Open Access

OBM Genetics

LIDSEN Publishing Inc.

Case Report

Interstitial 1p36 Deletion Syndrome Encompassing *CAMTA1* Gene: A Case Report

Nydia Rena Benita Sihombing [1], Nani Maharani [1], Agustini Utari [1, 2], Tri Indah Winarni [1, *]

1. Center for Biomedical Research (CEBIOR), Faculty of Medicine, Universitas Diponegoro, Jalan Prof. Mr. Sunario, Semarang 50275, Indonesia; E-Mails: nydiarbs@gmail.com; maharani.nani@fk.undip.ac.id; agustiniutari@gmail.com; triindahw@gmail.com
2. Department of Pediatrics, Faculty of Medicine, Universitas Diponegoro, Jalan Prof. Mr. Sunario, Semarang 50275, Indonesia

* **Correspondence:** Tri Indah Winarni; E-Mail: triindahw@gmail.com

Academic Editor: Ying S. Zou

Special Issue: Genetic Testing

OBM Genetics
2025, volume 9, issue 1
doi:10.21926/obm.genet.2501284

Received: November 29,2024
Accepted: January 26, 2025
Published: February 05, 2025

Abstract

Deletion of chromosome 1p36 encompassed various genes; however, the role of the *CAMTA1* gene in the 1p36 region is less investigated. We report a child with developmental delay, a history of congenital heart abnormality, self-injurious behavior, nystagmus, and facial dysmorphism. Chromosomal microarray revealed a 257.2 kb deletion of chromosome 1p36.31, with *CAMTA1* as the only involved gene. We explore overlapping clinical features of both chromosome 1p36 deletion and *CAMTA1* intragenic deletion, including intellectual disability/developmental delay, behavior abnormalities, hypotonia, eye problems, and movement disorder. Based on previous studies, our case showed that haploinsufficiency in the first three exons of *CAMTA1* in the CG-1 domain gave rise to movement disorders. Regular follow-up and rehabilitation are paramount to improving a patient's quality of life. Furthermore, parental testing is warranted to determine parental origin and assist in reproductive and genetic counseling.

Keywords
1p36 deletion; behavioral abnormalities; *CAMTA1;* chromosomal microarray; developmental delay

1. Introduction

Chromosome 1p36 deletion is one of the most common terminal deletion syndromes, affecting approximately 1 in 5,000 live births [1]. While pure terminal deletions have been reported in the majority of cases, interstitial deletions are less commonly found in roughly 30% of cases, and the remaining 10% of cases were derivative chromosomes and complex rearrangements [2, 3]. Clinical features of the syndrome vary from developmental delay, intellectual disability, cardiovascular abnormalities, seizures, and vision problems [4].

The majority of cases of 1p36 deletion syndrome are not inherited; there is no history of disorders in the family members. The deletion occurs as a random event/*de novo* due to crossing-over errors in the first meiotic division (eggs or sperm) or in early fetal development for mosaic cases [5]. Determination of the parental origin has been reported that 60% of de novo 1p36 terminal deletions are derived from maternally inherited chromosomes [6, 7]. Besides distinctive facial features (straight eyebrows, deeply set eyes, midface retrusion, wide and depressed nasal bridge, long philtrum, pointed chin, large and late-closing anterior fontanel, micro brachycephaly, epicanthal folds, and low-set, posteriorly rotated, abnormal ears), individuals with 1p36 deletion have global developmental delay and intellectual disabilities [8]. Phenotype variability, but not the severity, is associated with the heterozygous size of deletion and various genes involvement, critical region for the various phenotype have been delineated and reported including *MMP23B, GABRD, SKI, PRDM16, KCNAB2, RERE, UBE4B, CASZ1, PDPN, SPEN, ECE1, HSPG2, and LUZP1* strongly implicated in 1p36 deletion syndrome phenotype [1, 2].

So far, the involvement of the calmodulin-binding transcription activator 1 (*CAMTA1*) gene in 1p36 deletion syndrome is less explored. Deep phenotyping in 1p36 deletion syndrome reported one out of 15 participants with deletion of 400 kb involving *CAMTA 1* gene having mild intellectual disabilities and gait ataxia [9]. The phenotype spectrum in *CAMTA1* pathogenic variants includes developmental delay, cerebellar dysfunction, and behavioral abnormalities [10]. We present an individual with developmental delay, congenital heart defect, and interstitial 1p36 deletion syndrome, encompassing deleted *CAMTA1* gene region.

2. Case Report

A one-year-old male baby came with difficulty feeding, bronchopneumonia, and developmental delay. He has had feeding problems in the last month. The patient is the first child of the family, with both parents aged 25 years. He was born prematurely at 36 weeks with asphyxia and a low birth weight of 1.5 kilograms. The mother had a history of oligohydramnios. The parents recalled no exposure to mutagenic agents. At 2.5 months old (corrected age 1.5 months), he had severe short stature (Height for Age Z score (HAZ): -5.14 SD), underweight (Weight for Age Z score (WAZ): -4.96 SD), and microcephaly (Head Circumference Z score (HCZ): -5.13 SD). On examination, his weight

was 3,795 grams (WAZ: -7.03 SD), length 63 cm (HAZ: -6.01 SD), and head circumference of 37 cm (HCZ: -7.34 SD). The patient had facial dysmorphic features such as microphthalmia, entropion, down-slanting palpebral fissures, malformed and low-set ears, and bulbous nose tip, as seen in Figure 1. He also had mature retinal vessels and nasolacrimal duct obstruction. On extremities, he had congenital talipes equinovarus, clinodactyly, and a single palmar crease on his right hand. Genital examination showed glandular hypospadias. Echocardiography showed atrial septal defect, with spontaneous closure at age 1.5 years.

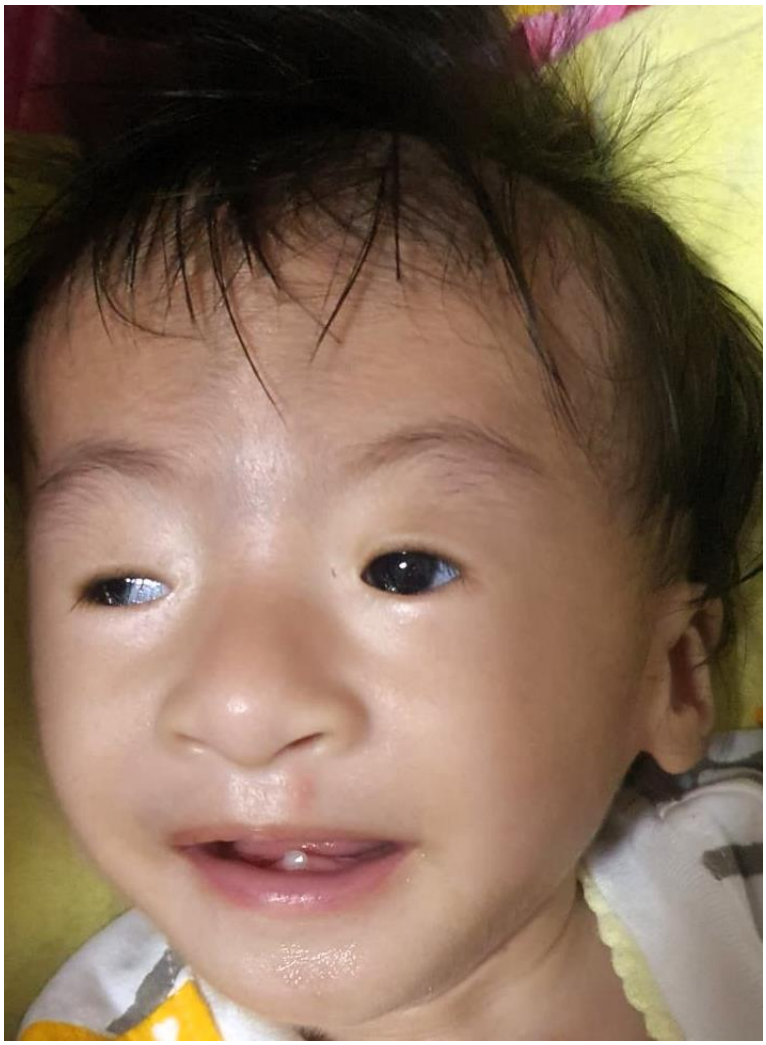

Figure 1 Frontal facial picture of the patient showed dysmorphology of the face, i.e., down-slanting palpebral fissures, strabismus, telecanthus, and bulbous nose tip.

At the last follow-up, he was 1 year and 8 months old. His parents were concerned about self-injurious behavior, and he could not sit alone. He was able to say words without meaning. On physical examination, strabismus and nystagmus were observed. The parents refused to do an MRI examination. Renal sonography showed no abnormality. Routine cytogenetic analysis revealed 46,XY karyotype, with no abnormality seen. Upon chromosomal microarray examination using Human CytoSNP-12 v2.1 Bead-Chip kit chromosomal microarray for NextSeq (Illumina) comprising 301,232 markers, the result showed an abnormal male with a loss of 257.2 kb in chromosome 1p36.31 (arr[GRCh37/hg19] 1p36.31(6,778,583-7,035,830)×1). The only known gene involved in the

deletion of chromosome 1p36 was *CAMTA1*, as shown in Figure 2. Another reported CNV was a 206.5 kb loss in chromosome 2q37.1 (arr[GRCh37/hg19] 2q37.1(235,369,660-235,576,220)×1). The deletion encompassed ADP ribosylation factor-like GTPase 4C (*ARL4C*) gene. This gene was not categorized as a disease-causing gene on the OMIM database [11]. A written informed consent for examination, genetic analysis, and publication has been obtained from the patient's parents.

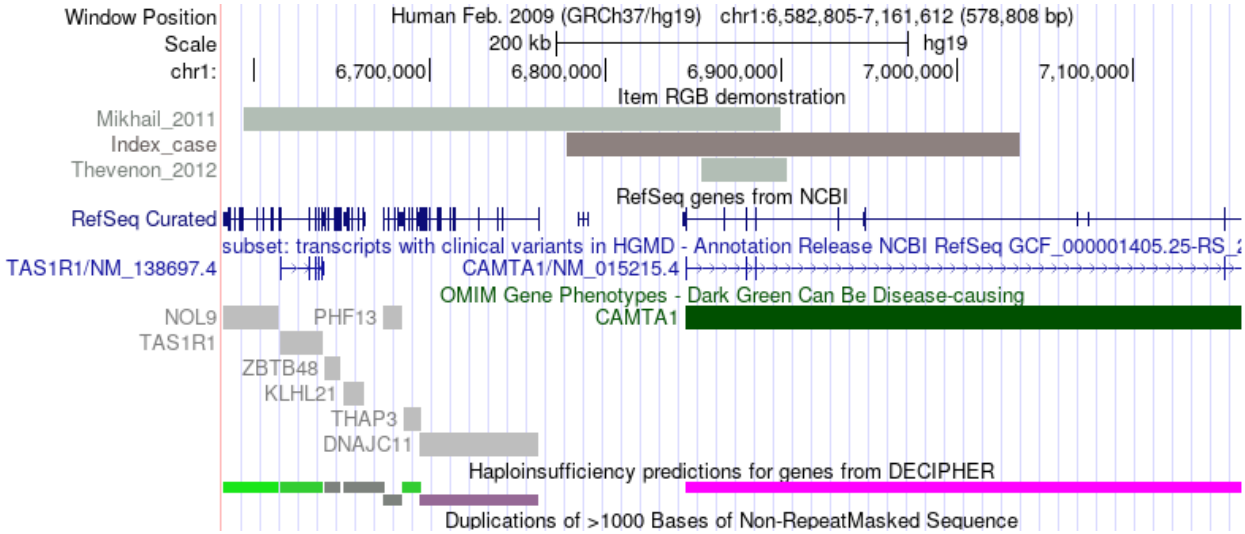

Figure 2 UCSC Genome Browser overview of our case, compared to two other cases involving *CAMTA1* gene [12, 13].

3. Discussion

To our knowledge, we described the first case of 1p36 interstitial microdeletion syndrome in Indonesia, which involved only the *CAMTA1* gene. Interstitial deletion encompasses 10-29% of all 1p36 deletion syndrome cases. Meanwhile, known deletion sizes are highly variable, from as small as 49 Kb up to more than 16 Mb [13, 14]. Some clinical features have been delineated and mapped into critical regions, such as intellectual disability/developmental delay, epilepsy, microcephaly, cardiovascular malformations, and limb abnormalities [3, 9]. The behavioral disorder is one of the characteristics seen in 1p36 deletion patients. Jacquin et al. found that 75% of the individuals with 1p36 deletion syndrome have behavior abnormalities, including aggressivity, self-injurious behavior, temper tantrums, low frustration tolerance, difficulties in social interaction, and stereotypies [3]. Meanwhile, deep phenotyping in 15 Korean patients with 1p36 deletion syndrome showed four individuals with behavioral characteristics, i.e., ADHD, aggressivity, and Rett-syndrome-like symptoms [9]. Table 1 compares previous studies of 1p36 deletion with our patient. Some clinical features were overlapping; however, no history of seizures, gastrointestinal anomalies, or spinal defects was found in our case.

Table 1 Clinical features of patients with 1p36 deletion.

Observed clinical features	**Seo et al., 2016 (n = 5)** [15]	**Shim et al., 2020 (n = 15)** [9]	**Jacquin et al., 2023 (n = 86)** [3]	**Our case**
Developmental delay and/or Intellectual disability	5/5	15/15	75/75	+
Dysmorphism	5/5	13/14	73/78	+
Hypotonia	1/5	n/a	53/63	+
Epilepsy/seizures	1/5	11/15	46/68	-
Growth retardation pre and/or postnatal	2/5	n/a	45/57	+
Brain malformation	2/5	10/12	41/62	n/a
Cardiomyopathy/cardiovascular malformations	4/5	14/14	36/77	ASD closed
Behavioral disorders	n/a	4/15	33/44	+
Hands abnormalities	n/a	7/15	33/51	+
Microcephaly	0/5	n/a	32/57	+
Eye/vision problems	0/5	4/15	28/40	+
Feet abnormalities	n/a	7/15	25/46	+
Gastrointestinal anomalies	1/5	1/15	24/36	-
Spinal defects	n/a	n/a	24/40	-
Joint abnormalities	n/a	n/a	13/31	-
Hearing loss	1/5	4/15	11/31	-
Skin abnormalities	n/a	n/a	11/31	-
Limbs abnormalities	n/a	n/a	9/28	+
Lungs abnormalities	n/a	n/a	8/22	-
Abnormalities of the external genitalia	1/5	4/15	8/27	+
Renal defects	n/a	n/a	6/27	-
Endocrinology/metabolic abnormalities	2/5	2	18	-

Note: ASD = atrial septal defect.

CAMTA 1 gene located at chromosome 1p36.31 encodes a calcium-responsive transcriptional regulator that is highly expressed in the cerebral cortex and cerebellum and plays a central role in the human central nervous system and has been reported to be involved in several processes, including embryonic development, growth control, sensory mechanisms, and memory [10, 16]. Besides, a novel antitumor gene that regulates proliferation and cell cycle in glioma by inhibiting AKT phosphorylation, the alterations in *CAMTA1* indicate that defects (expression, mutations, and rearrangements) in the gene alone are not sufficient to drive carcinogenesis [16, 17]. The *CAMTA1* gene's first three exons deletion, in our case, involved the CG-1 domain, which is responsible for nuclear localization and transcription regulation on neuronal cells. In previous research by Thevenon et al., the analysis suggested that the haploinsufficiency of *CAMTA1* would drive transcriptional misregulation to genes involved with neuronal proliferation and differentiation [13].

Previous studies reported that intragenic *CAMTA1* deletions/haploinsufficiency are associated with a spectrum of neurobehavioral phenotypes such as speech problems, developmental delay (DD), learning disabilities, intellectual disabilities (ID), attention deficit hyperactivity disorder (ADHD), irritability, aggressive behavior, movement disorders (gait ataxia, spasticity, motor weakness/low muscle tone, fine motor difficulties), epilepsy, gastrointestinal problems (gastroesophageal reflux, constipation, hernia), eye problems (strabismus, jerky ocular pursuit), and dysmorphic features include broad forehead, deep set eyes, down slanting palpebral fissure, broad nasal tip, long philtrum, small mouth, pointed chin, prominent and posteriorly rotated ears [18, 19].

Further MRI and PET scan studies on the patient of Thevenon et al. found several brain abnormalities, including cortical atrophy and hypometabolism of the bilateral superior parietal lobes, precuneus, and cuneus, as well as simplified gyration of gyrus dentatus [20]. Furthermore, *CAMTA1* deletion has consequences on the maturation and survival of Purkinje cells of the cerebellum, as observed in the *CAMTA1*-KO mice with ataxia [21]. These findings suggested that *CAMTA1* rearrangement is exclusively involved in giving rise to movement disorder phenotype.

Our patient showed behavioral disorders, i.e., temper tantrums, and when dealing with frustration, he often hit himself on the head or pulled his teeth. Neurobehavioral problems in both 1p36 deletion and *CAMTA1* intragenic deletion are commonly found, thus, management of his behavioral disorders should be addressed to avoid escalating problems. Further, overlapping characteristics of patients with other *CAMTA1*-specific deletions to our case are described in Table 2. All described individuals had brain abnormality from brain imaging, giving a basis to do a CT scan or MRI follow-up in our patient as soon as the parents have consented to.

Table 2 Clinical features of patients with *CAMTA1* deletion.

Observed clinical features	**Wijnen et al., 2020 (n = 4)** [19]	**Dzinovic et al., 2021 (n = 4)** [22]	**Jacobs et al. (n = 9)** [10]	**Shinawi et al. (n = 3)** [18]	**Mikhail et al., 2011** [12]	**Thevenon et al., family 3 (2012)** [13]	**Our case**
Developmental delay and/or Intellectual disability	2/4	3/3	5/7	3/3	+	+	+
Dysmorphism	2/4	n/a	6/7	3/3	-	+	+
Hypotonia	n/a	n/a	7/9	n/a	n/a	+	+
Epilepsy/seizures	n/a	n/a	n/a	1/3	-	-	-
Growth retardation pre and/or postnatal	n/a	n/a	n/a	n/a	n/a	IUGR	+
Brain malformation	1/3	1/3	4/8	3/3	n/a	Normal	n/a
Cardiomyopathy/cardiovascular malformations	n/a	n/a	n/a	n/a	n/a	n/a	ASD closed
Behavioral/neuropsychiatric abnormalities	2/4	2/3	4/7	2/3	+	-	+
Microcephaly	4/4	n/a	n/a	n/a	-	n/a	+
Eye/vision problems	n/a	1/3	5/9	2/3	n/a	n/a	microphthalmia, strabismus
Limbs abnormalities	n/a	n/a	n/a	n/a	n/a	n/a	+
Abnormalities of the external genitalia	n/a	n/a	n/a	n/a	n/a	n/a	+
Movement disorders symptoms	4/4	3/4	5/9	3/3	+	Ataxic gait, dysmetry, instability, dysarthria	Nystagmus
Rearrangement/pathogenic variant type	intragenic deletion, point mutation	intragenic deletion	point mutation	intragenic deletion	microdeletion	intragenic deletion	microdeletion

Note: IUGR = intrauterine growth retardation; ASD = atrial septal defect.

Hypotonia may have contributed to the feeding problems in our patient. Nystagmus was also found to be an early sign of movement abnormalities. Movement disorders and low muscle tone may further complicate an individual's developmental milestones and growth trajectory if malnutrition is observed. Thus, early physical therapy may improve quality of life, especially to help with feeding problems. Additionally, routine evaluation is warranted to observe movement disorder symptoms, seizures, and behavioral issues, to avoid worsening comorbidities. Meanwhile, the prognosis was primarily influenced by the existence of heart defects and the size of the deletion. Mortality data of 1p36 deletion syndrome was obtained from 8 children, with deletion size ranging from 3.7 to 8.3 Mb [3]. For *CAMTA1* rearrangement, most patients reported reaching adulthood [13, 19, 22]. Another critical aspect is parental counseling. Recent research suggested that more than one-third of the *CAMTA1* variants were inherited from an asymptomatic or mildly affected parent, which suggested reduced penetrance and variable expressivity events [23]. Consequently, it is recommended to do parental testing to confirm its inheritance, especially when both parents plan to have another child.

4. Conclusion

This report emphasized a *CAMTA1* deletion of 1p36 syndrome, which gives rise to syndromic developmental delay with behavioral problems, cardiac abnormalities, and movement disorders. Most of the patient's phenotypes were related to the 1p36 deletion syndrome, however, a distinct symptom of movement disorders (i.e., nystagmus) was seen as the basis of *CAMTA1* gene involvement, and we suggest adding *CAMTA1* as the critical gene of movement disorder phenotype of 1p36 deletion syndrome.

Acknowledgments

We are grateful to the patient and his parents for the cooperation to be included in this report. We thank Dr. Lydia Pratanu from National Women and Children Health Center RSAB Harapan Kita Jakarta, Indonesia for the collaboration in the genetic testing for this patient.

Author Contributions

Nydia Rena Benita Sihombing assisted the physical examination and wrote the initial draft of the case report. Nani Maharani assisted the physical examination and article writing. Agustini Utari was the clinician encountered first with the patient, did the physical examination, genetic counseling, and gave feedback to the case report. Tri Indah Winarni coordinated the study, article writing, and finalized the case report. All authors contributed to revision of the draft and approved the final draft.

Funding

This study was supported by the grant from Universitas Diponegoro, Semarang, Indonesia, with the grant number No:118-02/UN7.6.6/PP/2021.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Jordan VK, Zaveri HP, Scott DA. 1p36 deletion syndrome: An update. Appl Clin Genet. 2015; 8: 189-200.
2. Gajecka M, Mackay KL, Shaffer LG. Monosomy 1p36 deletion syndrome. Am J Med Genet C Semin Med Genet. 2007; 145: 346-356.
3. Jacquin C, Landais E, Poirsier C, Afenjar A, Akhavi A, Bednarek N, et al. 1p36 deletion syndrome: Review and mapping with further characterization of the phenotype, a new cohort of 86 patients. Am J Med Genet A. 2023; 191: 445-458.
4. Brazil A, Stanford K, Smolarek T, Hopkin R. Delineating the phenotype of 1p36 deletion in adolescents and adults. Am J Med Genet A. 2014; 164: 2496-2503.
5. Shimada S, Maegaki Y, Osawa M, Yamamoto T. Mild developmental delay and obesity in two patients with mosaic 1p36 deletion syndrome. Am J Med Genet A. 2014; 164: 415-420.
6. Wu YQ, Heilstedt HA, Bedell JA, May KM, Starkey DE, McPherson JD, et al. Molecular refinement of the 1p36 deletion syndrome reveals size diversity and a preponderance of maternally derived deletions. Hum Mol Genet. 1999; 8: 313-321.
7. Heilstedt HA, Ballif BC, Howard LA, Lewis RA, Stal S, Kashork CD, et al. Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. Am J Hum Genet. 2003; 72: 1200-1212.
8. Battaglia A, Hoyme HE, Dallapiccola B, Zackai E, Hudgins L, McDonald-McGinn D, et al. Further delineation of deletion 1p36 syndrome in 60 patients: A recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics. 2008; 121: 404-410.
9. Shim Y, Go YJ, Kim SY, Kim H, Hwang H, Choi J, et al. Deep phenotyping in 1p36 deletion syndrome. Ann Child Neurol. 2020; 28: 131-137.
10. Jacobs EZ, Brown K, Byler MC, D'haenens E, Dheedene A, Henderson LB, et al. Expanding the molecular spectrum and the neurological phenotype related to CAMTA1 variants. Clin Genet. 2021; 99: 259-268.
11. Online Mendelian Inheritance in Man, OMIM®. MIM Number: 604787 [Internet]. Baltimore, MD: Johns Hopkins University; 2020. Available from: https://omim.org/entry/604787.
12. Mikhail FM, Lose EJ, Robin NH, Descartes MD, Rutledge KD, Rutledge SL, et al. Clinically relevant single gene or intragenic deletions encompassing critical neurodevelopmental genes in patients with developmental delay, mental retardation, and/or autism spectrum disorders. Am J Med Genet A. 2011; 155: 2386-2396.
13. Thevenon J, Lopez E, Keren B, Heron D, Mignot C, Altuzarra C, et al. Intragenic CAMTA1 rearrangements cause non-progressive congenital ataxia with or without intellectual disability. J Med Genet. 2012; 49: 400-408.
14. Rocha CF, Vasques RB, Santos SR, Paiva CL. Mini-Review: Monosomy 1p36 syndrome: Reviewing the correlation between deletion sizes and phenotypes. Genet Mol Res. 2016; 15: gmr-15017942.
15. Seo GH, Kim JH, Cho JH, Kim GH, Seo EJ, Lee BH, et al. Identification of 1p36 deletion syndrome in patients with facial dysmorphism and developmental delay. Korean J Pediatr. 2016; 59: 16-23.

16. Alves G, Ornellas MH, Liehr T. The role of Calmodulin Binding Transcription Activator 1 (CAMTA1) gene and its putative genetic partners in the human nervous system. Psychogeriatrics. 2022; 22: 869-878.
17. He Z, Yang C, He Y, Gong B, Yin C, Feng J, et al. CAMTA1, a novel antitumor gene, regulates proliferation and the cell cycle in glioma by inhibiting AKT phosphorylation. Cell Signal. 2021; 79: 109882.
18. Shinawi M, Coorg R, Shimony JS, Grange DK, Al-Kateb H. Intragenic CAMTA1 deletions are associated with a spectrum of neurobehavioral phenotypes. Clin Genet. 2015; 87: 478-482.
19. Wijnen IG, Veenstra-Knol HE, Vansenne F, Gerkes EH, de Koning T, Vos YJ, et al. De novo variants in CAMTA1 cause a syndrome variably associated with spasticity, ataxia, and intellectual disability. Eur J Hum Genet. 2020; 28: 763-769.
20. Magnin E, Blagosklonov O, Sylvestre G, Minot D, Thevenon J, Faivre L, et al. Neuropsychological and neuroimaging phenotype induced by a CAMTA1 mutation. Brain Dev. 2014; 36: 711-715.
21. Long C, Grueter CE, Song K, Qin S, Qi X, Kong YM, et al. Ataxia and Purkinje cell degeneration in mice lacking the CAMTA1 transcription factor. Proc Natl Acad Sci USA. 2014; 111: 11521-11526.
22. Dzinovic I, Serranová T, Prouteau C, Colin E, Ziegler A, Winkelmann J, et al. Myoclonic dystonia phenotype related to a novel calmodulin-binding transcription activator 1 sequence variant. Neurogenetics. 2021; 22: 137-141.
23. Al-Kateb H, Au PY, Berland S, Cogne B, Demurger F, Fluss J, et al. CAMTA1-related disorder: Phenotypic and molecular characterization of 26 new individuals and literature review. Clin Genet. 2024; 105: 294-301.