DOI: 10.4274/jcrpe.galenos.2020.2020.0100

Case report

Clinical features in patients with Xq23 microdeletion: A case report and literature review (Xq23 **micro**deletions)

QIN Lu[1], ZHANG Fei-Zhou[1], LV Jian-Hai, TANG Lan-Fang

1Department of Pulmonology, Children's Hospital of Zhejiang University School of Medicine

2Department of Pediatrics, Shangyu Pepole's Hospital

What is already known on this topic?

Xq22.3-q23 microdeletion is a rare genomic disorder. Deletions in this region may present Alport syndrome with intellectual disability, midface hypoplasia and elliptocytosis (*AMME*, MIM 300194), growth retardation, language delay, and alterations of bones, heart and eyes. With the array CGH technology, more patients with Xq microdeletion have been reported. Until now, about 11 families and 21 patients with microdeletion at Xq22.3-q23 was reported. However, only 2 have been reported in the literature pertaining to the *AMMECR1* (MIM 300990) and *Chordin-like 1* (*CHRDL1* MIM 300350) genes, respectively. *AMMECR1* maps within the AMME complex interval. Disorder of this gene can cause midface hypoplasia, elliptocytosis, language disorder including early speech or language delay, infantile hypotonia, hearing loss, nephrocalcinosis and submucous cleft palate. Besides, *AMMECR1* is also associated with short stature, cardiac and skeletal abnormalities. Another gene *CHRDL1* has been identified as the causative gene of X-linked megalocornea (MGC1; MIM 309300), which is associated with distinctive secondary changes in the posterior crocodile shagreen and corneal arcus juvenilis.

What this study adds?

we reported a boy with Xq23 microdeletion, which involved *AMMECR1* and *CHRDL1* genes who presented microsomia, midface hypoplasia, kidney dysplasia, growth retardation and some alterations of bones and heart. Clinical symptoms such as intellectual disability and hearing loss were not found in this child. Meanwhile, our reviewed patients with Xq23 microdeletion or a deletion overlapping partially to highlight the rare condition and analyze the genotype-phenotype correlations.

Abstract

Xq22.3-q23 microdeletion is a rare genomic disorder. The purpose of this study is to emphasize the correlation between clinical phenotype and genotype of proximal deletion on chromosome Xq22.3-q23. A 5 years old boy had a 671Kb microdeletion on Xq23 **by** chromosomal microarray analysis (CMA), including *AMMECR1* and *CHRDL1* genes. He presented microsomia, midface hypoplasia, right kidney dysplasia and mildly motor retardation, which have never been reported before to be related with Xq23 deletion. To our knowledge, this is the first case with Xq23 microdeletion. A total of 9 cases with microdeletion at Xq22.3-q23 covered *AMMECR1* gene and 2 cases with *CHRDL1* mutation were reviewed. These data indicated that Xq23 microdeletion

with microsomia, midface hypoplasia, kidney dysplasia, mildly motor retardation was rare. The previous literature showed two novel point mutation in *AMMECR1* and *CHRDL1* with some phenotype different from the patient. Xq23 microdeletion should be considered for patients with microsomia, midface hypoplasia, kidney dysplasia and growth retardation.
Keywords: Xq23 microdeletion; Midface hypoplasia; Kidney dysplasia; Growth retardation.

Corresponding author: TANG Lan-Fang, No. 3333 Binsheng Road, Hangzhou 310051, China

+86-13868138022

6195007@zju.edu.cn

ORCID iD: 0000-0002-7994-7066

27.05.2020

07.12.2020

Introduction

Xq22.3-q23 microdeletion is a rare genomic disorder, which encompass the entire *COL4A5* gene and its adjacent genes extending towards the telomere, including *GUCY2F*, *NXT2*, *KCNE1L*, *ACSL4*, *TMEM164*, *MIR3978*, *AMMECR1*, *SNORD96B*, *RGAG1*, *TDGF3*, *CHRDL1*, *PAK3* and *DCX* (1) Deletions in this region may present Alport syndrome with intellectual disability, midface hypoplasia and elliptocytosis (AMME, MIM 300194), growth retardation, language delay, and alterations of bones, heart and eyes. The difference of phenotype is probably associated with the location and size of the deletion, which may include different genes. With the array CGH technology, more patients with Xq microdeletion have been reported. Until now, about 11 families and 21 patients with microdeletion at Xq22.3-q23 was reported. However, only 2 have been reported in the literature pertaining to the *AMMECR1* (MIM 300990) and *Chordin-like 1* (*CHRDL1* MIM 300350) genes, respectively. *AMMECR1* maps within the AMME complex interval.(2) Disorder of this gene can cause midface hypoplasia, elliptocytosis, language disorder including early speech or language delay, infantile hypotonia, hearing loss, nephrocalcinosis and submucous cleft palate. Besides, *AMMECR1* is also associated with short stature, cardiac and skeletal abnormalities.(2) Another gene *CHRDL1* has been identified as the causative gene of X-linked megalocornea (MGC1; MIM 309300), which is associated with distinctive secondary changes in the posterior crocodile shagreen and corneal arcus juvenilis.(3)

Herein, we reported a patient with Xq23 microdeletion, which involved *AMMECR1* and *CHRDL1* genes who presented microsomia, midface hypoplasia, kidney dysplasia, growth retardation and some alterations of bones and heart. Meanwhile, our reviewed patients with Xq23 microdeletion or a deletion overlapping partially to highlight the rare condition and analyze the genotype-phenotype correlations.

Case presentation

A 5-year-old boy presented our clinics for developmental delay with mildly motor retardation for 5 years. He was G_2P_2 of nonconsanguineous health parents and weighed 3.3 kg at birth without asphyxia. Antenatal screening implied right renal dysplasia and regular postpartum reexamination confirmed the diagnosis. Growth retardation with short stature were noted after birth. He can sit at the age of 9 months and walk at the age of 19 months. He can speak “mum” at about 11 months but still stuttered. His right kidney was surgically removed at the aged of 3 years 8 months. During the operation, thin right ureter and multiple cysts in the left kidney were noted. ECG and cardiac ultrasound examination showed type B pre-excitation syndrome and acleistocardia (ϕ 0.27 cm). No obvious abnormal signs of cardiopulmonary and diaphragm was found by chest X-ray. Abdominal ultrasound scan did not find abnormality of the liver, gallbladder or spleen. His father and mother were 163 cm and 153 cm, respectively while his 8 years old sister was also growing slowly (about 123 cm). There was no family history of hereditary disease in the patient’s family.

On physical examination, his height was 99.3 cm (<-2SD). Besides, he had characteristic features, comprising flat facial profile, mildly epicanthic folds, downslanting palpebral fissures, flat nasal bridge, bulbous nose, smaller left cheek, and slightly asymmetrical of nasolabial sulcus (Figure 1A). Flat lateral top of the skull, cyrtopisthocranius, low-set ears, low hairline and short neck were also noted (Figure 1B). In addition, malpositioned teeth and bilateral clinodactyly of the fifth finger were also noted (Figure 1C). However, his intelligence was normal.

Laboratory examination of thyroid, liver and kidney function, GC/MS for blood were regular or negative. X-ray scan showed 7 ossification centers in the right-hand carpal bone. Chromosomal microarray analysis (CMA) found a 671 Kb microdeletion located at Xq23, which involved *AMMECR1* and *CHRDL1* genes (Figure 2). It was regret that the parents refused to perform further genetic testing.

We reviewed the literature in English (PubMed and OMIM database) and Chinese. A total of 9 cases with microdeletion at Xq22.3-q23 covered *AMMECR1* gene and 2 case with *CHRDL1* mutation were founded. The clinical features were showed in Table1.

Discussion

We found a 671 **K**b microdeletion located at Xq23, which involved *AMMECR1* and *CHRDL1* genes. Although Xq22.3-q23 microdeletion has been reported, to our knowledge, this is the first case with Xq23 microdeletion. Literature describing *AMMECR1* disorder is also rare, its description and name (Alport syndrome, mental retardation, midface hypoplasia and elliptocytosis chromosomal region gene 1) is resulted from its cytogenic location within Xq22.3-q23 and its previous association with a very peculiar contiguous gene deletion syndrome originally named AMME. A deletion including *COL4A5* (Xq22.3) extending proximally to include *AMMECR1* which was first named AMME.(4) However, until now, the biological function of *AMMECR1* is unclear. It was reported to code a protein that has a putative nuclear localization signal and may, therefore, encode a factor that regulates transcription.(5) Besides, a 250 Kb deletion on Xq23 that involved the *CHRDL1* gene and segregated with the affected phenotype in the affected individual's family, they described an inherited congenital disorder which was named MGC1. This gene encodes ventroptin, a bone morphogenic protein antagonist with a proposed role in specification of topographic retinotectal projections and *CHRDL1* is differentially expressed in the human fetal brain, and there is high expression in cerebellum and neocortex.(6)

Similar with other 2 cases reported previously with the same mutation at Xq22.3-q23 of the *AMMECR1* gene by Andreoletti et al,(1) current case presented microsomia, right kidney dysplasia, mildly motor retardation, spoke early, stuttered, midface hypoplasia including flat facial profile, mildly epicanthic folds, downslanting palpebral fissures, flat nasal bridge, bulbous nose, short neck and so on. These suggested that in patients with growth retardation, midface hypoplasia, kidney dysplasia, motor retardation, language disorder as well as alteration of bones and heart, Xq23 microdeletion should be considered.

Compared the phenotype of the current patient with previous cases, we noted that current case did not show mental retardation, hearing loss and showed a language disorder, which was noted in Jonsson et al reported patients(4). However, the current case also presented bilateral clinodactyly of the fifth finger, cardiac and skeletal abnormalities and did not present elliptocytosis as well as hearing loss while the other 2 cases by Andreoletti et al. He's report showed varying degrees of hearing impairment and did not show the alteration of bones. Besides the older brother of the 2 cases showed scattered elliptocytes and anisocytosis. It was remarkable that the current case presented short stature, skeletal and cardiac abnormalities which was similar with the other 5 cases reported by Moysés-Oliveira et al,(2) but the previous reported patients also had hearing loss while the current case did not present. These suggested the microdeletion of Xq23 including *AMMECR1* is not directly related to mental retardation and hearing loss, but it has a direct impact on growth and development, facial malformation, bone and heart alterations. Besides, the phenotype of kidney abnormalities may be related to the gene *AMMECR1*, but the manifestations of renal are different. Moreover, current case did not present megalocornea or other eye lesions that this phenotype may be related to the mutation of *CHRDL1* gene.(7) It was notable that the Davidson et al(8) report about the patient presented global developmental delay, midface hypoplasia, walked at the age of 20 months and required speech therapy of the mutation of *CHRDL1*, which is similar with the current patient, but the current patient did not show intellectual disability while the patient had moderate intellectual disability at the age of 10 years, of course, it is not certain whether the current patient will develop mental retardation or not in the future. These explained the microdeletion of Xq23 involved *CHRDL1* does not necessarily lead to X-linked megalocornea and intellectual disability. However, the mutation of gene *CHRDL1* may related to the above phenotypes. Besides, compare Webb and Davidson et al's reports with the current patient, we can suggest that megalocornea-mental retardation (MMR syndrome), in some cases, may be di- or multigenic, because the current patient did not show any ocular abnormality and mental retardation. These suggested that the clinical features of Xq22 to Xq23 microdeletion were varied, although development disability, facial malformation, renal abnormality, cardiac and bone alteration are prevalent among individuals with deletions across the Xq22.3-q23 region. In summary, Xq23 microdeletion is a rare condition. In patients with growth retardation, midface hypoplasia, kidney dysplasia, motor retardation, language disorder as well as alteration of bones and cardiac, Xq23 microdeletion should be considered. A detailed family history, careful physical exam to identify distinctive clinical features and improved genetic diagnosis may directly benefit the patient by allowing management and counseling specific for the disorder.(9)

References

1. G, Andreoletti, EG, Seaby, JM, Dewing, I, O'Kelly, K, Lachlan, RD, Gilbert and S, Ennis.: a single point mutation causes developmental delay, midface hypoplasia and elliptocytosis. J Med Genet 2017;54(4):269-277.

2. M, Moysés-Oliveira, G, Giannuzzi, RJ, Fish, JA, Rosenfeld, F, Petit, MF, Soares, LD, Kulikowski, A, Di-Battista, M, Zamariolli, F, Xia, T, Liehr, N, Kosyakova, G, Carvalheira, M, Parker, EG, Seaby, S, Ennis, RD, Gilbert, RT, Hagelstrom, ML, Cremona, WL, Li, A, Malhotra, A, Chandrasekhar, DL, Perry, RJ, Taft, J, McCarrier, DG, Basel, J, Andrieux, T, Stumpp, F, Antunes, GJ, Pereira, M, Neerman-Arbez, VA, Meloni, M, Drummond-Borg, MI, Melaragno and A, Reymond. Inactivation of AMMECR1 is associated with growth, bone, and heart alterations. Hum Mutat 2018;39(2):281-291.

3. D, Mangialavori, E, Colao, A, Carnevali, D, Bruzzichessi, T, Grillone, N, Perrotti, R, Iuliano and V, Scorcia. Novel Mutation in the CHRDL1 Gene Detected in Patients With Megalocornea. Cornea 2015;34(8):976-9.

4. JJ, Jonsson, A, Renieri, PG, Gallagher, CE, Kashtan, EM, Cherniske, M, Bruttini, M, Piccini, F, Vitelli, A, Ballabio and BR, Pober. Alport syndrome, mental retardation, midface hypoplasia, and elliptocytosis: a new X linked contiguous gene deletion syndrome? J Med Genet 1998;35(4):273-8.

5. F, Vitelli, M, Piccini, F, Caroli, B, Franco, A, Malandrini, B, Pober, J, Jonsson, V, Sorrentino and A, Renieri. Identification and characterization of a highly conserved protein absent in the Alport syndrome (A), mental retardation (M), midface hypoplasia (M), and elliptocytosis (E) contiguous gene deletion syndrome (AMME). Genomics 1999;55(3):335-40.

6. TR, Webb, M, Matarin, JC, Gardner, D, Kelberman, H, Hassan, W, Ang, M, Michaelides, JB, Ruddle, CE, Pennell, S, Yazar, CC, Khor, T, Aung, M, Yogarajah, AG, Robson, GE, Holder, ME, Cheetham, EI, Traboulsi, AT, Moore, JC, Sowden, SM, Sisodiya, DA, Mackey, SJ, Tuft and AJ, Hardcastle. X-linked megalocornea caused by mutations in CHRDL1 identifies an essential role for ventroptin in anterior segment development. Am J Hum Genet 2012;90(2):247-59.

7. J, Han, JW, Young, RF, Frausto, SJ, Isenberg and AJ, Aldave. X-linked Megalocornea Associated with the Novel CHRDL1 Gene Mutation p.(Pro56Leu*8). Ophthalmic Genet 2015;36(2):145-8.

8. AE, Davidson, SS, Cheong, PG, Hysi, C, Venturini, V, Plagnol, JB, Ruddle, H, Ali, N, Carnt, JC, Gardner, H, Hassan, E, Gade, L, Kearns, AM, Jelsig, M, Restori, TR, Webb, D, Laws, M, Cosgrove, JM, Hertz, I, Russell-Eggitt, DT, Pilz, CJ, Hammond, SJ, Tuft and AJ, Hardcastle. Association of CHRDL1 mutations and variants with X-linked megalocornea, Neuhäuser syndrome and central corneal thickness. PloS one 2014;9(8):e104163.

9. YH, Jee, J, Baron and O, Nilsson. New developments in the genetic diagnosis of short stature. Curr Opin Pediatr 2018;30(4):541-547.

Figure 1. Photos of current case. (A) Flat facial profile, mildly epicanthic folds, downslanting palpebral fissures, flat nasal bridge, bulbous nose, short neck and the left cheek is smaller than the right cheek, slightly asymmetrical of nasolabial sulcus. (B) Flat lateral top of the skull, cyrtopisthocranius, low-set ears and low hairline. (C) Clinodactyly of the fifth finger.

Figure 2. Chromosomal microarray analysis found one 671 **K**b microdeletion located at Xq23 that covered the *AMMECR1* and *CHRDL1*genes.

Table 1. Clinical findings in patients with Xq22.3-23 deletion including AMMECR1 or partially overlapping this region.

Case & Ref	Case 1 [2]	Case 2 [2]	Case 3[1]	Case 4[1]	Case 5[4]	Case 6[4]	Case 7 [4]	Case 8[4]	Case 9[4]	Current case
Sex	male	male	male	male	female	male	male	male	male	male
Gene	COL4A6 to TDGF3	COL4A6 to TDGF3	AMMECR1	AMMECR1	AMMECR1	AMMECR1	AMMECR1	AMMECR1	AMMECR1	AMMECR1 to CHRDL1
Short stature	+	+	+	+	+	+	+	+	_	+
Hypotonia	+	+	+	+	NI	+	+	NI	NI	_
Hearing loss	+	+	+	+	+	+	+	NI	NI	_
Mental retardation	_	_	NI	NI	_	+	_	+	+	_
Motor delay	+	+	+	+	_	+	_	_	+	+
Midface hypoplasia	+	+	+	+	+	+	+	_	+	+
Ocular abnormality	+	+	_	+	NI	NI	NI	NI	NI	_
Language disorder	delay	delay	Early & delay,	+	NI	NI	NI	NI	delay	stuttered
Kidney abnormality	haematuria	haematuria	nephrocalcinosis	nephrocalcinosis	_	+	_	_	_	dysplasia
Cardiac & skeletal abnormality	+	+	_	_	+	+	+	+	_	+
Elliptocytosis	+	+	_	_	_	_	_	_	+	_

+, present; −, absent; NI, not investigated