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CASE REPORT

Clinical description of a neonate carrying the largest reported deletion involving the 10p15.3p13 region

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Key Clinical Message

Chromosome 10p deletion is a rare disorder. This is the largest deletion in chromosome 10p reported to date and the first to be diagnosed in the early neonatal period because of severe clinical manifestations. This rare case might help to understand the genotype-phenotype spectrum in infants with 10p deletion.

Keywords

10p monosomy, chromosomal microarray, *GATA3*, *ZMYND11*.

Introduction

Terminal deletion of chromosome 10p is a rare chromosomal disorder, and two main phenotypes have been defined, depending on the genomic position of the deletion in 10p13-10p14. Deletions or point mutations in glutamyl-aminotransferase-subunit A (*GATA3*) are responsible for hypoparathyroidism, sensorineural hearing loss, and renal anomalies (HDR syndrome) [1]. Haploinsufficiency of a more proximal region, designated DiGeorge critical region 2 (DGCR2), is associated with congenital cardiac defects and hypo- or aplasia of the thymus or T cell defects [2]. Partial deletions of 10p14-p15 are responsible for a syndrome with a distinct phenotype, comprised of more severe clinical manifestations including severe cognitive disability, language delay, autism, and characteristic clinical features [3]. Recently, a small subgroup of patients with microdeletions in 10p15.3 was defined as having a new microdeletion syndrome characterized by cognitive or neurodevelopmental delay and speech impairments [4]. In addition, 4.3 Mb deletions within 10p14 are associated with autism and characteristic clinical findings [5].

Here, we report a new case of a 16 Mb deletion at 10p15.3p13 in a Korean neonate, confirmed by chromosomal microarray analysis (CMA).

Case Description

A female infant was born by vaginal delivery at 38 and 2/7 weeks of gestation at obstetric clinic. The patient was second child of nonconsanguineous parents. At birth, her weight was 1830 g, length was 43.0 cm, and head circumference was 29.4 cm, all of which were <3rd percentile. From 30 weeks of gestation, intrauterine growth retardation (IUGR) with oligohydramnios was observed.

The baby was transferred to our hospital because of respiratory difficulties shortly after birth. Her facial appearance was "coarse," with a broad nasal root, small mouth with thin upper lips, retromicrognathia and low-set malformed, posteriorly rotated ears, and a disproportionately large head for her face, widely spaced nipples,

overriding fingers and thin, long toes, and clinodactyly were also observed (Fig. 1). The Ortolani test for screening of developmental dislocation of hip was positive. The initial chest radiograph showed normal lung volumes with mild cardiomegaly. She was initially treated with oxygen due to desaturation. However, endotracheal intubation and mechanical ventilator care were required because of recurrent apneic episodes with desaturation at 12 h after birth. Myoclonic seizures were observed at the time of apnea. Therefore, intravenous phenobarbital administration was started. Routine laboratory investigations were normal. Metabolic and cytogenetic evaluations were performed. Her plasma and urine amino acid profiles and lysosomal enzymes were normal, and analyses of blood and cerebrospinal fluid for herpes simplex, cytomegalovirus, rubella, and toxoplasma were normal. The initial findings for head and spine ultrasonography were negative. Neck sonography revealed thymus hypoplasia. Abdomen and pelvic sonography revealed uterine didelphys, double uterus and cervix, and small-sized both kidneys for the patient's age (Fig. 2A). Hip joint sonography revealed subluxation of both hip joints. On 2nd day, echocardiogram showed double outlet right ventricle (DOVR) with huge ventricular septal defect (VSD) measuring 9–10 mm and moderate pulmonary hypertension. A Pavlik harness was applied by the pediatric orthopedist. On the 3rd day, electroencephalogram showed negative findings. Because of the wax and wane of respiratory distress and persistent pulmonary hypertension, mechanical ventilator care was maintained. Enteral nutrition through orogastric tube was well tolerated. Follow-up laboratory tests revealed on-going hypocalcemia. Hypoparathyroidism was suspected, with characteristic findings of hypocalcemia and undetectable or normal serum concentrations of parathyroid hormone (PTH) (serum calcium: 6.6 mg/dL (ref.: 8.2–10.8), ionized calcium: 0.82 mmol/L (ref.: 1.13–1.32), and PTH 18.0 pg/mL (ref.:15.0–65.0). After repeated intravenous infusions of calcium gluconate solution, low-phosphate formula milk and oral elemental calcium, cholecalciferol, and calcitriol were administered from the 13th day after birth. Brain MRI MRI illustration performed at 13 days revealed patchy diffusion-restrictions in left fronto-parietal white matter and tiny T1WI high-signal foci in right occipital convexity and left posterior fossa (Fig. 2B). After gradual weaning, extubation was performed at 19 days. On 41th day of birth, brace was removed because follow-up hip sonogram revealed improving of hip joint subluxation. Auditory brainstem response test revealed moderate sensorineural deafness with hearing losses of 80 dB at the mid- and higher frequencies in both ears. A neurologic examination at discharge revealed increased muscle tone and increased deep tendon reflexes. Due to swallowing dysfunction, only orogastric tube feeding was available. At 43th day after birth, she was discharged after instruction of the parents for tube feeding (Tables 1 and 2).

At follow-up visits 1 and 2 weeks after discharge, the patient's state was unchanged or slightly aggravated. The patient was not able to control her head. Her body weight was 2550 g, length was 50.0 cm, and head circumference was 34.0 cm, all of which were <3rd percentile. A follow-up electroencephalogram registered normal activity without definite epileptiform discharge, and phenobarbital was therefore discontinued after maintenance therapy for 6 weeks. The patient is scheduled for cardiac surgery in the near future, as well as continued physical therapy and routine follow-up by pediatrics, pediatric orthopedics, rehabilitation medicine, and otorhinolaryngology.

Genetic Testing

Whole blood was used to perform genetic testing. Karyotype analysis revealed a deletion in 10p. Microarray analysis was performed using the CytoScan 750K high-resolution genotyping SNP array (Affymetrix, Santa Clara, CA). The array contains >750,436 CNV markers, including 200,436 genotype-able SNP probes and 550,000 nonpolymorphism probes. All data were visualized and analyzed using the Chromosome Analysis Suite (ChAS) software package (Affymetrix, USA). Based on comparison with human reference genome 37 (NCBI37/hg19) at the National Center for Biotechnology, a 16 Mb deletion was identified at 10p15.3p13 [arr 10p15.3p13(100,047–16,314,195)x1] (Fig. 3). This deletion with partial monosomy 10p is summarized in Figure 4.

Discussion

Chromosome 10p terminal deletions have been described in approximately 50 cases to date, since the first description by Elliott et al. in 1970 [3, 6–12]. Two distinct phenotypes associated with 10p13-10p14 have been defined, which depend on location of the deletion. Haploinsufficiency of a region located distal to 10p14 designated HDR1 is responsible for HDR syndrome, while more centromeric deletions are associated with what has been called "DiGeorge syndrome 2 (DGS2)". Characteristic clinical findings in affected individuals with DGS2 are cardiac defects and thymus hypo/aplasia or T cell defects [5]. HDR syndrome (OMIM#146255), also known as Barakat syndrome [13], is autosomal dominant. *GATA3* (OMIM#131320), which is located within the band 10p14, has been identified as responsible for the phenotype of HDR syndrome. This gene was shown to be essential in the embryonic development of parathyroid glands, auditory system, kidneys, thymus, and central nervous

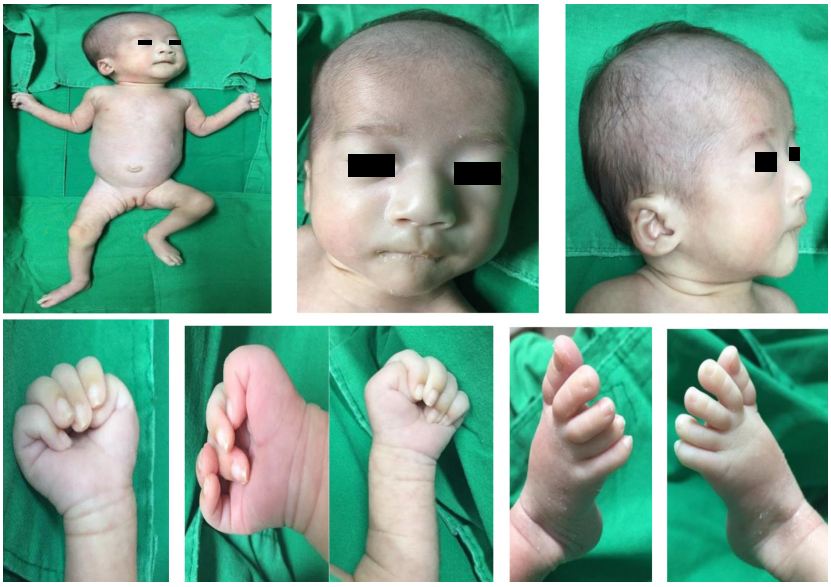

Figure 1. Photographs of the patient. A broad nasal root, small mouth with thin upper lips, retromicrognathia and low-set malformed posteriorly rotated ears, and a disproportionately large head for her face were observed, along with widely spaced nipples, overriding fingers, and thin, long toes, and clinodactyly.

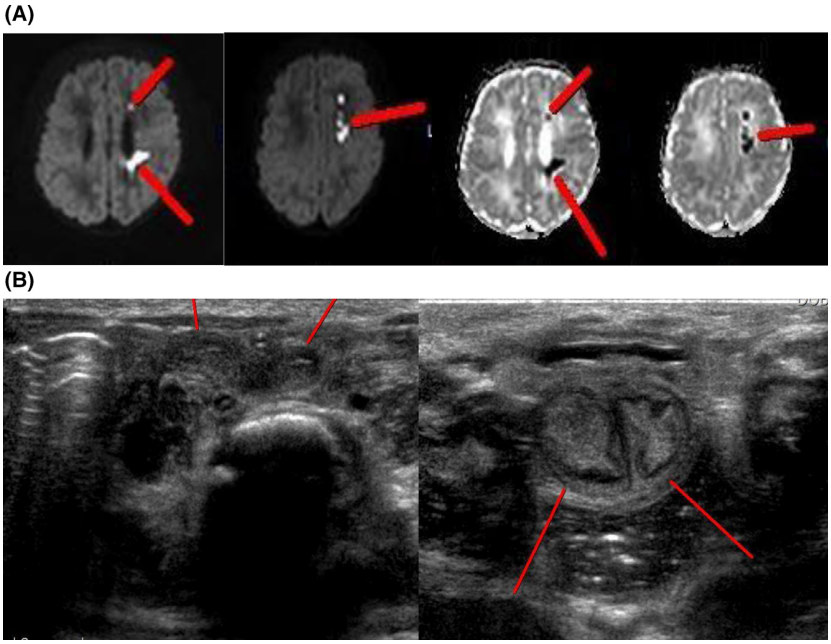

Figure 2. (A) Brain MRI c DWI shows patchy diffusion restrictive lesions in the left fronto-parietal white matter. (B) Uterine didelphys, showing the double uterus and double cervix.

system [2, 14]. Sensorineural hearing loss, which is observed in all affected infants, seems to be caused by haploinsufficiency and/or mutations of *GATA 3* [15–17]. The DiGeorge anomaly, also called DiGeorge syndrome (DGS, OMIM#199400), is a congenital developmental disorder including cardiac defects, thymus hypoplasia/aplasia, and facial dysmorphism. Classic DGS is caused by a microdeletion of 22q11.2 and accounts for more than half of all cases. With much lower frequency, terminal deletion in 10p13-14 is another cause of DiGeorge anomaly and is defined as DGS2. Congenital cardiac defects and thymus hypoplasia/aplasia are the main clinical features of DGS2 (OMIM#601362), and its critical region has been proposed to be between the D10S547 and D10S585

Table 1. Summary of clinical findings from our patient compared with the previous published patients with partial deletion 10p.

		10p13-p14			Microdeletion 10p15.3		
	Present in patient	HDR syndrome	DSG2	4.3 Mb in 10p14	Familial case Eggert et al. [20]	Monozygotic twins Vargiami et al. [19]	12/19 enrolled patients Descipio et al. [4]
Hypoparathyroidism	+	+					
Hearing loss	+	+			–	+	None
Renal disease	+	+					
Cardiac anomalies	+		+		1/2	–	At least 2
Thymus hypoplasia/aplasia	+		+				
Autism	Not determined yet			+			
Dysmorphism	+			+			
Cognitive/behavioral delay	Not determined yet				2/2	+	At least 10
Motor delay	Not determined yet, but expected already				2/2	+	At least 10
Speech/language delay	Not determined yet				2/2		At least 10
Craniofacial dysmorphism	+				2/2	+	At least 9
Brain anomalies	+				–	+	At least 4
Hypotonia	+				–	–	7/11
Hand/foot anomalies	+				2/2	–	5/11
Seizures	+				–	–	3/7
Visual impairment	?				–	+	None
Genital tract anomalies	+				–	–	At least 2?
Hip dislocation/subluxation	+				–	–	
Constipation	–				1/2	–	At least 4
Omphalocele	–				–	+	None
Craniosynostosis	–				–	+	None
IUGR	+				–	–	At least 2
Oligohydramnios	+				–	–	At least 1

markers (genomic position 10.6-11.3 Mb from the 10p-telomere) [8]. Although *CUCBP2* has been proposed as a candidate gene for the phenotype of DGS2, there is no evidence to support it [10]. The DGS2 phenotype is reported to be more severe than that of the regular 22q11.2 deletion syndrome, including significant cognitive disability and immune deficiency, as well as cardiac defects [18].

By reviewing a total of 14 patients with overlapping 10p deletions, Lindstrand et al. revealed that partial deletions of 10p14-15 represent a syndrome with a distinct phenotype and identified a 1.6 Mb region of 10p15.3 that is associated with cognitive disability and language impairment, as well as a second region of 4.3 Mb in 10p14 that is associated with autism and characteristic clinical features. Both of these regions are located outside the previously reported critical region of DGS2 [3].

Microdeletion syndrome 10p15.3 has only recently been described in a small number of patients. Because only 25 cases of microdeletion syndrome 10p15.3 have been reported to date [3, 19, 20] and clinical data were obtained for only 17 of the 23 published cases, extremely limited information is available for clinical phenotype. Microdeletion syndrome 10p15.3 has common phenotypes including cognitive/behavioral delay, language impairments, motor delay, craniofacial dysmorphism, brain anomalies, and seizures. Zinc finger MYND domain containing protein (*ZMYND11*, OMIM #608668) is also called BS69 has a splicing variant named BRAM1. *ZMYND11* is localized in the nucleus while BRAM1 is localized in the cytoplasm. *ZMYND11* is expressed in various human tissues, including the brain. Several patients with a microdeletion of 10p15.3 involving *ZMYND11* have been reported [4, 21]. It has been suggested that *ZMYND11* mutations might be causative of intellectual disability [4]. Facial dysmorphism is also a prominent feature of microdeletion syndrome 10p15.3. Affected infants have a characteristic dysmorphology including a large forehead, bristly hair, short and down-slanting palpebral fissures, hypertelorism, wide intercanthal distance, epicanthal folds, a flat nose, a high curved palate and low-set, malformed, posteriorly rotated ears, and a small mouth.

The combined information from the present and previous reported cases support that the partial deletion 10p13-p15 constitutes a contiguous gene syndrome. This patient carries deletions of several critical parts of the

Table 2. RefSeq Genes included in the deleted region (chr10:100,047–16,314,195).

RefSeq genes	OMIM phenotype	MIM number
ZMYND11	Mental retardation, autosomal dominant 30	#616083
KLF6	Gastric cancer, somatic	#613659
	Prostate cancer, somatic	#176807
AKR1C2	46XY sex reversal 8	#614279
AKR1C4		
IL2RA	Immunodeficiency 41 with lymphoproliferation and autoimmunity	#606367
GATA3	Hypoparathyroidism, sensorineural deafness, and renal dysplasia	#146255
DHTKD1	2-aminoadipic 2-oxoadipic aciduria	#204750
	Charcot-Marie-Tooth disease, axonal, type 2Q	#615025
OPTN	Amyotrophic lateral sclerosis 12	#613435
	Glaucoma 1, open angle, E	#137760
PHYH	Refsum disease	#266500
FRMD4A	Corpus callosum agenesi with facial anomalies and cerebellar ataxia	#616819
DCLRE1C	Omenn syndrome	#603554
	Severe combined immunodeficiency, Athabascan type	#602450
ITGA8	Renal hypo-dysplasia/aplasia 1	#191830

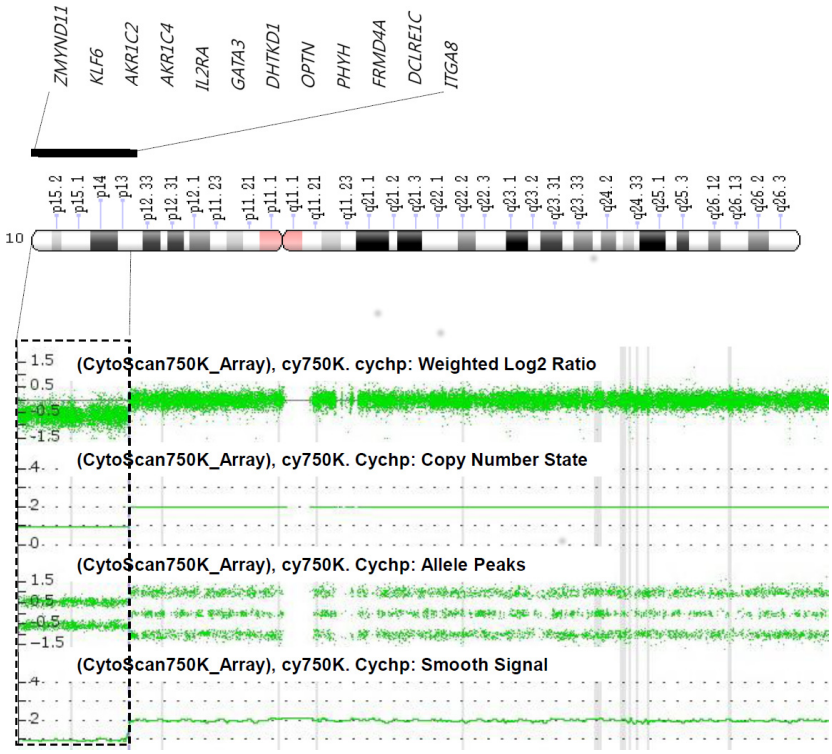

Figure 3. CGH analysis showing the extent of the 10p deletion.

above-mentioned region. First, this patient's deletion encompasses both the HDR and DGS2 critical regions. Thus, our patient shows a variety of clinical features of HDR syndrome and DGS2, including hypoparathyroidism, hearing loss, cardiac anomaly, and thymus hypoplasia. In addition, both critical regions (the 4.3 Mb of 10p14, which is associated with autism and dysmorphic face, and the 1.6 Mb in 10p15.3, which is associated with cognitive disability and language delay), are also involved. Genitourinary tract evaluation revealed uterine didelphys, double uterus, and double cervix and relatively small kidneys measuring 3.3 cm for term neonates. Urinary tract anomalies have already been reported in each of the three previously published cases (hydronephrosis in patient 2 and hypospadias in patient 5, described by DeScipio et al., and small kidneys with vesico-urethral reflux in patient described by Fernandez et al.) [4, 22]. Specific neurologic manifestations

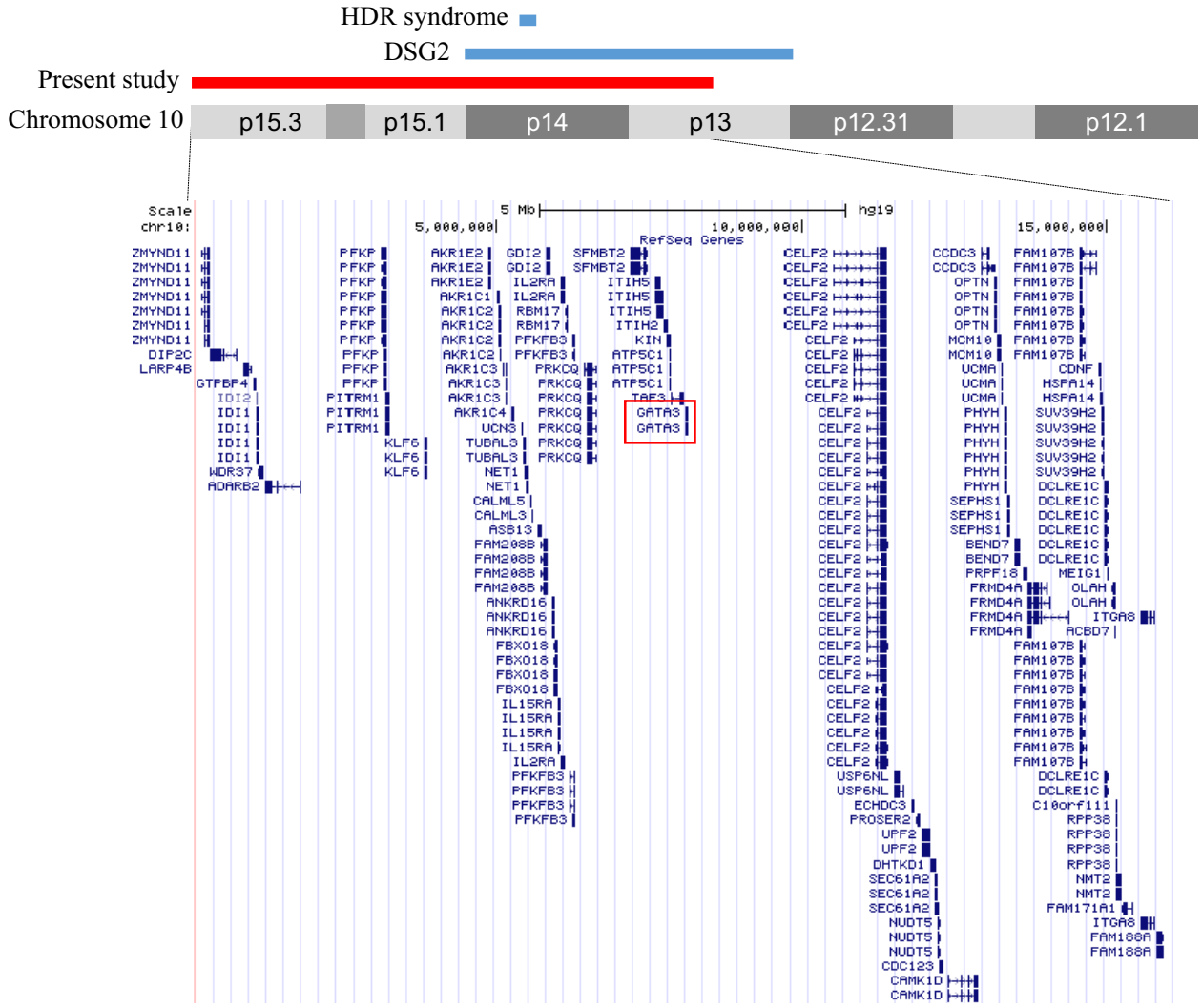

Figure 4. Size of the deletion in this patient with partial monosomy 10p.

involving 10p14-p15 have yet to be determined because the patient is still very young age. However, adverse neurologic outcomes are expected based on the test results and clinical course to date.

To the best of our knowledge, this is the largest deletion in chromosome 10p reported to date. This patient presented with a severe phenotype in the early neonatal period, and this is the first case to be diagnosed in the neonatal period, in contrast to most cases, which are diagnosed after the neonatal period due to progressive developmental delay.

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Conflict of Interest

None declared.

Authorship

SBK: contributed to data collection, data analysis, and the writing the first draft. Y-EK and HYJ: contributed to review and analyze genetic testing results as specialist in genetics. JMJ: contributed to review and analyze clinical data and critical revision of the manuscript. Y-JL: contributed to review and analyze radiologic results as pediatric radiologist and critical revision of the manuscript. MLC: contributed to plan and organize research, and critical revision of the manuscript. All authors approved of the final manuscript as submitted.

Reference

1. Ferraris, S1., A. G. Del Monaco, E. Garelli, A. Carando, B. De Vito, P. Pappi, et al. 2009. HDR syndrome: a novel 'de novo' mutation in GATA3 gene. Am. J. Med. Genet. Part A 149A:770–775.
2. Van Esch, H., P. Groenen, M. A. Nesbit, S. Schuffenhauer, P. Lichtner, G. Vanderlinden, et al. 2000. GATA3 haploinsufficiency causes human HDR syndrome. Nature 406:419–422.
3. Lindstrand, A., H. Malmgren, A. Verri, E. Benetti, M. Eriksson, A. Nordgren, et al. 2010. Molecular and clinical characterization of patients with overlapping 10p deletions. Am. J. Med. Genet. Part A 152A:1233–1243.
4. DeScipio, C., L. Conlin, J. Rosenfeld, J. Tepperberg, R. Pasion, A. Patel, et al. 2012. Subtelomeric deletion of chromosome 10p15.3: clinical findings and molecular cytogenetic characterization. Am. J. Med. Genet. Part A 158A:2152–2161.
5. Melis, D., R. Genesio, P. Boemio, E. Del Giudice, G. Cappuccio, A. Mormile, et al. 2012. Clinical description of a patient carrying the smallest reported deletion involving 10p14 region. Am. J. Med. Genet. Part A 158A:832–835.
6. Elliott, D., G. H. Thomas, C. J. Condron, N. Khuri, and F. Richardson. 1970. C-group chromosome abnormality (? 10p-). Occurrence in a child with multiple malformations. Am. J. Dis. Child. 119:72–73.
7. Gottlieb, S., D. A. Driscoll, H. H. Punnett, B. Sellinger, B. S. Emanuel, and M. L. Budarf. 1998. Characterization of 10p deletions suggests two nonoverlapping regions contribute to the DiGeorge syndrome phenotype. Am. J. Hum. Genet. 62:495–498.
8. Schuffenhauer, S., P. Lichtner, P. Peykar-Derakhshandeh, J. Murken, O. A. Haas, E. Back, et al. 1998. Deletion mapping on chromosome 10p and definition of a critical region for the second DiGeorge syndrome locus (DGS2). Eur. J. Hum. Genet. 6:213–225.
9. Van Esch, H., P. Groenen, S. Daw, A. Poffyn, M. Holvoet, P. Scambler, et al. 1999. Partial DiGeorge syndrome in two patients with a 10p rearrangement. Clin. Genet. 55:269–276.
10. Lichtner, P., T. Atti_e-Bitach, S. Schuffenhauer, J. Henwood, P. Bouvagnet, P. J. Scambler, et al. 2002. Expression and mutation analysis of BRUNOL3, a candidate gene for heart and thymus developmental defects associated with partial monosomy 10p. J. Mol. Med. (Berl) 80:431–442.
11. Skrypnyk, C., T. O. Goecke, F. Majewski, and O. Bartsch. 2002. Molecular cytogenetic characterization of a 10p14 deletion that includes the DGS2 region in a patient with multiple anomalies. Am. J. Med. Genet. 113:207–212.
12. Yatsenko, S. A., A. N. Yatsenko, K. Szigeti, W. J. Craigen, P. Stankiewicz, S. W. Cheung, et al. 2004. Interstitial deletion of 10p and atrial septal defect in DiGeorge 2 syndrome. Clin. Genet. 66:128–136.
13. Barakat, A. Y., J. B. D'Albora, M. M. Martin, and P. A. Jose. 1977. Familial nephrosis, nerve deafness, and hypoparathyroidism. J. Pediatr. 91:61–64.
14. Van Esch, H., and K. Devriendt. 2001. Transcription factor GATA3 and the human HDR syndrome. Cell. Mol. Life Sci. 58:1296–1300.
15. Zahirieh, A., M. A. Nesbit, A. Ali, K. Wang, N. He, M. Stangou, et al. 2005. Analysis of a novel GATA3 mutation in a family with the hypoparathyroidism, deafness, and renal dysplasia syndrome. J. Clin. Endocrinol. Metab. 90:2445–2450.
16. Chiu, W. Y., H. W. Chen, H. W. Chao, L. T. Yann, and K. S. Tsai. 2006. Identification of three novel mutations in the GATA3 gene responsible for familial hypoparathyroidism and deafness in the Chinese population. J. Clin. Endocrinol. Metab. 91:4587–4592.
17. Bemardini, L. , L. Sinibaldi, A. Capalbo, I. Bottillo, B. Mancuso, B. Torres, et al. 2009. HDR (Hypoparathyroidism, Deafness, Renal dysplasia) syndrome associated to GATA3 gene duplication. Clin. Genet. 76:117–119.
18. Van Esch, H., P. Groenen, J. P. Fryns, Van de Ven W., and K. Devriendt. 1999. The phenotypic spectrum of the 10p deletion syndrome versus the classical DiGeorge syndrome. Genet. Couns. 10: 59–65.
19. Vargiami, E., A. Ververi, M. Kyriazi, E. Papathanasiou, G. Gioula, and S. Gerou, et al. 2014. Severe clinical presentation in monozygotic twins with 10p15.3 microdeletion syndrome. Am. J. Med. Genet. Part A 164A:764–768.
20. Eggert, M., S. Müller, U. Heinrich, and Y. Mehraein. 2016. A new familial case of microdeletion syndrome 10p15.3. Eur. J. Med. Genet. 59:179–182.
21. Cobben, J. M., M. M. Weis, F. S. van Dijk, R. De Reuver, C. de Kruiff, W. Pondaag, et al. 2014. A de novo mutation in ZMYND11, a candidate gene for 10p15.3 deletion syndrome, is associated with syndromic intellectual disability. Eur. J. Med. Genet. 57: 636–638.
22. Fernández, R. M., J. Sánchez, L. García-Díaz, A. González-Meneses, and G. Antiñolo. 2016. Interstitial 10p deletion derived from a maternal ins(16;10)(q22; p13p15.2): report of the first familial case of 10p monosomy affecting to two familial members of different generations. Am. J. Med. Genet. Part A 170A:1268–1273.

