Case Report
J Genet Med 2022;19(2):105-110
https://doi.org/10.5734/JGM.2022.19.2.105
ISSN 1226-1769 (Print) 2383-8442 (Online)

JGM Journal of Genetic Medicine

The first Korean case of 2p15p16.1 microdeletion syndrome, characterized by facial dysmorphism, developmental delay, and congenital hypothyroidism

Jin Young Cho[1,2], Tae Kwan Lee[2], Yoo Mi Kim[1,3], and Han Hyuk Lim[1,2,*]

[1]Department of Pediatrics, Chungnam National University College of Medicine, Daejeon, Korea
[2]Department of Pediatrics, Chungnam National University Hospital, Daejeon, Korea
[3]Department of Pediatrics, Chungnam National University Sejong Hospital, Sejong, Korea

The microdeletion syndrome of chromosome 2p15p16.1 (MIM: 612513) is an extremely rare contiguous gene deletion syndrome. Microdeletions of varying sizes in the 2p15-16.1 region are associated with developmental delay, intellectual disability, autism spectrum disorder, hypotonia, and craniofacial dysmorphism. Previous studies have identified two critical regions: the proximal 2p15 and distal 2p16.1 regions. *BCL11A, PAPOLG*, and *REL* genes play crucial roles in patients with 2p16.1 microdeletion. To our knowledge, only 39 patients have been reported as having 2p15p16.1 microdeletion syndrome. Here, we present another patient with 2p15p16.1 microdeletion syndrome. A nine-month-old boy was referred to our clinic for the psychomotor delay, facial dysmorphism, and congenital hypothyroidism. During his follow-up visits, he was diagnosed with global developmental delay, intellectual disability, abnormal behavior, hypotonia, microcephaly, and abnormal electroencephalography. Using a chromosomal microarray for genetic analysis, a novel, de novo, 622 kb microdeletion of 2p16.1 was identified as one of the critical regions of the 2p15p16.1 microdeletion syndrome. This is the first case of its kind in Korea. We have discussed our case and literature reviews to clarify the relationship between the genes involved and clinical phenotypes in 2p15p16.1 microdeletion syndrome.

Key words: Developmental disability, Intellectual disability, Craniofacial abnormalities, Chromosome 2.

Introduction

Chromosomal microarray (CMA) has been a first-line, powerful tool for evaluating unknown etiologies in patients with neurodevelopmental impairments and congenital anomalies [1]. Furthermore, certain copy number variants (CNVs) detected by the CMA test, such as microdeletions and microduplications, are associated with developmental delay, intellectual disability (ID), and/or autism spectrum disorders [2].

Rajcan-Separovic et al. [3] reported a novel chromosomal microdeletion with similar clinical phenotypes in 2007. They described two unrelated patients with idiopathic ID, autistic behavior, facial dysmorphism, and somatic congenital anomalies associated with an interstitial microdeletion of the 2p15-p16.1 region. Since the first report, over 30 patients with 2p15p16.1 microdeletion syndrome have been documented [4,5].

Received: 17 September 2022, Revised: 26 October 2022, Accepted: 31 October 2022, Published: 31 December 2022
*Corresponding author: Han Hyuk Lim, M.D., Ph.D. https://orcid.org/0000-0002-5297-5913
Department of Pediatrics, Chungnam National University Hospital, Chungnam National University College of Medicine, 282 Munhwa-ro, Jung-gu, Daejeon 35015, Korea.
Tel: +82-42-280-7825, Fax: +82-42-255-3158, E-mail: damus@cnuh.co.kr
Conflict of interest: The authors declare that they do not have any conflicts of interest.

Chromosome 2p15p16.1 microdeletion syndrome (MIM: 612513), a rare contiguous gene deletion syndrome (chr2:59.0-61.5 Mb; involving chromosome 2p15-p16.1), is a neurodevelopmental disorder characterized by psychomotor delay, ID, and facial dysmorphism. Furthermore, many patients with 2p15p16.1 microdeletion syndrome have autistic behavior as well as brain, urogenital, or skeletal abnormalities [6].

Two critical regions in the 2p15p16.1 microdeletion syndrome have been identified: the proximal 2p15 and distal 2p16.1 regions [5]. Although the genotype and phenotype correlation of two regions remains uncertain, previous studies have described the overlapping characteristics in each region [5].

Here, we present the case of an infant with facial dysmorphism, developmental delay, and congenital hypothyroidism caused by a novel, de novo 2p16.1 microdeletion as one of the critical regions of 2p15p16.1 microdeletion syndrome, and we review the literature on the genes involved in our case.

This study was approved by the Institutional Review Board of Chungnam National University Hospital (IRB No. 2022-10-031). Written informed consent was obtained from the patient and the patient's parents for publication of this case report.

Case

A nine-month-old boy was referred to an outpatient clinic for the psychomotor delay and the inability to roll over or flip. He was the first child of healthy, non-relative parents with no family history of inherited disorders including thyroid disease. He was born via vaginal delivery at 40 weeks gestation with a birth weight of 3,490 g (10-50th percentile). The patient showed elevated thyroid stimulating hormone (TSH) (10.6 μIU/mL) on neonatal screening test, but further evaluation of hypothyroidism had not been performed until first visit to our clinic. Automated auditory brainstem response test was normal. Intermediate esotropia has been observed since he was 1 month old, and he was diagnosed with conventional esotropia at 5 months. He began covering treatment and planned bilateral rectus recession surgery before the age of 1 year.

At his first visit, his weight, height, and head circumference were 9.9 kg (75-90th percentile), 76.4 cm (90-95th percentile), and 43.1 cm (3-5th percentile), respectively. Physical examinations revealed the following: microcephaly, telecanthus, broad nasal root, low nasal bridge, flat mid face, long philtrum, low set ear, micrognathia, no cardiac murmur, palpable gonads with

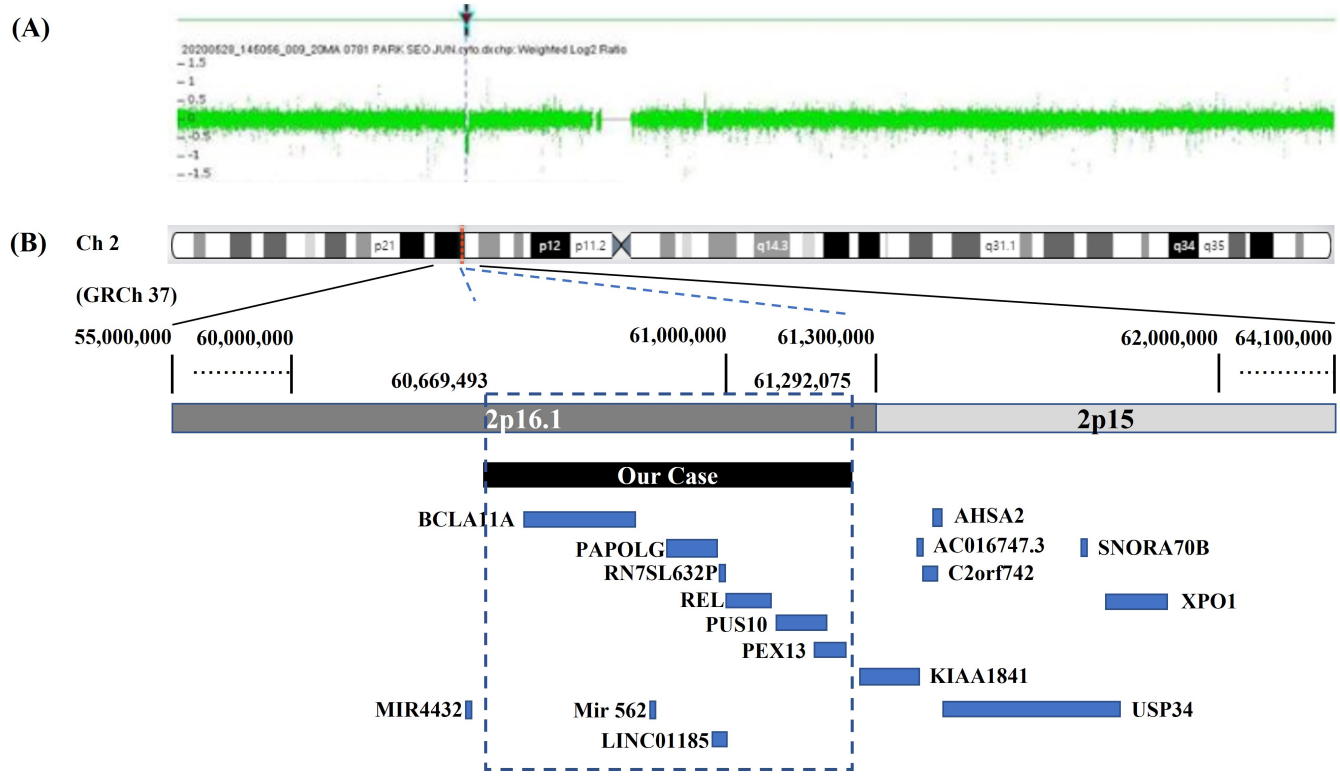

Fig. 1. Mapping of the 2p15p16.1 microdeletion and our case (black bar). (A) The patient's chromosomal microarray revealed the 622 kb microdeletion of 2p16.1 (GRCh37:2:60,669,493-61,292,075), and (B) schematic representation of 2p15-p16.1 microdeletion syndrome and coding genes. Dashed box lines indicate the involved region in this study. This figure was modified from data UCSC database (GRCh37/hg19) (https://genome.ucsc.edu).

normal shaped scrotum and penis, and whitish nevus on back. He looked floppy and hypotonic. The motor grades of the upper and lower extremities were all III-IV. The deep tendon reflex was hypoactive. On laboratory examination, the level of free thyroxine (T4) was 1.0 ng/dL (normal range 0.7-1.48), whereas the level of TSH was elevated (18.2 μIU/mL, normal range 0.35-4.94). Aspartate aminotransferase, alanine transaminase, triglyceride, creatine phosphokinase, and lactate dehydrogenase were 63 U/L (normal range 13-33), 50 U/L (normal range 8-42), 195 mg/dL (normal range 45-150), 160 U/L (normal range 56-244), and 780 U/L (normal range 200-400), respectively.

Table 1. Clinical manifestations of 2p15p16.1 deletion syndrome

Parameters	2p15 deletion (%)	2p16.1 deletion (%)	Our case
Growth parameter			
IUGR	27	0	–
Short stature	30	20	–
Craniofacial			
Dysmorphic	100	60	+
Microcephaly	54	33	+
Strabismus	29	50	+
Vision impairment	44	25	–
Hearing loss	25	0	–
Thorax			
Wide distance of nipple	20	20	–
Extra nipple	20	0	–
Pectus excavatum	75	20	–
Scoliosis	78	20	–
Camptodactyly	33	0	–
Organ defect			
Cardiac malformation	17	20	–
Kidney anomaly	10	0	–
Genital malformation	27	20	–
Neurological			
Feeding difficulty	75	100	+
Abnormal EEG	0	50	+
Developmental delay	100	100	+
Hypotonia	91	100	+
Intellectual disability	100	100	+
Speech delay	80	100	+
Autism	43	50	–
ADHD	40	50	–
Behavior abnormality	67	60	+
Brain anomalies			
Enlarged ventricle	14	40	–
Cerebral atrophy	0	40	–
Cerebellar hypoplasia	0	20	–
Corpus callosum abnormality	43	20	–
Other cerebral malformation	43	40	–
Hypothyroidism	?	?	+

IUGR, intrauterine growth retardation; EEG, electroencephalogram; ADHD, attention deficit hyperactivity disorder.

The results of the chest x-ray, electrocardiogram, abdominal sonography, and brain magnetic resonance imaging (MRI) were unremarkable. His bone age was 9-12 months. A spine x-ray revealed mild anterior scalloping of the lumbar vertebral bodies. On the Bayley Scale of Infant and Toddler Development III, he had global developmental delay: his cognitive age, acceptance language age, expression language age, fine motor development age, and gross motor development age were 6 months, 4.3 months, 3.3 months, 4.3 months, and 4.3 months, respectively. He started rehabilitation treatment. At 10 months of his age, the levels of free T4, triiodothyronine, and TSH were 0.62 ng/dL, 1.14 ng/dL, and 75.41 μIU/mL, respectively. He was diagnosed with hypothyroidism, and levothyroxine was administered immediately.

The patient and his parents underwent chromosome microarray testing to evaluate the underlying causes of dysmorphism and developmental delay. The patient's karyotype was 46, XY, and chromosome microarray revealed 622 kb deletion in 2p16.1 and 661 kb duplication in 7p22.3. His father had a 662 kb duplication in 7p22.3 and a 2.3 Mb duplication in 8p23.2, whereas his mother had a 1.2 Mb deletion in 16p11.2. Because no pathogenic reports have been found, the copy number variation in parents was presumed to be benign. Thus, the 622 kb microdeletion in 2p16.1 was a de novo inheritance.

At the age of 24 months, he began crying or laughing unexpectedly, even while sleeping. He could babble but could not speak a word at that age, so he underwent language rehabilitation therapy.

At the age of 28 months, the Bayley Scale of Infant and Toddler Development III was rechecked. His cognitive age, acceptance language age, expression language age, fine motor development age, and gross motor development age were determined to be 7, 6, 6, 8, and 11 months, respectively. Furthermore, a general speech-language test revealed severe speech delay.

At the age of 36 months, his weight, height, and head circumference were 14.9 kg (50-75th percentile), 99.1 cm (90-95th percentile), and 47.2 cm (3-5th percentile), respectively. The patient began babbling and walking with a grip. He was attached to his mother but uninterested in others. He began swallowing without chewing well, so he underwent swallowing rehabilitation. His brain MRI was normal at the age of 36 months, but

his electroencephalogram (EEG) showed occasional suspicious sharp wave discharges from the left frontal areas. He showed no signs of seizures. While taking synthyroid, thyroid function was well controlled and he tried to stop levothyroxine at 36 months of his age to determine whether his hypothyroidism is permanent or not. After 2 months of holding medication, 0.93 ng/dL of free T4 and 16.4127 μIU/mL of TSH were measured. Thyroid sonography was normal. Thyroid scan showed diffusely enlarged both lobes, markedly increased uptake in both lobes. Currently, we are considering to restart levothyroxine.

Discussion

We described the first Korean case of 2p15p16.1 microdeletion syndrome. In our patient, global developmental delay, ID, and dysmorphic craniofacial features were associated with a novel, de novo 622 kb microdeletion of chromosome 2p16.1. Moreover, congenital hypothyroidism was detected in our case.

2p15p16.1 microdeletion (ICD10: Q93.5) is a synonym of del (2) (p15p16.1) or monosomy of 2p15p16.1, and its prevalence is extremely rare, estimated at <1:1,000,000 of populations (https://www.orpha.net). Based on DECIPHER (www.decipher-genomics.org) and PubMed (https://pubmed.ncbi.nlm.nih.gov) databases, microdeletions of various sizes in chromosome 2p15-p16.1 have been reported in 39 patients [5,7], the majority of whom had de novo inheritance. The severity of the phenotype was not related to the size of the CNVs [8].

ID, global developmental delay, hypotonia, speech delay, strabismus, abnormal behavior, craniofacial dysmorphic features (microcephaly, telecanthus, broad nasal root, long philtrum, thin upper lip, low set ear) are heterogenous clinical phenotypes shared by our patient and previously reported cases (Table 1) [8-13]. Although many cases of 2p15p16.1 microdeletion, similar to other microdeletion syndromes, had organ defects such as pre- and post-natal growth retardation, skeletal deformities, and brain abnormalities, our case did not manifest these issues until now. However, because these somatic deteriorations due to genetic causes can express slowly with age, even patients without these phenotypes should undergo routine echocardiography, brain MRI, abdomen sonography, and skeletal x-rays to detect accompanying deformities.

To our knowledge, there have been no reports of thyroid abnormalities in patients with 2p15p16.1 microdeletion. However, our patients had congenital hypothyroidism. His congenital hypothyroidism may have been caused by thyroid dyshormonogenesis and not by ectopic thyroid or thyroid hypoplasia. In an animal model, the *Dnajc17* gene on chromosome 2 was identified as a potential modifier for the organogenesis and function of the thyroid gland: elevated TSH, decreased thyroid hormones, and increased risk of thyroid hemiagenesis. These results revealed that a highly conserved locus on mouse chromosome 2 is associated with susceptibility to congenital hypothyroidism [14]. Additionally, some studies have demonstrated that congenital hypothyroidism is caused by various genetic alterations of chromosome 2p (2p12-2pter), which carry a defective thyroid peroxidase (TPO) [15,16]. However, no known pathologic variants are currently associated with TPO in the 2p15p16.1 region. Further investigation is required for this phenotype.

Previous microarray studies have identified two critical regions in the 2p15p16.1 microdeletion syndrome: 1) the proximal part, 2p15, accounts for *XPO1, SNORA70B*, and *USP34* genes, and 2) the distal part, at 2p16.1, includes the *BCL11A* gene [5,12,17]. The 622 kb deletion region at 2p16.1 in this case involves five protein-coding genes [*BCL11A* (MIM: 606557), *PAPOLG* (MIM: 616865), *REL* (MIM: 164910), *PUS10* (MIM: 612787), and *PEX13* (MIM: 601789)]. Among the five genes, the genes with a high probability of loss of function intolerance (pLI) are *BCL11A* (0.97), *PAPOLG* (1.00), and *REL* (1.00).

According to the SysID database (https://www.sysid.dbmr.unibe.ch/), there are currently 1500 primary and 1248 candidate ID genes [18]. ID-associated genes are enriched for those involved in chromatin remodeling and transcriptional regulation, and the BRG1/BRM-associated factor (BAF) chromatin remodeling complex accounts for over 1% of ID cases [19]. Additionally, mutations in the *BCL11A* gene have been identified in some patients with ID [19].

BCL11A (B cell leukemia/lymphoma 11A) gene, BAF chromatin remodeling complex subunit BCL11A, encodes a C2H2-type zinc-finger protein that is highly expressed in the germinal center of B lymphocytes as well as the fetal brain, especially in the cortex, caudate, hippocampus, and putamen [20,21]. *BCL11A* may play a role in lymphoid malignancy and hematopoiesis by acting as a transcriptional repressor in B cells and regulating primary adult erythroid cells, respectively. BCL11A may also play a critical role in neural development, including axonal branching and neurite outgrowth [7]. Additionally, the hereditary persistence of fetal hemoglobin has been identified in patients with ID syndrome with *BCL11A* mutation [19].

Peter et al. [17] reported a young male with a de novo 203 kb deletion containing a single gene, *BCL11A*. He had generalized hypotonia, childhood apraxia of speech, expressive language delay, mild learning disability, attention deficit without cranial,

skeletal, or internal organ defect, microcephaly, and autism.

Korenke et al. [22] presented a case of a 13-year-old boy with a novel frameshift deletion in the *BCL11A* gene. The patient had well-controlled epilepsy, ID syndrome, and severe language delay. His epilepsy gene panel revealed heterozygous variants in 2 genes, *GRIN2B* and *KDM5C*, encompassing the exon of the *BCL11A* gene. Yoshida et al. [23] also reported a haploinsufficiency of the *BCL11A* gene, which shares major physical features of ID syndrome and intractable epileptic components. Our patient showed abnormal EEG, but no epileptic phenotype was detected.

The *PAPOLG* (poly (A) polymerase, gamma) gene encodes an enzyme that adenylates small RNAs at their 3′ ends, activating endonucleolytic cleavage, the first step of polyadenylation [24]. This gene is expressed in multiple regions of the brain and is involved in basic cellular processing associated with ID [6]. The *REL* (Rel protooncogene, NF-κB subunit) gene encodes c-Rel, a transcription factor of the Rel/NF-κB family responsible for T and B cell function in the immune system [25]. *REL* also plays a role in memory and synaptic plasticity [6].

Hancarova et al. [6] reported a patient with a 0.45 Mb deletion of 2p16.1, which contained the *BCL11A, PAPOLG*, and *REL* genes. This case is highly similar to our patient in terms of locus, defect size, and accompanying genes. At the age of 6 months, she was referred to a geneticist for delayed psychomotor development. The patient displayed microcephaly, facial asymmetry, mild ptosis, telecanthus, strabismus, a wide distance between nipples, hypotonia, growth retardation, and autistic features. Her clinical features gradually progressed and worsened with age. The brain MRI was normal, but the EEG showed abnormal activity.

Lévy et al. [5] studied three patients with the 2p15-p16.1 microdeletion. Patients 1 and 2 had 2p15 microdeletion, whereas patient 3 had 2p16.1 microdeletion. Patient 1 had a 183 kb deletion at 2p15, encompassing the *XPO1, SONRA70B*, and *USP34* genes. The patient miscarried at 34+2 weeks, revealing a short, thin corpus callosum and a short supratentorial measurement. The fetal autopsy revealed hypertelorism, a bulging philtrum, anteverted nostrils, and retrognathia. Patient 2 had an interstitial deletion at 2p15, encompassing *XPO1, SNORA70B*, and *USP34* genes. The patient had a motor delay, feeding difficulty with lactose intolerance, extensive eczema, a large fontanelle, hypertelorism, mild ptosis, a long smooth philtrum, hyperopia, and astigmatism. Brain MRI showed multiple brain malformations, including agenesis of the corpus callosum, the fusion of lateral ventricles, thalami, and hydrocephalus. Patient 3 had an interstitial deletion at 2p16.1, encompassing *BCL11A* and *PAPOLG* genes. He had feeding difficulties due to gastroesophageal reflux at the age of 2 months, hyperlaxity of large joints, developmental delay, and autism spectrum disorder at the age of 4. The brain MRI at 18 months and 4 years showed enlarged lateral ventricles, cortical and subcortical atrophy, and mild cerebellar atrophy. EEG was normal.

In conclusion, we identified a novel, de novo 2p15p16.1 microdeletion in a male infant with ID, dysmorphology, and developmental delay. This is the first case in Korea. To clarify the relationship between involved genes and clinical phenotypes in 15p16.1 microdeletion syndrome, additional patients must be identified using microarrays, and further functional studies must be performed.

Acknowledgements

We thank the patient and his parents for their cooperation. This work was not supported by any funds.

Authors' Contributions

Conception and design: JYC, HHL. Acquisition of data: JYC, TKL. Analysis and interpretation of data: JYC, HHL. Drafting the article: JYC, YMK. Critical revision of the article: JYC, HHL. Final approval of the version to be published: all authors.

References

1. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010;86:749-64.
2. Arican P, Olgac Dundar N, Ozyilmaz B, Cavusoglu D, Gencpinar P, Erdogan KM, et al. Chromosomal microarray analysis in children with unexplained developmental delay/intellectual disability. J Pediatr Genet 2019;8:1-9.
3. Rajcan-Separovic E, Harvard C, Liu X, McGillivray B, Hall JG, Qiao Y, et al. Clinical and molecular cytogenetic characterisation of a newly recognised microdeletion syndrome involving 2p15-16.1. J Med Genet 2007;44:269-76.
4. Shimojima K, Okamoto N, Yamamoto T. Characteristics of 2p15-p16.1 microdeletion syndrome: review and description of two additional patients. Congenit Anom (Kyoto) 2015;55:125-32.
5. Lévy J, Coussement A, Dupont C, Guimiot F, Baumann C, Viot G, et al. Molecular and clinical delineation of 2p15p16.1 microdeletion syndrome. Am J Med Genet A 2017;173:2081-7.

6. Hancarova M, Simandlova M, Drabova J, Mannik K, Kurg A, Sedlacek Z. A patient with de novo 0.45 Mb deletion of 2p16.1: the role of BCL11A, PAPOLG, REL, and FLJ16341 in the 2p15-p16.1 microdeletion syndrome. Am J Med Genet A 2013;161A:865-70.
7. Shimbo H, Yokoi T, Aida N, Mizuno S, Suzumura H, Nagai J, et al. Haploinsufficiency of BCL11A associated with cerebellar abnormalities in 2p15p16.1 deletion syndrome. Mol Genet Genomic Med 2017;5:429-37.
8. Bagheri H, Badduke C, Qiao Y, Colnaghi R, Abramowicz I, Alcantara D, et al. Identifying candidate genes for 2p15p16.1 microdeletion syndrome using clinical, genomic, and functional analysis. JCI Insight 2016;1:e85461.
9. Balci TB, Sawyer SL, Davila J, Humphreys P, Dyment DA. Brain malformations in a patient with deletion 2p16.1: a refinement of the phenotype to BCL11A. Eur J Med Genet 2015;58:351-4.
10. Basak A, Hancarova M, Ulirsch JC, Balci TB, Trkova M, Pelisek M, et al. BCL11A deletions result in fetal hemoglobin persistence and neurodevelopmental alterations. J Clin Invest 2015;125:2363-8.
11. Chabchoub E, Vermeesch JR, de Ravel T, de Cock P, Fryns JP. The facial dysmorphy in the newly recognised microdeletion 2p15-p16.1 refined to a 570 kb region in 2p15. J Med Genet 2008;45:189-92.
12. Fannemel M, Barøy T, Holmgren A, Rødningen OK, Haugsand TM, Hansen B, et al. Haploinsufficiency of XPO1 and USP34 by a de novo 230 kb deletion in 2p15, in a patient with mild intellectual disability and cranio-facial dysmorphisms. Eur J Med Genet 2014;57:513-9.
13. Mimouni-Bloch A, Yeshaya J, Kahana S, Maya I, Basel-Vanagaite L. A de-novo interstitial microduplication involving 2p16.1-p15 and mirroring 2p16.1-p15 microdeletion syndrome: Clinical and molecular analysis. Eur J Paediatr Neurol 2015;19:711-5.
14. Amendola E, Sanges R, Galvan A, Dathan N, Manenti G, Ferrandino G, et al. A locus on mouse chromosome 2 is involved in susceptibility to congenital hypothyroidism and contains an essential gene expressed in thyroid. Endocrinology 2010;151:1948-58.
15. Bakker B, Bikker H, Hennekam RC, Lommen EJ, Schipper MG, Vulsma T, et al. Maternal isodisomy for chromosome 2p causing severe congenital hypothyroidism. J Clin Endocrinol Metab 2001;86:1164-8.
16. Fu C, Xie B, Zhang S, Wang J, Luo S, Zheng H, et al. Mutation screening of the TPO gene in a cohort of 192 Chinese patients with congenital hypothyroidism. BMJ Open 2016;6:e010719.
17. Peter B, Matsushita M, Oda K, Raskind W. De novo microdeletion of BCL11A is associated with severe speech sound disorder. Am J Med Genet A 2014;164A:2091-6.
18. Maia N, Nabais Sá MJ, Melo-Pires M, de Brouwer APM, Jorge P. Intellectual disability genomics: current state, pitfalls and future challenges. BMC Genomics 2021;22:909.
19. Dias C, Estruch SB, Graham SA, McRae J, Sawiak SJ, Hurst JA, et al. BCL11A Haploinsufficiency causes an intellectual disability syndrome and dysregulates transcription. Am J Hum Genet 2016;99:253-74.
20. Satterwhite E, Sonoki T, Willis TG, Harder L, Nowak R, Arriola EL, et al. The BCL11 gene family: involvement of BCL11A in lymphoid malignancies. Blood 2001;98:3413-20.
21. Funnell AP, Prontera P, Ottaviani V, Piccione M, Giambona A, Maggio A, et al. 2p15-p16.1 microdeletions encompassing and proximal to BCL11A are associated with elevated HbF in addition to neurologic impairment. Blood 2015;126:89-93.
22. Korenke GC, Schulte B, Biskup S, Neidhardt J, Owczarek-Lipska M. A novel de novo frameshift mutation in the BCL11A gene in a patient with intellectual disability syndrome and epilepsy. Mol Syndromol 2020;11:135-40.
23. Yoshida M, Nakashima M, Okanishi T, Kanai S, Fujimoto A, Itomi K, et al. Identification of novel BCL11A variants in patients with epileptic encephalopathy: expanding the phenotypic spectrum. Clin Genet 2018;93:368-73.
24. Perumal K, Sinha K, Henning D, Reddy R. Purification, characterization, and cloning of the cDNA of human signal recognition particle RNA 3'-adenylating enzyme. J Biol Chem 2001;276:21791-6.
25. Beaussant-Cohen S, Jaber F, Massaad MJ, Weeks S, Jones J, Alosaimi MF, et al. Combined immunodeficiency in a patient with c-Rel deficiency. J Allergy Clin Immunol 2019;144:606-8.e4.