dysmorphism including hypertelorism, upslanting palpebral fissures, bilateral epicanthus, bilateral inferior iris coloboma (Fig. 2-A), mild ptosis of the right eye, marked philtrum, abnormal teeth position, and posteriorly rotated low-set ears with thick lobes. He also had a short neck, a mild pectus excavatum (Fig. 2-B), an abnormally elevated left scapula (Fig. 2-C), a supernumerary palmar crease with fetal pads on both hands and clinodactyly of the 4th left toe, and the two 5th toes.

X-ray showed an elevated left scapula. Ultrasound of the left shoulder identified a bony deformity in the posterior-superior part of the left shoulder. No solid or cystic mass was detected. Chest computed tomography (CT) revealed a bilateral supernumerary cervical rib arising from C7, a small millimetric left subclavicular ossicle, a bifid aspect of the anterior arches of the 3rd right rib, and the 3rd and 5th left ribs. No omo-vertebral bone was identified. Specialized ophthalmological examination showed strong myopia with bilateral chorioretinal and iris coloboma. Both abdominal ultrasound and echocardiogram revealed no abnormalities and the complete blood count was normal.

Methods

Clinical evaluation

The patient had been under the care of an ophthalmologist since the age of nine months and a pediatric orthopedist since the age of four years. Later, at age six, he was referred to the genetics department for evaluation by a clinical geneticist.

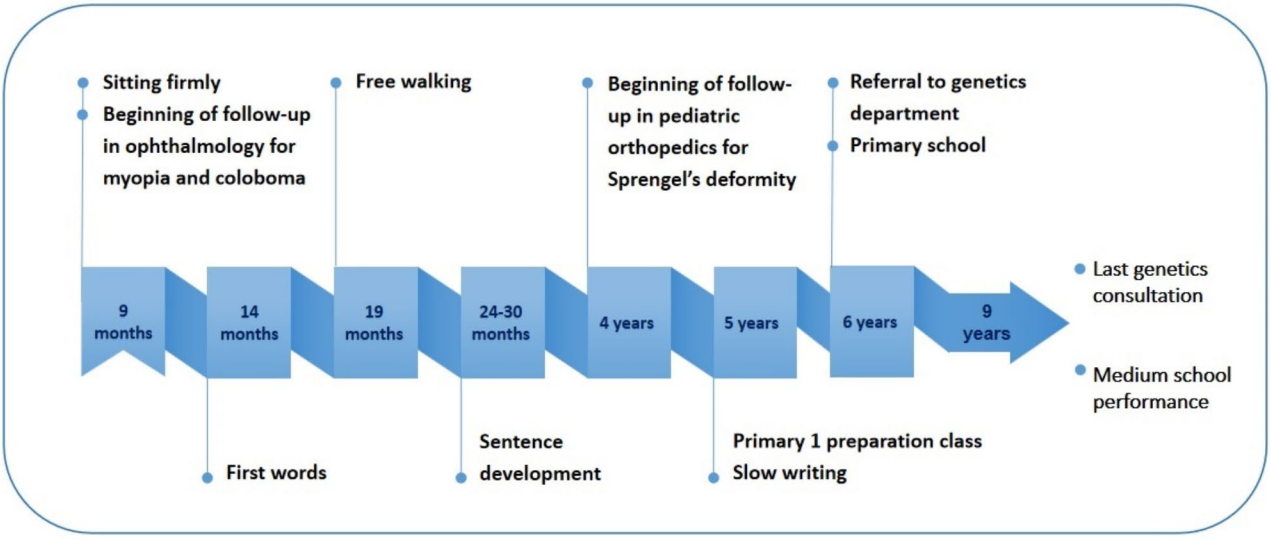

Fig. 1 Timeline of the patient's clinical milestones

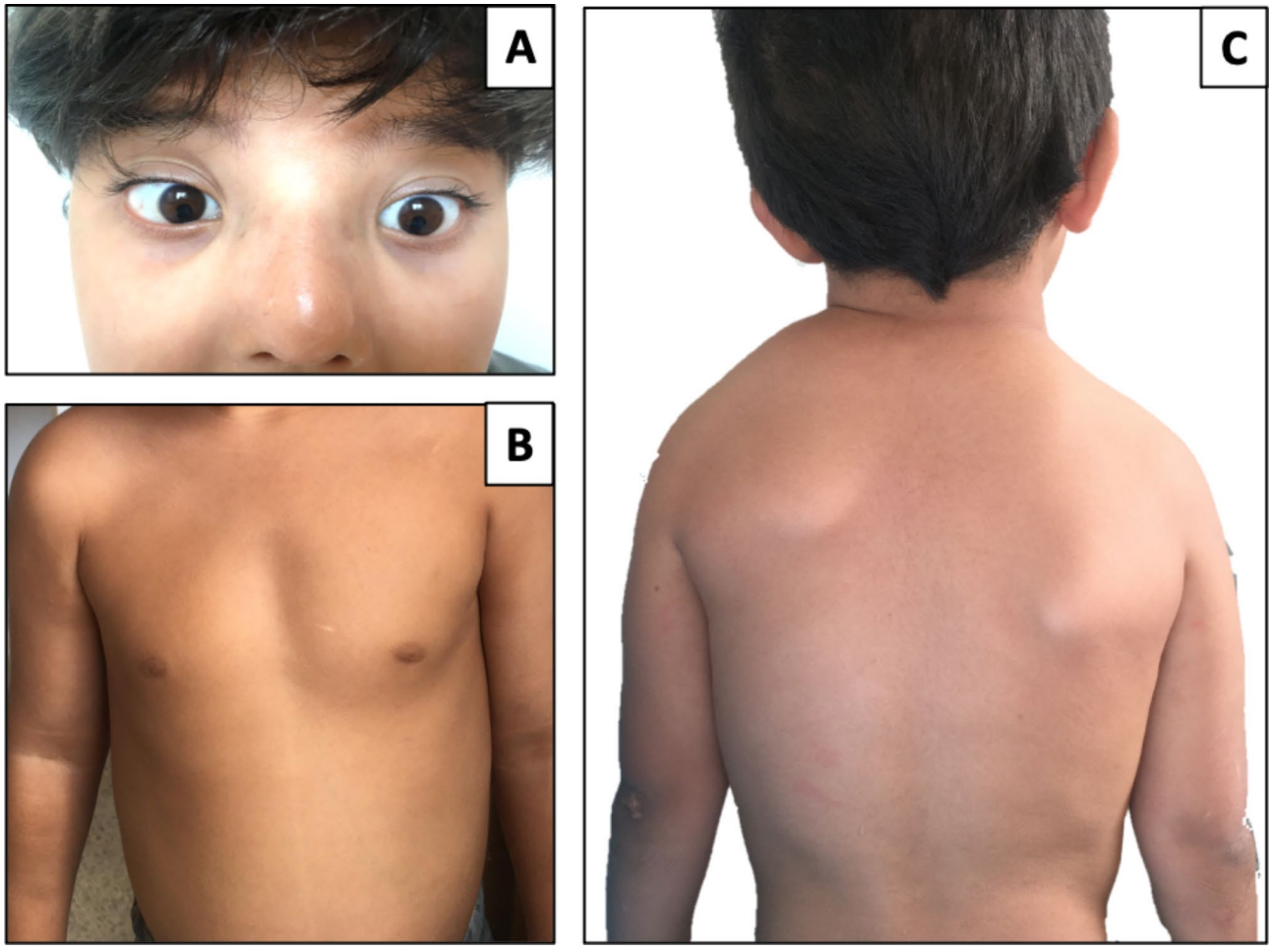

Fig. 2 Photographs of the proband at the age of six years. (**A**) Bilateral iris coloboma. (**B**) Pectus excavatum. (**C**) Sprengel's deformity

Conventional cytogenetic analysis

Standard R-band karyotyping with a 400-band resolution was performed on cultured peripheral lymphocytes in the patient and his parents, according to the Dutrillaux and Lejeune protocol [51].

Molecular cytogenetic analysis

Multiple fluorescence in situ hybridization (FISH) assays were performed on metaphase spreads using commercial chromosome 11-specific fluorescently labeled probes (Kreatech): centromeric probe (SE 11), whole chromosome painting probe (wcp11), short arm subtelomeric probe (ST 11pter, D11S1363), long arm subtelomeric probe (ST 11qter, D11S4437), 11q22.3 region-specific probe (ON ATM (11q22) / GLI (12q13)), and 11q23.3 region-specific probe (ON MLL (11q23) / SE 11). The slides were initially pretreated. Probes and target DNA were then co-denatured at 75 °C for 5 min and hybridized for 10 to 48 h at 37 °C. Following hybridization, the slides were washed with saline-sodium citrate (SSC) solution and counterstained using 4',6-diamidino-2-phenylindole dihydrochloride (DAPI). The signals were examined using an epifluorescence Zeiss Axio® Imager M1 microscope.

An aCGH (Agilent® Technologies, Santa Clara, CA) was performed on oligonucleotide-based Sure Print G3 Human CGH 4×180 K microarray platform, with an overall median probe spacing of 13 kb, according the protocol provided by the manufacturer. In brief, normal male control DNA (reference DNA) and patient's DNA were differentially labeled with Cy3 (cyanine 3-deoxyuridine triphosphate) and Cy5 (cyanine 5-deoxyuridina triphosphate), respectively, using Agilent SureTag Complete DNA Labeling Kit (Agilent Technologies). Labeled DNA was then cleaned with purification columns (Agilent Technologies) and hybridized on array at 67 °C for 24 h. Microarrays were washed using Agilent Oligo aCGH Wash Buffers and scanning was performed using Agilent Microarray Scanner. Data were analyzed with CytoGenomics Software (Agilent®) configured to human genome assembly GRCh37/hg19. The following databases were used to assess the clinical significance of genomic aberrations: the University of California Santa Cruz (UCSC) Genome Browser, the Database of Chromosomal

Imbalance and Phenotype in Humans Using Ensemble Resources (DECIPHER), Online Mendelian Inheritance in Man (OMIM) database, and PubMed. The clinical features of our patient were correlated with the Copy Number Variation (CNV) region and the involved genes, as well as with other cases published in the literature and databases.

Results

Karyotype showed a large deletion in the long arm of chromosome 11 (Fig. 3-B). FISH analyses revealed two complete wcp11 signals with no signal of translocated chromosome 11 material (Fig. 3-C). Subtelomeric 11p and 11q probes showed signals in place proving that the deletion was interstitial (Fig. 3-D). Locus-specific FISH showed two MLL signals in place at 11q23.3 (Fig. 3-E) and one signal at 11q22.3 confirming the deletion of ATM locus (Fig. 3-F). We concluded that the distal breakpoint was located between 11q22.3 and 11q23.3. Both parents showed normal karyotypes; therefore, the deletion was considered de novo.

Molecular characterization by aCGH confirmed the 11q interstitial deletion with breakpoints mapping at 11q14.1 (83,835,113) and 11q22.3 (109,702,695). The size of the deletion was 25.8 Mb. This region contains 234 RefSeq genes, 113 protein-coding genes, and 94 OMIM-listed genes including 31 disease-associated genes of which 10 are monoallelic genes. The karyotype was interpreted as: 46,XY,del(11)(q14.1q22.3).ish del(11)(D11S1363+,D11Z1+,ATM-,MLL+, D11S4437+).arr[GRCh37] 11q14.1q22.3(83835113_109702695)x1 dn (Fig. 4).

Discussion

We describe a 9-year-old boy with minor abnormalities including Sprengel's deformity, mild motor development delay, and normal intelligence, in whom we identified a 25.8 Mb de novo interstitial 11q deletion encompassing the 11q14.1-q22.3 region which includes 31 disease-associated genes.

Most deletions reported in the literature in the long arm of chromosome 11 are terminal (11q23.3-q25) and have been associated with Jacobsen syndrome, a well-characterized genetic disorder (MIM #147791). However, interstitial 11q deletions (11q13-q23) are rarer and very heterogeneous in size and phenotype [44]. So far, a total of 61 published cases (52 pure 11q deletions and 9 associated with other genetic abnormalities) have been described in the literature (see Additional file 1). The majority of the interstitial deletions characterized by aCGH (29 cases) were between 3 and 13 Mb, with extremes going from 743 kb [34] to 40.2 Mb [25]. In the majority of cases, the proximal breakpoint was located at 11q14 (33 cases) and the distal breakpoint at 11q22 (22 cases). Our patient shares these common breakpoints. The phenotype remains highly heterogeneous and poorly delineated. It includes poor growth, developmental delay, hypotonia, intellectual disability, seizures,

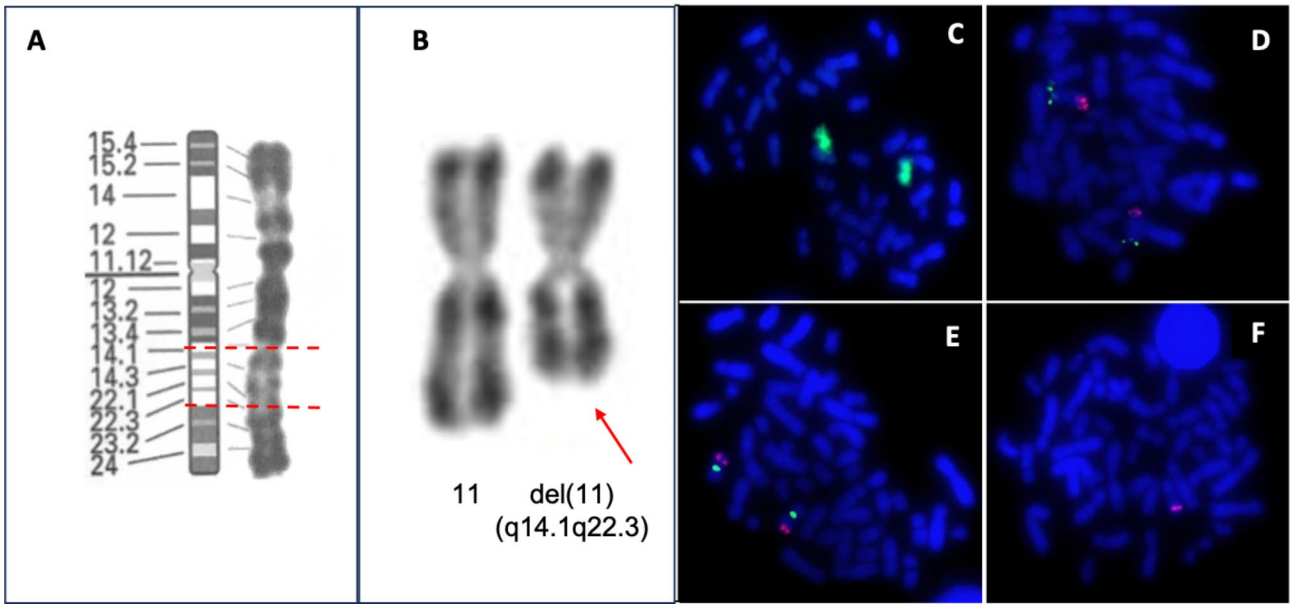

Fig. 3 Partial R-banding karyotype of the proband and FISH images. (**A**) Chromosome 11 ideogram in R band showing the deleted region between dashed lines. (**B**) R-banding karyotype showing partial deletion of the long arm of one chromosome 11 (arrow). (**C**) FISH using wcp11 probe (green) showed no insertion or translocation. (**D**) FISH using ST 11pter (green) and ST 11qter (red) probes showed normal hybridization. (**E**) FISH using ON MLL (11q23) (red) / SE 11 (green) probe showed no MLL deletion. (**F**) FISH using ON ATM (11q22) (red) / GLI (12q13) (green) probe showed the absence of ATM signal on the deleted chromosome 11 (GLI signal is not shown)

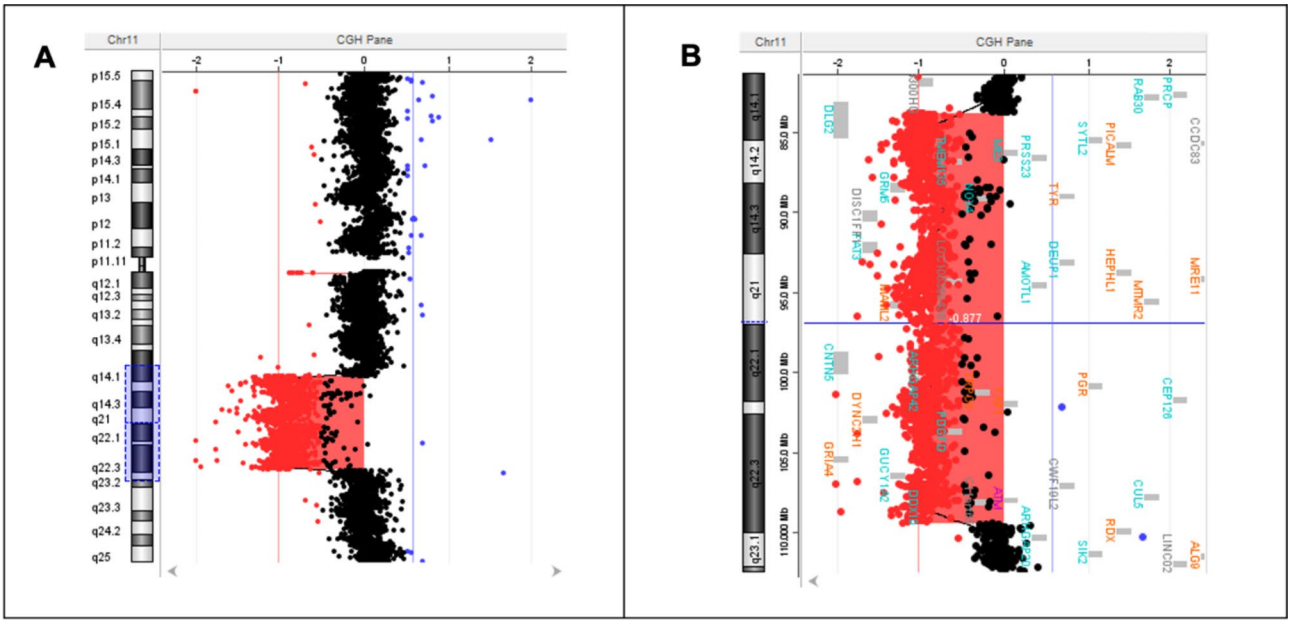

Fig. 4 High-resolution cytogenomic analysis of the proband using comparative genomic hybridization on Agilent 180 K microarray. (**A**) The whole view of chromosome 11. (**B**) The enlarged deleted region: The data illustrate the presence of a 25.8 Mb deletion in 11q14.1-q22.3 region (arr[GRCh37] 11q14.1q22.3(83835113_109702695)x1)

facial dysmorphism, palatal abnormalities, and malformations of the heart, brain, eyes, and kidneys (Table 1). Our review showed that the clinical heterogeneity is not correlated with the size of the deletion. In fact, both the smallest [34] and the largest deletions [25] reported were associated with severe phenotypes including dysmorphic features, developmental delay, cardiac, brain and renal abnormalities. Some authors suggested that palate anomalies and seizures were associated with more distal deletions (11q22-q23), while kidney/genital anomalies and cardiac malformations were reported in both proximal (11q13-q21) and distal ones (11q21-q23.3), and did not appear to correlate with the size of the deletion [36]. However, these correlations were not confirmed by our literature review (see Additional file 1). In addition, the inherited cases exhibited intrafamilial variability, as illustrated in the family described by Li et al. [24]. This family included a proband with mild intellectual disability and short stature, along with four unaffected members: two brothers, their father, and grandfather, all sharing the same deletion.

Our patient presented initially with Sprengel's deformity as the main complaint. This malformation is characterized by an underdeveloped and undescended scapula causing cosmetic and functional impairment [49]. Eulenberg was the first to describe three cases of congenital elevation of the scapula in 1863 [52]. Twenty eight years later, Sprengel reported four other patients with an upward displacement of the scapula and his name became associated with the condition [53]. In the human embryo, the scapula forms through germ layer differentiation around the 5th week of pregnancy [54]. In Sprengel's deformity, the scapula develops normally but fails to descend to its normal position, which leaves it elevated and malrotated. Sprengel's deformity has been associated with other anomalies including Klippel-Feil syndrome, rib anomalies, scoliosis and spinal dysraphism [48, 49]. Matsuoka et al. studied the origin of neck and shoulder in transgenic mice and concluded that this anatomical region, including the scapula, has a dual origin as it is the interface of neural crest and ectoderm, which could explain the observed associations [55]. Further, Rancourt et al. studied two adjacent genes in mice, *Hoxb5* and *Hoxb6*, and suggested that they function together to specify the brachio-cervico-thoracic structures of the mammalian vertebral column. Interestingly, homozygous *Hoxb5* mutations resulted in a scapular displacement similar to Sprengel's deformity in humans, while homozygous *Hoxb6* mutations often led to a missing first rib and a bifid second rib [56]. In mice, the *HoxB* locus is located on chromosome 11, whereas the human equivalent is on chromosome 17. In humans, several genes have been involved in scapula's development, such as *EMX2* (10q26.11), *PAX1* (20p11.22), and *HOXC6* (12q13.13) [57]. However, none of these genes is located on, or regulated by chromosome 11. Guo et al. reported a patient with 3q29 microdeletion who had Sprengel's deformity and Chiari malformation type II. They concluded that two genes in the deleted region, *XXYTL1* and *ACAP2*, could have a critical role during somitogenesis

Table 1 Clinical findings in our patient and previously reported patients with pure 11q interstitial deletion

Clinical features	Number of patients in the literature*	Percentage	Present case
Neurodevelopment			
Intellectual disability	19/49	39%	-
Developmental delay	22/49	45%	Mild
Speech delay	11/49	22%	-
Hypotonia	11/49	22%	-
Seizures	8/49	16%	-
Strabismus	9/49	18%	-
Growth			
Intrauterine growth retardation	4/50	8%	-
Postnatal growth retardation	18/49	37%	-
Malformations			
Trigonocephaly	6/49	12%	-
Dolichocephaly	3/49	6%	-
Microcephaly	5/50	10%	-
Brain anomalies (hydrocephalus, hypoplastic/absent corpus callosum, cortical atrophy, white matter abnormalities)	3/50	6%	Unexplored
Kidney/urinary tract anomalies (left renal malrotation, horseshoe kidney, bilateral duplication of ureters, vesicoureteral reflux)	6/50	12%	-
Heart anomalies (mitral valve prolapse, tricuspid insufficiency, pulmonary stenosis, double outlet right ventricle, ventricular septal defect, atrial septal defect, right atrial and ventricular enlargement, patent ductus arteriosus)	11/50	22%	-
Cleft lip/palate	11/50	22%	-
Skeletal anomalies**	16/49	33%	-
Retinal dysgenesis/exudative vitreoretinopathy	5/49	10%	-
Iris/chorioretinal coloboma	4/50	8%	+
Myopia	3/49	6%	+
Dysmorphic features			
Hypertelorism	12/49	24%	+
Epi/telecanthus	9/49	18%	+
High-arched palate	16/49	33%	-
Ear anomalies	18/49	37%	+
Micro/retrognathia	15/49	31%	-
Ptosis	12/49	24%	+

*Frequencies were calculated using our review of the literature (see Additional file 1). We counted patients with only pure 11q deletions (without associated genetic anomalies). We also excluded patients with unavailable information [37, 47].**Skeletal anomalies are detailed in the discussion section

and their dysfunction may disrupt embryonic development, leading to spinal dysraphism and shoulder defects [50]. Further, some authors suggested autosomal dominant transmission of Sprengel's deformity through familial case studies [58, 59]. However, the condition has not been clearly linked to any specific gene and its exact etiology remains unknown [48]. Several skeletal abnormalities have been reported in association with 11q deletions. These include overlapping toes [5, 39, 41], broad thumbs and halluces [5, 21], adducted thumbs [19], triphalangeal thumb [8], arachnodactyly [27], tapering fingers [30, 39], hypoplastic first rib [33], rib agenesis [19], syndactyly [27, 41, 46], brachydactyly [37, 41, 46], camptodactyly [30], clinodactyly [30, 35, 37], club foot [29, 33] and scoliosis [30, 33, 40]. Another skeletal phenotype has been identified in one patient with an interstitial 11q deletion (11q21-q22.2) described by Ikegawa et al. in 1998, presenting with severe pseudoachondroplasia (PSACH) characterized by short-limb dwarfism, normal face, and normal intellect. However, the authors could not prove the causal link between the deleted region and PSACH and suggested that the association may just be fortuitous [18]. The only disease-causing gene involved in a skeletal phenotype in the 11q14.1-q22.3 region is the *MMP13* gene (MIM*600108). Missense mutations in this gene were associated with autosomal dominant spondyloepimetaphyseal dysplasias (SEMDs) and metaphyseal anadysplasia (MIM#602111), a group of skeletal disorders characterized by poor growth and defective modeling of the spine and long bones. However, the phenotype does not include Sprengel's deformity or rib abnormalities.

Our patient presented with rib abnormalities and clinodactyly which have already been described in the literature with 11q deletion [19]. However, scapular abnormalities have never been reported previously in association with this deletion. Based on the Mouse Genome Informatics database (MGI), no genes within the mouse genomic region equivalent to the deleted region in our case were associated with Sprengel's deformity in mice. Thus, Sprengel's deformity found in our patient might be due to an unknown gene in the 11q region or maybe a fortuitous association. More genetic studies in other patients with Sprengel's deformity would address the question.

In addition to the skeletal anomalies, our patient was diagnosed with iris and chorioretinal coloboma. This feature has already been reported in 11q interstitial deletions in at least four patients [15, 25, 30, 41]. It has been linked to the *YAP1* gene (MIM*606608) located at 11q22.1 and known to be responsible for coloboma, ocular, with or without hearing impairment, cleft lip/palate, and/or impaired intellectual development [60].

Global developmental delay and intellectual disability have been associated with 11q interstitial deletions with variable severity [13, 27]. The OMIM morbid genes known to be associated with an intellectual disability in the 11q region are the *EED* gene (MIM*605984) at 11q14.2, where heterozygous missense mutations are responsible for Cohen-Gibson syndrome (MIM#617561) including overgrowth, intellectual disability, and developmental delay [61], and the *GRIA4* gene at 11q22.3, where heterozygous missense mutations are associated with neurodevelopmental disorder with or without seizures, and gait abnormalities. None of these features was found in our patient except for a mild developmental delay.

Further major abnormalities found in patients with 11q interstitial deletions such as growth retardation, microcephaly, cleft lip/palate, heart defects, kidney malformations, retinal dysgenesis, and exudative vitreoretinopathy [36] were absent in our patient.

Among the less frequent manifestations reported in constitutional 11q deletions, neuroblastoma has been reported in five patients [25, 26, 35, 39, 62]. These patients had deletions within the 11q22.3-q23.3 region. Indeed, the neuroblastoma locus is presumed to be at 11q22–q23 but the causative genes are not identified yet [39]. Since this putative locus is not included in the present deletion, we believe our patient's probability of developing neuroblastoma is low. Despite the large deletion size (25.8 Mb), the proband had a mild phenotype. This outstanding contrast supports the absence of genotype-phenotype correlation reported in the literature [36, 44].

Conclusion

The present case as well as our review of the literature highlight the clinical heterogeneity and the lack of genotype-phenotype correlation in interstitial 11q deletions. Sprengel's deformity found in our patient might be a new finding in 11q deletion or more probably a fortuitous association since it is a common congenital shoulder defect. Further genetic studies in other patients with Sprengel's deformity would verify this hypothesis.

Abbreviations

aCGH	Array Comparative Genomic Hybridization
ATM	Ataxia-Telangiectasia Mutated
CT	Computed tomography
DNA	Desoxyribonucleic acid
FISH	Fluorescent in situ hybridization
GRCh37	Genome Reference Consortium Human version 37
hg19	19th human genome assembly
MLL	Mixed-lineage leukemia
ON	Oncology
PSACH	Pseudoachondroplasia
SD	Standard deviation
SE 11	Satellite enumeration 11
SEMDs	Autosomal dominant spondyloepimetaphyseal dysplasias
SSC	Saline-sodium citrate
ST 11pter	Subtelomeric 11p arm
ST 11qter	Subtelomeric 11q arm
wcp11	Whole chromosome painting 11

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13039-024-00695-z.

Additional file 1: Interstitial 11q deletions - Review of the literature. Clinical and cytogenetic details of cases with interstitial 11q deletions reported in the literature.

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Author contributions

Clinical evaluation: MZ, FM and MNN; Genetic analysis and data interpretation: LK, SJ and HB; Writing—original draft preparation: DI; Writing—review and editing: LK; Supervision: MT and RM; All authors have read and agreed to the published version of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information file.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the parents of the proband for the genetic studies.

Consent for publication

Written informed consent was obtained from the parents of the proband for photographs publication.

Competing interests

The authors declare no competing interests.

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