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.

CAS*K* 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].

Table 1
Summary table of reported *CASK* mutations

Publication	No.	Sex	Age	POP	LOC	Mutation	AAC	TOM	Geno	phenoty
Juliane Najm et.al. (2008)	1	F	-	-	-	-	-	-	-	MICPCH
	2	F	-	-	-	-	-	-	-	MICPCH
	3	F	-	-	-	-	-	-	-	MICPCH
	4	F	-	-	Ex21	c.1915C > T	p.(R639*)	Non	Hete	MICPCH
	5	M	-	-	Ex9	c.915G > A	p.=	Spl	-	MICPCH
Shin Hayashi, et al. (2008)	6	F	5y	-	-	arrXp11.4p11.3 (41,500,243–45,480,187) x1	-	-	-	MICPCH nystagn
Giulio Piluso et al. (2009)	7	M	-	Ita	Ex2	c.83G > T	p. (R28L)	Mis	Hemi	FG, ID, hypotor
Patrick S Tarpey et al. (2009)	8	M	-	-	-	c.829C > T	p.(Y268H)	Mis	-	ID
	9	-	-	-	Ex22	c.2129A > G	p.(D710G)	Mis	-	ID, nysta
	10	-	-	-	-	c.2767C > T	p.(W914R)	Mis	-	ID, nysta
	11	-	-	-	-	c.1188C > T	p.(P396S)	Mis	-	ID
Anna Hackett et al. (2010)	12	M	-	-	Ex22	c.2129A > G	p.(D710G)	Mis	-	ID, nysta
	13	M	-	-	Ex27	c.2756T > C	p.(W919R)	Mis	-	ID, nysta epilepsy
	14	M	-	-	Ex8	c.802T > C	p. (Y268H)	Mis	-	ID, epile
	15	M	-	A-A	Ex13	c.1186C > T	p.(P396S)	Mis	-	ID, unst
	16	M	-	-	Ex23	c.2183A > G	p.(Y728C)	Mis	-	ID, cereb
	17	M	-	-	Ex26	c.2521-2A > T	p.(841_868 and p.841_843 del ALK)	Mis	-	ID, nysta
Ute Moog et al. (2011)	18	F	10m	Fre	In2	c.173-2A > C	-	Frs	-	ID, smal
	19	F	10m	Fre	Ex3	c.174T > A	p.(D58E)	-	-	ID, smal
	20	F	5y	Bri	In8	c.831 + 2T > G	-	Frs	-	ID, epile
	21	F	2y 10m	Fre	In17	c.1668 + 1G > A	-	Spl	-	BCH, hy
	22	F	4y	Ame	Ex5	c.379C > T	p.(E127*)	-	-	Axial hy peripher
	23	F	8y	Ame	Ex17	c.1639C > T	p.(Q547*)	-	-	BCH, hy strabisn

Abbreviations: POP: Population; LOC: Location; AAC: Amino acid change; TOM: Type of mutation; Geno: Genotype; F: Female; M: Male; Ita: Italian; A-A: Africar Bri: British; Ame: American; Jap: Japanese; Ger: German; Ind: Indian; MEC: Mixed-European Caucasian; Eur: European; Chi:Chinese; Ex: Exon; In: Intron; Non: N Mis: Missense; Frs: Frameshift; Hete: Heterozygote; Hemi: Hemizygote; MICPCH: microcephaly with pontine and cerebellar hypoplasia; ID: intellectual disabili delay; FG: FG syndrome ; BCH: brain stem and cerebellar hypoplasia;PCH: pontine and cerebellar hypoplasia; FD: feeding difficulties; OS: Ohtahara syndrome WS: West syndrome; PHPV: persistent hyperplasia of primary vitreous; ASD: autism spectrum disorder.

Publication	No.	Sex	Age	POP	LOC	Mutation	AAC	TOM	Geno	phenoty
	24	F	2y4m	Ame	In5	c.430-2 A > T	-	Spl	-	BCH, hy dyskine
Jun-ichi Takanashi et al. (2012)	25	F	7y	Jap	-	c.173_173 + 1delGG	-	-	-	MICPCH
	26	F	11y	Jap	-	c.2302 + 1 del T	-	-	-	MICPCH
	27	F	8y	Jap	-	c.1910G > A	p.(G637D)	-	-	MICPCH
	28	M	2y	Jap	-	c.1061T > C	p.(L348P)	-	-	MICPCH epilepsy
	29	F	24y	Jap	Ex4	c.316C > G	p. (R106 *)	-	-	MICPCH
Lydie Burglen et al. (2012)	30	F	7y	-	Ex1-8	Xp11.4 deletion 0.3 Mb	-	-	-	PCH, ID,
	31	F	3y	-	Ex 1–27	Xp11.3-p11.4 deletion 3 Mb	-	-	-	ID, DD, c
	32	F	14y	-	Ex1	Xp11.4 deletion 0.5 Mb	-	-	-	ID, DD, F
	33	F	13y	-	Ex21	c.1968G > A	p.(W656*)	Non	-	ID, DD, F
	34	F	3y	-	In21	c.2040-2 A > G	-	Spl	-	ID, DD, c
	35	F	1y	-	Ex22	c.2080C > T	p.(Q694*)	Non	-	ID, DD, F
	36	F	1y	-	Ex22	c.2074C > T	p.(Q692*)	Non	-	ID, DD, e
	37	F	10y	-	In24	c.2302 + 5G > A	-	Spl	-	ID, DD, c
	38	F	14y	-	In21	c.2039 + 1G > T	-	Spl	-	ID, DD, F
	39	F	8y	-	Ex21	c.1970G > A	p.(W657*)	Non	-	ID, DD, F stereoty
	40	F	3y 6m	-	Ex15	c.1501dupA	p.(M501fs)	Frs	-	ID, DD, F stereoty
	41	M	15y	-	Ex4	c.[=/316C > T]	p.(R106*) mos	Non	-	ID, DD, F stereoty
	42	M	13y	-	In3	c.278 + 1G > A	-	Spl	-	ID, DD, F
Vassili Valayannopoulos,et al. (2012)	43	F	13y	-	-	c.1970G > A	p.(W657*)	-	-	MICPCH difficult
	44	F	8y	-	Ex16	c.1577delG	p.(R526Sfs-X74)	Frs	-	MICPCH spastici
	45		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
	47	M	4y	-	Ex1	c.1A > G	p.(M1V)	-	Hemi	MICPCH

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Publication	No.	Sex	Age	POP	LOC	Mutation	AAC	TOM	Geno	phenoty
Shin Hayashi et al. (2012)	48	F	2y 8m	Jap	Ex2	c.79C > T	p.(R27*)	Non	-	ID, DD, deafnes
	49	F	2y	Jap	-	c.316C > T	p.(R106*)	Non	-	ID., deaf microce
	50	F	2y 8m	Jap	Ex27	c.2632C > T	p.(Q878*)	Non	-	ID, hype
	51	F	11m	Jap	Ex3	c.243_244delTA	p.(Y81*)	Frs	-	microce
	52	F	7y 9m	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 9m	Jap	-	arrXp11.4p11.3 (41,009,876–44,100,501) x1	-	-	-	MICPCH
	55	F	2y	Jap	-	arrXp11.4p11.3 (41,337,795–42,468,013) x1	-	-	-	MICPCH
	56	F	12y	Jap	-	arrXp11.4 (41,405,593–41,570,391) x3	-	-	-	MICPCH
	57	F	2m	Jap	-	arrXp11.4 (41,382,179–41,540,922) x3 arrXp11.22 (56,012,908–56,275,153) x3	-	-	-	MICPCH strabisn
Nakamura K. et al. (2014)	58	M	-	-	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, corti
Ute Moog et al. (2015)	60	M	7m	-	Ex7	c.704_708del	p.(K236Efs* 10ex7dn)	Frs	-	MICPCH DD, epil
	61	M	10m	-	-	dup ex10–16dn	-	-	-	MICPCH DD, epil
	62	M	5y	-	-	c.1A > G ex1dn	-	-	-	MICPCH DD, epil
	63	M	15m	-	-	c.79C > T	p.(R27*ex2 dn)	-	-	MICPCH DD, epil
	64	M	7m	-	-	dup ex4–20 mos	-	-	-	MICPCH DD, epil hyperto
	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	Geno	phenoty
	67	M	20m	-	-	dup ex1–5 mat	-	-	-	Microce
Tomoshi Nakajiri et al. (2015)	68	F	13y	Jap	Ex21	c.1896dupC	p.(C633Lfs*2)	Frs	Hete	MICPCH
Patrick Rump et al. (2016)	69	F	22y	-	-	c.2302 + 2T > G	-	-	Hete	MICPCH
Lucía Rivas et al. (2017)	70	F	5y	-	-	deletion254.01 Kb	-	-	-	MICPCH
Shin Hayashi et al. (2017)	71	F	1y	-	-	c.868G > T	p.(E290*)	-	-	MICPCH
	72	F	5m	-	-	c.761-762delCT	p.(S246*)	-	-	MICPCH hypotor
	73	F	15y	-	-	c.1006-1012del ACCTCCT	p.(T336Qfs*23)	-	-	MICPCH DD, hyp
	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 epilepsy
	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 4m	-	-	c.317G > C	p.(R106P)	-	-	MICPCH
	81	M	2y	-	-	c.[=/1493_1503 + 10delATGAACCAATGGTAAGTAGGAinsGG]	p.(D498Gfs*12)	-	-	MICPCH
	82	F	6y4m	-	-	arrXp11.4p11.3 (41,618,898–43,755,475) x1	-	-	-	MICPCH epilepsy
	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 glaucon
	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	phenoty
	89	F	24m	-	-	c.106C > T	p.(Q36*)	-	-	MICPCH
P. Dunn, et al. (2017)	90	M	6y 6m	-	Ex26	c.2521-2 A > G	-	-	-	FG, nyst
Toshiyuki Seto et al. (2017)	91	M	5y	-	Ex15	c.1424G > T	p.(S475I)	Mis	-	microce
	92	F	3y	-	-	c.1424G > T	p.(S475I)	Mis	-	DD, ASD
Babylakshmi Muthusamy et al. (2017)	93	M	14y & 17y	Ind	-	E550_dup	Stop gain and in-frame insertion	-	Hemi	microce clinoda
Xiuhua Bozarth et al. (2018)	94	F	-	ME-C	-	c.2179–2181del GTA	p.(V727del)	-	Hete	infantile strabisn
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 strabisn
	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 ce
	100	F	21y	Eur	-	c.C109T	p.(Q37*)	Non	-	ID, DD, v
	101	F	6y	Eur	-	c.T626C	p.(L209P)	Nonsy-nonym-ous	-	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 27d	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 ID, DD, e

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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 text 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,spasm 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/Liprinα 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 severer 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.764gG > A, 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

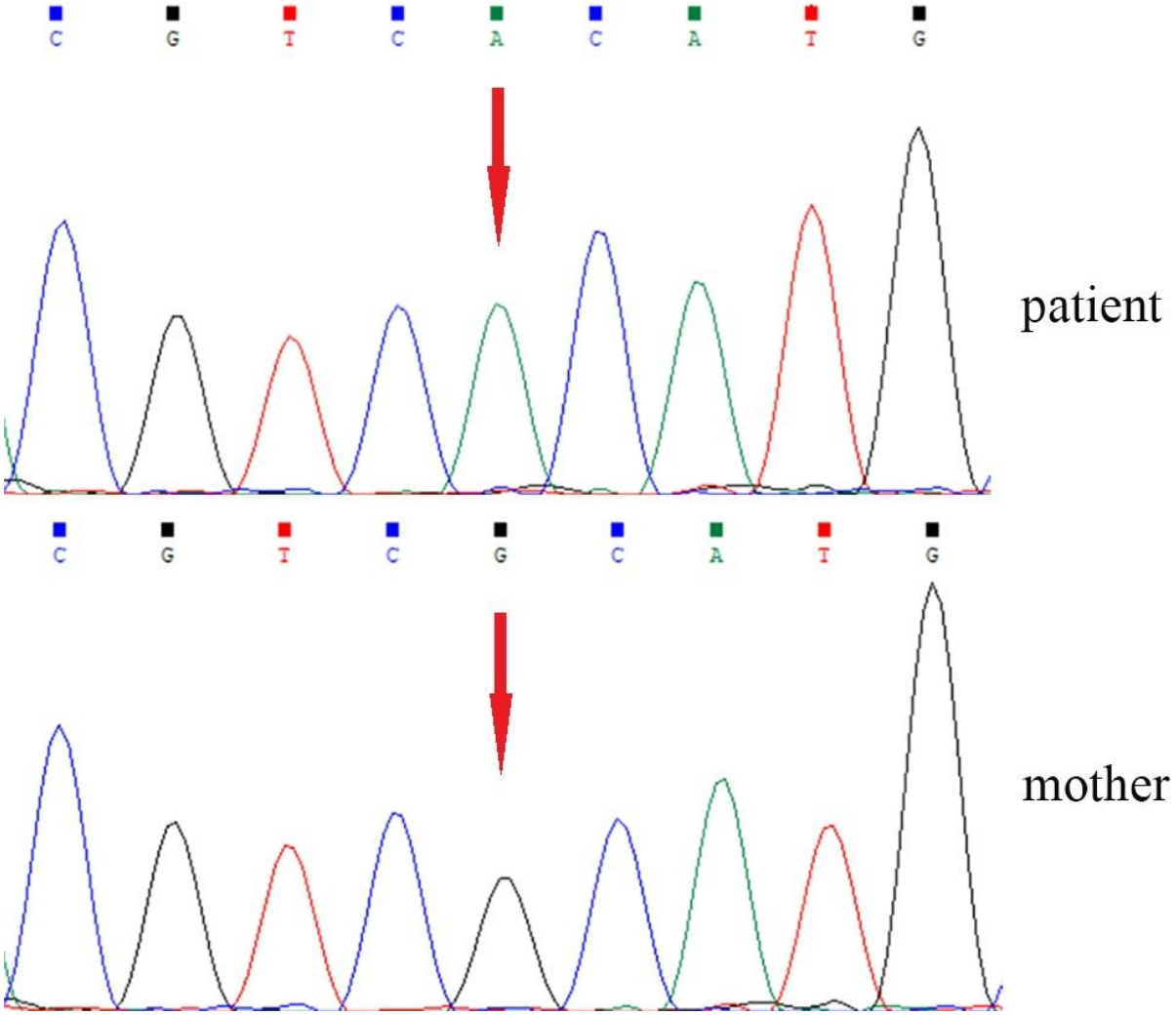

Figure 1

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

Figure 2

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

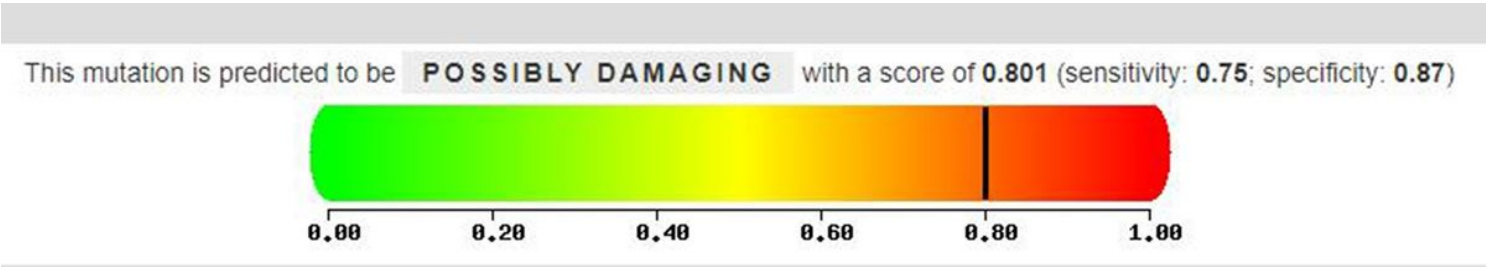

Figure 3

Prediction of functional effects of CASK mutation.

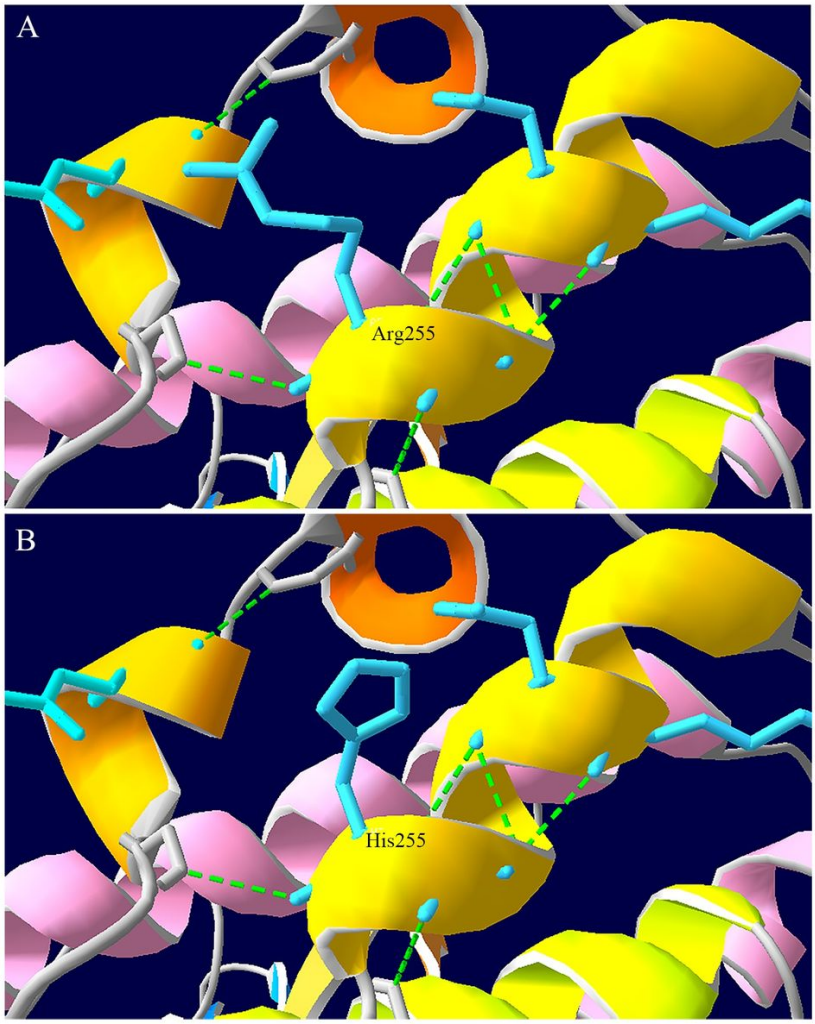

Figure 4

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.