A de novo variant in CASK gene causing intellectual disability and brain hypoplasia: A Case Report and Literature Review

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Case report

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Abstract

Background The pathogenic variation of CASK gene can cause CASK related mental disorders. The main clinical manifestations are microcephaly with pontine and cerebellar hypoplasia, X-linked mental disorders with or without nystagmus and FG syndrome. The main pathogenic mechanism is the loss of function of related protein caused by mutation. We reported a Chinese male newborn with a de novo variant in CASK gene.

Case presentation We present an 18-day-old baby with intellectual disability and brain hypoplasia. Whole-exome sequencing was performed, which detected a hemizygous missense mutation c.764G>A of CASK gene. The mutation changed the 255th amino acid from Arg to His. Software based bioinformatics analyses were conducted to infer its functional effect.

Conclusions In this paper, a de novo mutation of CASK gene was reported. Moreover, a detailed description of all the cases described in the literature is reported.

CASK mutations cause a variety of clinical phenotypes. Its diagnosis is difficult due to the lack of typical clinical symptoms. Genetic testing should be performed as early as possible if this disease is suspected. This case provides an important reference for the diagnosis and treatment of future cases.

1. Background

CASK gene located in Xp11.4[1] and is an important gene in mammals, which plays a very important role in metabolic regulation and affects the development of postnatal brain[2]. CASK gene mutations cause a wide range of human phenotypes. The pathogenic mutations can lead to CASK related mental disorders. It is reported that CASK gene mutation can mainly lead to these phenotypes: severe intellectual disability, microcephaly with pontine and cerebellar hypoplasia (MICPCH, OMIM:300749) in women. In men, mild to severe X-related mental disorders were observed with or without nystagmus, microcephaly and other malformations, and FG syndrome. The varied clinical phenotypes depend on the types of mutations [3–5].

CASK gene encodes calcium/calmodulin dependent serine protein kinase, which belongs to the membrane associated guanosine kinase (MAGUK) scaffold protein family. MAGUK protein plays an important role in the ionic channel targeting, anchoring and signal transduction of synapses, as well as regulating neural activity. CASK is a special member of p55 subfamily and is the only MAGUK which contains the calcium/calmodulin dependent kinase (CaMK) domain at its N-terminal. CASK protein contains five domains, including two L27 (Lin2, lin7) domains, one PDZ domain and one integrated SH3 and GUK domain [6].

The CASK disorder is rare. ZHANG Yi et al.[7] reported a case of Chinese children in 2019 which is the first one in China. Here, we reported the second case and identified a de novo mutation c.764G>A (p. Arg255His) of CASK gene in China. Bioinformatics software were used to predict the effects of the missense mutation on the function of the CASK protein. Additionally, we reviewed the previously reported cases of CASK gene mutations from different ethnic groups (Table 1), which contained the nucleotide changes, amino acid changes and clinical phenotypes caused by gene mutations[31–46].
| Publication                        | No. | Sex | Age | POP | LOC | Mutation | AAC | TOM | Geno | phenotype |
|-----------------------------------|-----|-----|-----|-----|-----|----------|-----|-----|------|-----------|
| Juliane Najm et al. (2008)        | 1   | F   | -   | -   | -   | -        | -   | -   | -    | MICPCH    |
|                                   | 2   | F   | -   | -   | -   | c.1915C>T | p.(R639*) | Non | Hete | MICPCH    |
|                                   | 3   | F   | -   | -   | -   | c.915G>A  | p. = | Spl | -    | MICPCH    |
| Shin Hayashi, et al. (2008)       | 4   | F   | 5y  | -   | arXp11.4p11.3 (41,500,243–45,480,187) x1 | -   | -   | -    | MICPCH-nystag |
|                                   | 5   | M   | -   | x1  | Ex9 | c.83G>T   | p. (R28L) | Mis | Hemi | FG, ID, hypotor |
| Giulio Piluso et al. (2009)       | 6   | M   | -   | -   | Ex2 | c.829C>T  | p.(Y268H) | Mis | -    | ID        |
| Patrick S Tarpey et al. (2009)    | 7   | M   | -   | -   | Ex27| c.2756T>C | p.(W919R) | Mis | -    | ID, nystag |
|                                   | 8   | M   | -   | -   | Ex8 | c.802T>C  | p. (Y268H) | Mis | -    | ID, epilep  |
| Anna Hackett et al. (2010)        | 9   | F   | 5m  | -   | Ex22| c.2129A>G | p.(D710G) | Mis | -    | ID, nystag |
|                                   | 10  | M   | -   | -   | Ex13| c.1186C>T | p.(W914R) | Mis | -    | ID, nystag |
|                                   | 11  | M   | -   | -   | Ex23| c.2183A>G | p.(P396S) | Mis | -    | ID        |
|                                   | 12  | M   | -   | -   | Ex22| c.2129A>G | p.(D710G) | Mis | -    | ID, nystag |
|                                   | 13  | M   | -   | -   | Ex27| c.173-2A>C | -   | Frs | -    | ID, small  |
|                                   | 14  | M   | -   | -   | Ex8 | c.831+2T>G | -   | Spl | -    | BCH, hy   |
|                                   | 15  | M   | -   | -   | Ex3 | c.1668+1G>A | -   | Spl | -    | BCH, hy   |
|                                   | 16  | M   | -   | -   | Ex5 | c.379C>T  | p.(E127*) | -   | -    | Axial hy peripher |
|                                   | 17  | F   | 10m | Fre | In2 | c.173-2A>C | -   | Frs | -    | ID, small  |
|                                   | 18  | F   | 10m | Fre | In3 | c.1747T>A | p.(D58E) | -   | -    | ID, small  |
|                                   | 19  | F   | 5y  | Bri | In8 | c.831+2T>G | -   | Frs | -    | ID, epilep |
|                                   | 20  | F   | 2y  | Fre | In17| c.1668+1G>A | -   | Spl | -    | BCH, hy   |
|                                   | 21  | F   | 4y  | Ame | Ex5 | c.379C>T  | p.(Q547*) | -   | -    | BCH, hystrabism |
|                                   | 22  | F   | 8y  | Ame | Ex17| c.1639C>T | p.(E127*) | -   | -    | Axial hy peripher |
|                                   | 23  | F   | 10m | Ame | Ex17| c.1639C>T | p.(Q547*) | -   | -    | BCH, hystrabism |

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| Publication | No. | Sex | Age | POP | LOC | Mutation | AAC | TOM | Genotype | phenotype |
|-------------|-----|-----|-----|-----|-----|----------|-----|-----|-----------|-----------|
| Jun-ichi Takanashi et al. (2012) | 24  | F   | 2y4m | Ame | In5 | c.430-2 A > T | -   | Spl | -         | BCH, hy   |
| Lydie Burglen et al. (2012) | 25  | F   | 7y   | Jap | -   | c.173_173 + 1delGG | -   | -   | -         | MICPCH    |
| Lydie Burglen et al. (2012) | 26  | F   | 11y  | Jap | -   | c.2302 + 1 del T | -   | -   | -         | MICPCH    |
| Jun-ichi Takanashi et al. (2012) | 27  | F   | 8y   | Jap | -   | c.1910G > A | p.(G637D) | -   | -         | MICPCH    |
| Jun-ichi Takanashi et al. (2012) | 28  | M   | 2y   | Jap | -   | c.1061T > C | p.(L348P) | -   | -         | MICPCH    |
| Jun-ichi Takanashi et al. (2012) | 29  | F   | 24y  | Jap | -   | c.316C > G | p.(R106*) | -   | -         | MICPCH    |
| Vassili Velayanopoulos et al. (2012) | 30  | F   | 7y   | -   | Ex1-8 | Xp11.4 deletion 0.3 Mb | -   | -   | -         | PCH, ID,   |
| Vassili Velayanopoulos et al. (2012) | 31  | F   | 3y   | -   | Ex1-27 | Xp11.3-p11.4 deletion 3 Mb | -   | -   | -         | ID, DD, c  |
| Vassili Velayanopoulos et al. (2012) | 32  | F   | 14y  | -   | Ex1 | Xp11.4 deletion 0.5 Mb | -   | -   | -         | ID, DD, F  |
| Vassili Velayanopoulos et al. (2012) | 33  | F   | 13y  | -   | Ex21 | c.1968G > A | p.(W656*) | Non | -         | ID, DD, F  |
| Vassili Velayanopoulos et al. (2012) | 34  | F   | 3y   | -   | In21 | c.2040-2 A > G | -   | Spl | -         | ID, DD, c  |
| Vassili Velayanopoulos et al. (2012) | 35  | F   | 1y   | -   | Ex22 | c.2080C > T | p.(Q694*) | Non | -         | ID, DD, F  |
| Vassili Velayanopoulos et al. (2012) | 36  | F   | 1y   | -   | Ex22 | c.2074C > T | p.(Q692*) | Non | -         | ID, DD, c  |
| Vassili Velayanopoulos et al. (2012) | 37  | F   | 10y  | -   | In24 | c.2302 + 5G > A | -   | Spl | -         | ID, DD, c  |
| Vassili Velayanopoulos et al. (2012) | 38  | F   | 14y  | -   | In21 | c.2039 + 1G > T | -   | Spl | -         | ID, DD, F  |
| Vassili Velayanopoulos et al. (2012) | 39  | F   | 8y   | -   | Ex21 | c.1970G > A | p.(W657*) | Non | -         | ID, DD, F  |
| Vassili Velayanopoulos et al. (2012) | 40  | F   | 3y   | -   | Ex15 | c.1501dupA | p.(M501fs) | Frs | -         | ID, DD, F  |
| Vassili Velayanopoulos et al. (2012) | 41  | M   | 15y  | -   | Ex4  | c.[ =/316C > T] | p.(R106*) | Non | -         | ID, DD, F  |
| Vassili Velayanopoulos et al. (2012) | 42  | M   | 13y  | -   | In3  | c.278 + 1G > A | -   | Spl | -         | ID, DD, F  |
| Hirotomo Saitsu et al. (2012) | 43  | F   | 13y  | -   | -   | c.1970G > A | p.(W657*) | -   | -         | MICPCH-difficult |
| Hirotomo Saitsu et al. (2012) | 44  | F   | 8y   | -   | Ex16 | c.1577delG | p.(RS26Fsf-X74) | Frs | -         | MICPCH-spastici |
| Hirotomo Saitsu et al. (2012) | 45  | F   | 13y  | -   | Ex21 | c.1968G > A | p.(W656*) | -   | -         | MICPCH-difficult |
| Hirotomo Saitsu et al. (2012) | 46  | M   | 4y   | -   | Ex2  | (NG_016754.1: g.17883_129055del deletion 111Mb | -   | -   | -         | MICPCH-difficult |
| Hirotomo Saitsu et al. (2012) | 47  | M   | 4y   | -   | Ex1  | c.1A > G | p.(M1V) | Hemi | -         | MICPCH-difficult |

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| Publication                  | No. | Sex | Age  | POP  | LOC | Mutation                      | AAC          | TOM  | Geno | phenotype     |
|-----------------------------|-----|-----|------|------|-----|-------------------------------|--------------|------|------|---------------|
| Shin Hayashi et al. (2012)  | 48  | F   | 2y   | Jap  | Ex2 | c.79C > T                     | p.(R27*)     | Non  | -    | ID, DD, deafness |
|                             | 49  | F   | 2y   | Jap  | -   | c.316C > T                    | p.(R106*)    | Non  | -    | ID, deaf microce |
|                             | 50  | F   | 2y   | Jap  | Ex27| c.2632C > T                   | p.(Q878*)    | Non  | -    | ID, hype      |
|                             | 51  | F   | 11m  | Jap  | Ex3 | c.243_244delTA                | p.(Y811)     | Frs  | -    | microce       |
|                             | 52  | F   | 7y   | Jap  | In4 | c.357-1G > A                  | p.S119Rfs7X, p.H120Rfs22X | Spl  | -    | microce       |
|                             | 53  | F   | 14y  | Jap  | -   | c.2041-1G > C                 | p.W608Cfs29X, p.W608Cfs3X | Spl  | -    | Microce       |
|                             | 54  | F   | 1y   | Jap  | -   | arXp11.4p11.3 (41,009,876–44,100,501) x1 | -     | -    | -    | MICPCH-       |
|                             | 55  | F   | 2y   | Jap  | -   | arXp11.4p11.3 (41,337,795–42,468,013) x1 | -     | -    | -    | MICPCH-       |
|                             | 56  | F   | 12y  | Jap  | -   | arXp11.4 (41,405,593–41,570,391) x3 | -     | -    | -    | MICPCH-       |
|                             | 57  | F   | 2m   | Jap  | -   | arXp11.4 (41,382,179–41,540,922) x3 arXp11.22 (56,012,908–56,275,153) x3 | -     | -    | -    | MICPCH-strabism|
| Nakamura K. et al. (2014)   | 58  | M   | -    | Jap  | Ex3 | c.227_228del                 | p.(E76Vfs*6) | Frs  | Hemi | PCH, TC       |
| JacquesL. Michaud et al. (2014) | 59  | F   | 36m  | -    | Ex2 | c.82C > T                    | p.(R28*)     | -    | -    | ID, cortic   |
| Ute Moog et al. (2015)      | 60  | M   | 7m   | -    | Ex7 | c.704_708del                 | p.(K236Efs*10ex7dn) | Frs  | -    | MICPCH-DD, epile |
|                             | 61  | M   | 10m  | -    | -   | dup ex10–16dn                | -     | -    | -    | MICPCH-DD, epile |
|                             | 62  | M   | 5y   | -    | -   | c.1A > G ex1dn               | -     | -    | -    | MICPCH-DD, epile |
|                             | 63  | M   | 15m  | -    | -   | c.79C > T                    | p.(R27*ex2 dn) | -    | -    | MICPCH-DD, epile |
|                             | 64  | M   | 7m   | -    | -   | dup ex4–20 mos               | -     | -    | -    | MICPCH-DD, epile |
|                             | 65  | M   | 16m  | -    | -   | del ex1mos                   | -     | -    | -    | MICPCH-DD, hyp |
|                             | 66  | M   | 29m  | -    | -   | del ex3–9 mos                | -     | -    | -    | MICPCH-       |

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| Publication                        | No. | Sex | Age | POP | LOC | Mutation | AAC | TOM | Genotype | phenotype |
|-----------------------------------|-----|-----|-----|-----|-----|----------|-----|-----|----------|-----------|
| Tomoshi Nakajiri et al. (2015)   | 67  | M   | 20m | -   | -   | dup ex1–5 mat | -   | -   | Microce  |           |
| Patrick Rump et al. (2016)       | 68  | F   | 13y | Jap | Ex21| c.1896dupC | p.(C633Lfs*2) | Frs | Hete     | MICPCH    |
| Lucía Rivas et al. (2017)        | 69  | F   | 22y | -   | -   | c.2302 + 2T > G | -   | -   | MICPCH    |           |
| Shin Hayashi et al. (2017)       | 70  | F   | 5y  | -   | -   | deletion254.01 Kb | -   | -   | MICPCH    |           |
|                                  | 71  | F   | 1y  | -   | -   | c.868G > T | p.(E290*) | -   | -        | MICPCH    |
|                                  | 72  | F   | 5m  | -   | -   | c.761-762delCT | p.(S246*) | -   | -        | MICPCH    |
|                                  | 73  | F   | 15y | -   | -   | c.1006-1012del ACCTCCT | p.(T336Qfs*23) | -   | -        | MICPCH    |
|                                  | 74  | F   | 4y2m| -   | -   | c.2103delT | p.(F710Lfs*26) | -   | -        | MICPCH    |
|                                  | 75  | F   | 1y  | -   | -   | c.1677dupG | p.(R560Afs*20) | -   | -        | MICPCH    |
|                                  | 76  | F   | 17y | -   | -   | c.2508delT | p.(L837*) | -   | -        | MICPCH    |
|                                  | 77  | F   | 11y | -   | -   | c.1896dupC | p.(C633Lfs*2) | -   | -        | MICPCH    |
|                                  | 78  | F   | 1y  | -   | -   | c.1582 + G > A | -   | -   | MICPCH    |           |
|                                  | 79  | F   | 3y  | -   | -   | c.2302 + 1G > T | -   | -   | MICPCH    |           |
|                                  | 80  | M   | 4y  | -   | -   | c.317G > C | p.(R106P) | -   | -        | MICPCH    |
|                                  | 81  | M   | 2y  | -   | -   | c.1493_1503 + 10delATGAACCAATTGGTAAGTAGGAInsGG | p.(D498Gfs*12) | -   | -        | MICPCH    |
|                                  | 82  | F   | 6y4m| -   | -   | arrXp11.4p11.3 (41,618,898–43,755,475) x1 | -   | -   | MICPCH    |
|                                  | 83  | F   | 4y  | -   | -   | arrXp11.4p11.3 (41,145,925–46,090,321) x1 | -   | -   | MICPCH    |           |
|                                  | 84  | F   | 12y8m| -  | -   | arrXp11.4p11.3 (41,163,139–44,592,980) x1 | -   | -   | MICPCH    |
|                                  | 85  | F   | -   | -   | arrXp11.4 (41,442,660–41,527,850) x3 | -   | -   | Died     |           |
| Bernt Popp et al. (2017)         | 86  | F   | 5y  | Ger | Ex2 | c.68del | p.(F23Sfs*18) | Frs | -        | MICPCH    |
| Stephanie C. DeLuca et al. (2017) | 87  | F   | 54m | -   | -   | c.2221 + 1G > C | -   | -   | MICPCH    |           |
|                                  | 88  | F   | 89m | -   | Ex17| c.1609C > T | p.(R537*) | -   | -        | MICPCH    |

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| Publication | No. | Sex | Age | POP | LOC | Mutation | AAC | TOM | Geno | phenotype |
|-------------|-----|-----|-----|-----|-----|----------|-----|-----|------|------------|
| P. Dunn, et al. (2017) | 89  | F   | 24m | -   | -   | c.106C>T | p.(Q36*) | -   | -    | MICPCH-   |
| Toshiyuki Seto et al. (2017) | 90  | M   | 6y  | Ex26 | c.2521-2 A>G | - | - | - | FG, nyst |
| 91 | M | 5y | - | Ex15 | c.1424G>T | p.(S475I) | Mis | - | microce |
| 92 | F | 3y | - | - | c.1424G>T | p.(S475I) | Mis | - | DD, ACE |
| Babylakshmi Muthusamy et al. (2017) | 93  | M   | 14y & 17y | Ind | - | E550_dup | Stop gain and in-frame insertion | - | Hemi microce clindocae |
| Xiuhua Bozarth et al. (2018) | 94  | F   | - | ME-C | c.2179–2181del GTA | p.(V727del) | Hete | infantile strabism |
| Leslie E. W. LaConte et al. (2018) | 95  | F   | 12y | - | - | c.1556T>C | p.(M519T), | Mis | - | MICPCH-gait ata |
| 96 | F | 5y | - | - | c.1989G>A | p.(G659D) | Mis | Hete | MICPCH-strabism |
| 97 | F | 9y | - | - | c.626T>C | p.(L209P) | - | - | MICPCH-motor d |
| Hiroaki Murakami et al. (2019) | 98  | F   | 5y | - | - | c.2041C>T | p.(R681*) | Non | - | microce |
| Francesca Cristofoli et al. (2019) | 99  | F   | 25y | Eur | - | c.1315-7 A>G | p.(M438-A 439 insH*) | Spl | - | ID, DD, c small cr |
| 100 | F | 21y | Eur | - | c.C109T | p.(Q37*) | Non | - | ID, DD, v |
| 101 | F | 6y | Eur | - | c.T626C | p.(L209P) | Nonsymmetric | - | ID, DD, F |
| 102 | F | 17y | Eur | - | c.2302 + 1 G>A | p.(G741-H768 delinsD) | Spl | - | ID, DD, V |
| ZHANG Yi, et al. (2019) | 103 | M | 3m | Chi | Ex20 | c.1818-1821dup AACT | p.(T608Nfs*16) | Frs | Hemi | MICPCH |
| Presented case (2020) | 104  | M   | 18d | Chi | Ex8 | c.764G>A | p.(R255H) | Mis | Hemi | microce |

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2. Case Presentation
The patient was an 18-day-old male baby, gravida 3, para 1, born in full term with a birth weight of 2790g. The condition of intrauterine distress was unknown, and the history of asphyxia was denied. Crying after birth but slightly weak. Apgar score was unknown. The couple denied the family genetic disease history. The patient was hospitalized in Tianjin Children's hospital mainly due to sucking weakness. When he was fed for the first time after birth, he was not willing to take the initiative to suck. He was fed with a spoon and could swallow. The infant rarely cries and cry weakly, with no fever and hoarseness, moaning and other symptoms. Admission examination: weight 2840g, length 50cm, head circumference 33cm. The child's consciousness was weak and he occasionally had inspiratory laryngitis, hypotonia of the extremities. Holding reflex and embracing reflex were normal, the foraging reflex (±), sucking reflex (±). When he was crying, the corners of his mouth inclined to the left. His left nasolabial groove became slightly shallow along with right hand slightly hanging wrist, right foot slightly turned inward, and his right-hand pass-through palm. Laryngoscope showed that the arytenoid epiglottic folds on both sides were close to each other, and the mucosa was slightly tense. The cricoarytenoid joint were adducted, and the throat entrance was slightly blocked. Head Magnetic Resonance
Imaging(MRI) showed that the bilateral frontal parietal lobes had slightly intense T1 and T2 signal shadows. The extracerebral space was widened, and the posterior angles of bilateral lateral ventricles were widened. Brainstem auditory evoked potential test showed deafness in the left ear and abnormality in the right brainstem. Active electroencephalogram test and cerebrospinal fluid test were normal. Neuroelectrophysiological examination showed that there was no abnormality in facial nerve detection. After admission, the patient was given anti-infective treatment of Latamoxef disodium, expectorant therapy of ambroxol and other symptomatic treatment. Six days after hospitalization, there was no fever in the child and the supplementary feeding became better. The family members required to be discharged from the hospital.

Telephone follow-up at the age of 4–5 months, the symptoms of sucking weakness were slightly better than before. Later, spasms occurred at the age of 6 months and he was diagnosed epilepsy which was characterized by cyanosis of lips and clenching of both hands. After 9 months of oral medication with Sodium Valproate and Topiramate, there was no obvious improvement in condition. At present, the child was 14 months old, with a weight of 6000g. He has microcephaly compared with children of the same age (family members did not measure the head circumference), accompanied by severe developmental delay and intellectual disability. He still can't raise head, speak and walk.

The results of Whole-exome sequencing (WES) showed that there was a hemizygous missense mutation c.764G > A in exon 8 of CASK gene in proband. The mutation changed the 255th amino acid from Arg to His. Because of the gene is located on the X chromosome, the paternal sample of the child does not need to be detected. Sanger sequencing of the child showed that the mutation was not detected in his mother (Fig. 1). The pathogenicity classification of mutations by American College of Medical Genetics (ACMG) guidelines [8] indicated that c.764G > A (p.Arg255His) is of likely pathogenic. The mutation was not found in any public database (HGMD, 1000 Genomes, gnomAD and ESP6500).

Prediction of functional effects of CASK mutation showed the c.764G > A mutation was possibly damaging (Fig. 2). Amino acid sequence alignment showed that the mutation occurred at a highly conserved residue in CASK with surrounding amino acid residues being conserved between orthologs (Fig. 3). Protein structure 3D modeling was performed. It was shown that the mutation (p. Arg255His) had a damaging effect on the CASK protein structure stability (Fig. 4).

3. Discussion And Conclusions

CASK is widely distributed in different brain regions of mice. The insertion mutation and targeted knockout of CASK gene cause the death of mice within 1–2 days after birth. The mice exhibit a cleft palate and apoptosis of thalamic cell increased. The research results indicate the important role of CASK gene in the nervous system [9]. In human fetal tissues, CASK is most expressed in brain, followed by kidney and lung, and the expression level of CASK in brain is 3–5 times higher than other organs [10]. Although CASK is expressed in neurons, it is not limited to neurons. Studies have shown that CASK is widely present in basement membrane, lateral membrane or lateral basement membrane in different epithelial cells [11].

The structure of CASK suggests that CASK plays an important role in signal transduction, intercellular connection, cytoskeleton and binding to membrane proteins[12]. CASK interacts with a variety of cell proteins and plays different roles according to the time and location of expression [13]. Firstly, it is involved in the formation of synapses and the interaction between synapses [14]. For example, CASK regulates axon growth and branch by interacting with Bcl11A[15]. Interaction between CASK and syndecan-2 regulates maturation of dendritic protein [16]. At presynaptic sites, CASK forms compound with MALS/Mint-1/Liprin through its CaMK and L27A domains. This compound is involved in the organization of synaptic vesicles and regulates the release of neurotransmitters[17]. Secondly, CASK involves protein transport of NMDA glutamate receptor and synaptic target of N-type calcium channel. Through its PDZ and SH3 domains, CASK forms targeted interaction and regulation with-neurexin-1 and ion channel synapses in a CDK5-dependent manner. Thirdly, CASK regulating gene expression and neurodevelopment. CASK can enter the nucleus and bind to a specific DNA sequence in the Tbr-1 complex. As a co-activator of Tbr-1, CASK induces the transcription of this sequence, so as to regulate the expression of genes related to the development of cerebral cortex, such as RELN [13]. Protein kinase A phosphorylation regulates the interaction between CASK and Tbr-1 and it is an important regulatory factor of CASK in the nucleus [18]. Y-P30 can control the nuclear localization of CASK in a cell adhesion molecule dependent manner [19]. CASK is involved in many cellular pathways, including mitochondrial, synaptic and protein metabolism. The dysfunction of these cells may be the basis of complex neurological diseases related to CASK dysfunction [20].

In 2008, Najm J et al. first reported the heterozygous deletion and mutation of CASK gene in girls and boys with severe pontine and cerebellar hypoplasia [21]. Since then, 104 pathogenic mutations of CASK gene have been identified through next generation sequence (Table 1). According to these publications, CASK mutations cause a variety of clinical phenotypes. These cases shown that CASK gene does not have a hot mutation site that causes pathogenic clinical phenotype. Inactivated mutation is more common in female patients, and the clinical phenotype is more serious.

MICPCH is a rare X-linked disease, usually seen in women, characterized by neurodevelopmental delay, microcephaly, and pontocerebellar hypoplasia. The main clinical phenotypes of the disease are severe developmental delay or mental disability, microcephaly after birth, often accompanied by slow growth, language development disorders, axial muscle tone reduction with or without increased limb muscle tone, optic nerve hypoplasia and / or other eye abnormalities, such as nystagmus. Patients often have special facial phenotypes including microcephaly, protruding broad bridge and tip of nose, small nose or short nose, small jaw deformity, big ears, with varying degrees of pons and cerebellum hypoplasia and progressive aggravation, as well as hearing loss, epilepsy etc. [22, 23]. There are also some female patients without microcephaly and pontine dysplasia. Bozarth X et al. reported a case of early-onset infantile spasm caused by CASK frame deletion mutation in a girl. Brain MRI showed focal supratentorial brain malformation. EEG showed peak rhythm disorder, but no MICPCH [24].

The relationship between genotype and phenotype of CASK mutation is not clear. CASK inactivating mutations appear to account for the majority of MICPCH cases and with severe phenotypes [25]. It is fatal to men in the prenatal or neonatal period. Najm J et al reported a male child died at 2 weeks after birth. In addition to deletion or duplication mutation, women with MICPCH phenotype also have heterozygous deletion mutations, including nonsense, frameshift and splice site mutations [21]. In general, CASK missense mutation is common in boys with X-linked mental disability. The clinical phenotype is not very serious,
and it is usually asymptomatic in girls. However, Laconte L E W et al. reported three women with CASK missense mutation in heterozygote, and they have severe mental disability, microcephaly and hindbrain hypoplasia [26].

The child in our case was born with weakness sucking, decreased muscle tension of limbs, abnormal face, right hand and right foot deformity, deafness of left ear, epilepsy, microcephaly, serious developmental delay and mental disorder. The results of next generation sequencing showed that there was a hemizygote missense mutation c.764g>G, p. (Arg255His) in exon 8 of CASK gene in children. According to the classification of gene variation by ACMG, the mutation could be classified as likely pathogenic. The patient was a male child with pathogenic missense mutation. Compared with literature reports published, the missense mutation is a de novo variant, and the clinical phenotype of the patient is consistent with the published cases.

MRI of CASK mutation patients showed that the size of the corpus callosum was normal, the proportion of brain/ corpus callosum was low, and the area of brain, pons, midbrain, cerebellar vermis and hemispheres were reduced. Some studies have shown that MRI results of hypoplasia and normal or large corpus callosum in the middle and posterior brain of girls with microcephaly and neurodevelopmental delay should indicate the possibility of CASK mutation, especially in the case of low brain / corpus callosum ratio [27].

In terms of disease diagnosis, WES is a powerful tool for the diagnosis of highly heterogeneous neurodevelopmental disorders [28]. Children with microcephaly will face lifelong psychomotor, cognitive and communication disorders. For this kind of children, their motor development is often delayed for several years, and they are far behind the children of the same age in intelligence and communication ability. These children usually have serious speech disorders. DeLuca SC et al. conducted intensive treatment on three girls with CASK gene heterozygote mutation and MICPCH. Conducting targeted trials to improve fine and coarse motor skills, visual motor coordination, social and communication skills. Studies have shown that MICPCH children respond to intensive therapy aimed at improving function or independence [29]. The therapy can improve the life track and affect the quality of life. CASK is highly conserved in structure. LaConte LE et al. used a high-throughput imaging method to measure the misfolding tendency of CASK mutants, and proved that a chemical chaperone may be helpful to save the misfolding of CASK caused by missense mutations. It providing a possibility for the treatment of structural mutations in the future [30].

In summary, we reported a de novo mutation of CASK gene. Moreover, a detailed description of all the cases described in the literature is reported. All published cases suggest that the mutation of CASK can cause a variety of clinical phenotypes. Its diagnosis is difficult due to the lack of typical clinical symptoms. Genetic testing should be performed as early as possible if this disease is suspected. We believe that this case provides an important reference for the diagnosis and treatment of future cases.

Abbreviations

MICPCH: microcephaly with pontine and cerebellar hypoplasia; MAGUK: the membrane associated guanosine kinase; CaMK: the calcium/ calmodulin dependent kinase; WES: Whole-exome sequencing; ACMG: American College of Medical Genetics; MRI: Magnetic Resonance Imaging

Declarations

Ethics approval and consent to participate

Our article was published with the consent of the child's parents and approved by the Ethics Committee of Tianjin Children's hospital.

Consent for publication

Written informed consent was obtained from the child's parent for the publication of this case report, including any data contained within.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author's Contributions

YL and JBS designed this study and data interpretation. YZ prepared the manuscript. YYN and YM presented the clinical information of the patient and performed literature review. JZ and XWX performed the bioinformatics analyses. FZ provided the clinical treatment and consultation for the patient. All authors read and approved the final manuscript.

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Figures
Electropherograms of Sanger sequencing of the CASK confirming the c.764G>A missense mutation.

Conservation analysis of CASK protein sequences across different species. Amino acid positions of both mutations are highlighted in red box.
Figure 4

Three-dimensional structure model of CASK protein. Native Arg A and mutant His B side-chains at position 255 are shown in blue. The H-bonds are shown in dotted green line.