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CASE REPORT

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The first report of primary hypotonia with abnormal electromyogram and *CBS* mutation in a Chinese child

Zhehuan Zhang[1], Suzhen Xu[2], Tianchen Wu[1], Wenwen Xu[1], Bingbing Wu[2] and Chenhao Yang[1*]

Abstract

Background Classic Homocystinuria (HCU) is the second most treatable aminoacidopathy. It affects multiple organs in varying degrees, and early recognition and treatment is crucial to improve the prognosis. Mutations in the *CBS* gene result in classic HCU, the most common form. Genetic testing is important for the accurate diagnosis of this severe disorder.

Method Case report.

Result A 6-year-old boy presented with high myopia, ectopia lentis, and hypotonia. A brain MRI showed no abnormality, and his electromyogram implicated myogenic damage. His serum homocysteine was 277.5 μmol/L (normal ≤ 15 μmol/L), and methionine was 352.56 μmol/L (normal 0–80 μmol/L); thus, he was diagnosed with classic HCU. Compound heterozygous mutations at two different sites on the cystathionine beta-synthase (*CBS*) gene (c.767G > T, c.949 A > G) were identified; the former had not been reported previously.

Conclusions This study reported a novel mutation of *CBS* gene (c.767G > T). To our knowledge, this is the first report of this novel clinical manifestation of primary hypotonia in homocystinuria patients.

Keywords Homocystinuria, Homocysteine, Hypotonia, *CBS* gene, Genetic mutation

Background

The worldwide prevalence of Homocystinuria (HCU) is approximately 0.38/100,000 [1], with considerable differences between ethnic groups. Classic HCU is the most common type of HCU and is the second most common treatable aminoacidopathy after phenylketonuria [2].

Classic HCU is autosomal recessive and caused by an inherited deficiency of cystathionine beta-synthase (*CBS* deficiency, OMIM 236200). It has variant clinical features affecting multiple organs, and the most common manifestations include ectopia lentis, skeletal deformity (Marfanoid features, scoliosis, and osteoporosis), vascular thromboembolic, and intellectual disability [3]. Almost a quarter of untreated patients die before the age of thirty [4], but it is a treatable condition, with early recognition and treatment crucial to improve the prognosis.

Herein, we report a novel mutation of the *CBS* gene and a new clinical manifestation of hypotonia. Our findings may enrich our knowledge of the genotype and phenotype of this severe disease.

*Correspondence:
Chenhao Yang
ychben@hotmail.com
[1]Department of Ophthalmology, National Children's Medical Center-Shanghai, Children's Hospital of Fudan University, Shanghai, China
[2]Center for Molecular Medicine,National Children's Medical Center-Shanghai, Children's Hospital of Fudan University, Shanghai, China

Case presentation

A 6-year-old boy was referred to the ophthalmology outpatient clinic of the Children's Hospital of Fudan University, complaining of blurred vision due to a rapidly progressing myopia (-3.00 DS to about – 10.00 DS in the past 1.5 years). A binocular lens dislocated to the superonasal was detected by ophthalmologic examination (Fig. 1). The visual acuity with his old spectacles was 20/200 in both eyes, with a refractive error of -9.00/-4.50 × 175 in the right eye and – 8.00/-3.50 × 175 in the left eye. The best corrected visual acuity was 20/50 and 20/40 in the right and left eyes.

His serum homocysteine (Hcy) level was 277.5 μmol/L (normal ≤ 15 μmol/L), and methionine was 352.56 μmol/L (normal 0–80 μmol/L). The patient was diagnosed with classic HCU.

A physical examination did not reveal obvious skeletal malformations. His IQ was 72 (normal>70) according to the Wechsler Intelligence Scale for Children in Chinese (WISC-C) [5]. As the boy presented with no clinical manifestations of thrombosis, no further examinations were performed.

The patient was 130 cm tall and weighed 22 Kg, with no apparent marfanoid features. He was prone to occasionally falling when walking and had difficulty jumping as high as the peer average (additional file). His physical examination revealed normal limb muscle strength. On manual palpation of the muscles and passive motion assessment of the joints, the child was found to have mildly decreased muscle tone and joint hyperextensibility. The electromyogram showed a motor unit potential (MUP) with a small, short multiphase in the tibialis anterior, deltoid, biceps brachii, and vastus medialis, as well as normal motor and sensory nerve conduction velocity and amplitude in the detected muscles. The head MRI was unremarkable (Fig. 2).

The child was classified as the B6-nonresponsive type based on the pyridoxine responsiveness test and was treated with vitamin B6 in combination with oral betaine. The patient had low medication adherence, and his serum Hcy level decreased to about 150–200 μmol/L. The symptom of hypotonia did not improve significantly until his last follow-up two years later.

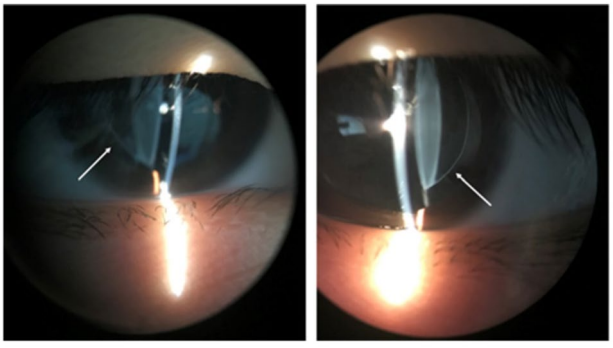

Fig. 1 Slit-lamp examination showed a superonasal displacement of the crystalline lens. The white arrow indicates the edge of the dislocated lens

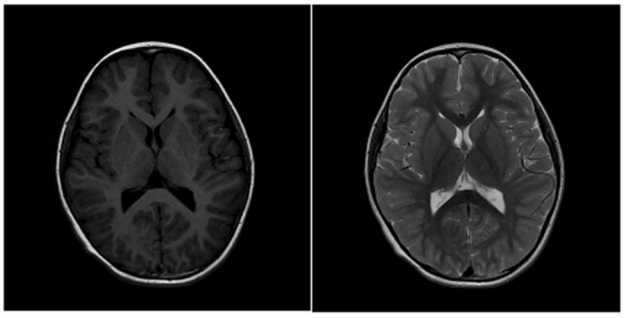

Fig. 2 Brain MRI showed no abnormality

Genetic analysis

The Whole Exome Sequencing (WES) was done in this boy. Two mutations of the *CBS* gene, c.767G > T (p.G256V) in exon 9 and c.949 A > G (p.R317G) in exon 10, were identified by comparison with the *CBS* reference gene (NM_000071.3). The former had not been described previously according to the Human Gene Mutation Database (HGMD®). Sanger sequencing was performed to verify the mutated sites, and the heterozygous mutation (c.767G > T) was also detected in the patient's father (Figs. 3 and 4a and b). However, blood samples of his mother and elder sister had not been collected due to impeded traffic movement during the COVID-19. The heterozygous mutation (c.949 A > G) might theoretically originate from his mother or be de novo. The mutations

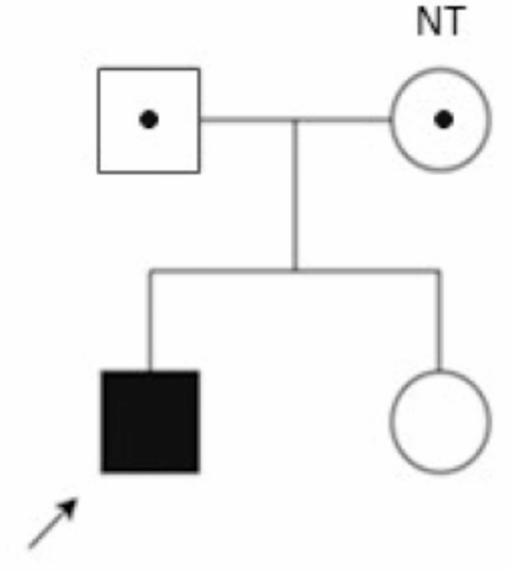

Fig. 3 Pedigree of the family. Black symbols represent affected persons and symbols with a dot are carriers (The mother was a presumed carrier). The proband is indicated by an arrow.NT: not tested

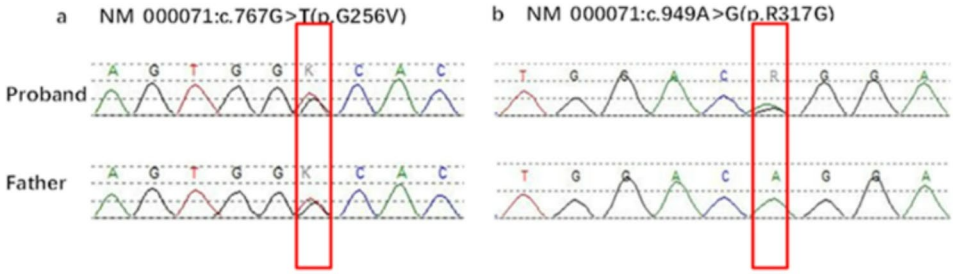

Fig. 4 Sanger sequencing of the patient and his father. The mutation c.767G > T (p.G256V) was from the father

were checked in mutation databases on human populations, including the Human Gene Mutation Database (HGMD®, http://www.hgmd.org), 1000 Genomes database (http://www.internationalgenome.org/), dbSNP database (https://www.ncbi.nlm.nih.gov/snp/), clinvar database (https://www.ncbi.nlm.nih.gov/clinvar/), and ExAC database (http://gnomad.broadinstitute.org). The mutation c.767G > T had not been reported ever before.

The two variant sites were queried in the gnomAD database (v4.1.0). The results showed that the variants were absent from the database, indicating an extremely low or zero frequency in the general population. This provides population-level support for the pathogenicity of the variants. Gene-level constraint for *CBS* was assessed using the ClinGen Dosage Sensitivity Map. The gene has a pLI score of 0 and a LOEUF score of 0.73 in gnomAD, which is is consistent with its autosomal recessive inheritance pattern. The pLI and LOEUF metrics reflect gene-level constraint for loss-of-function variants and do not directly inform the pathogenicity assessment of the specific missense variants reported here.

In silico analyses and structural modeling

The evolutionary conservation of the mutated residues was analyzed with UCSC genome browser (http://genome.ucsc.edu). The protein sequence of human *CBS* (NP_000062.1) was aligned with sequences of the following orthologous proteins: Chimp, Gorilla, Rhesus, Mouse, Cow, Goat, Dog, and Elephant, showing that residues G256 and R317 were conserved among all species aligned (Fig. 5).

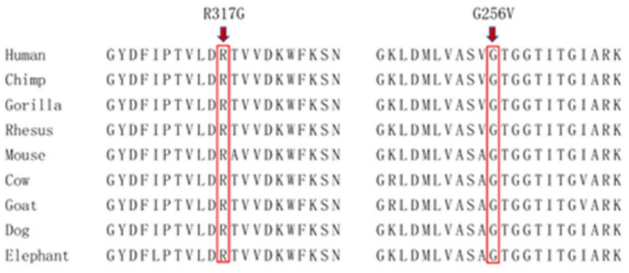

Fig. 5 Orthologous protein sequence alignment of *CBS* from multiple species. Mutated residues R317 and G256 are boxed

Crystal structural models of the wild-type (WT) and mutant *CBS* proteins were conducted with the SWISS-MODEL online server, and the predicted structures were displayed by PyMol software (Version 2.3.0). The crystal structure of the *CBS* WT protein is displayed in Fig. 6a-c. The structural analysis was based on the coordinates of the human *CBS* catalytic core in complex with heme (PDB 1JBQ) [6], which provides the definitive spatial reference for cofactor and residue positions.

The mutant P35520_G256V was made by replacing 256Gly with Val, which turns the residue to pyridoxal 5'-phosphate and occupies more space (Fig. 6d). Residue G256 is located in the immediate vicinity of the pyridoxal 5'-phosphate (PLP) cofactor, which is covalently bound to the active site and indispensable for catalysis [7]. The substitution G256V introduces a larger hydrophobic side chain, predicted to cause steric clash with the surrounding structure, including the PLP-binding pocket. Given that even subtle perturbations near PLP can severely impair *CBS* activity [8], this mutation is strongly predicted to compromise enzymatic function.

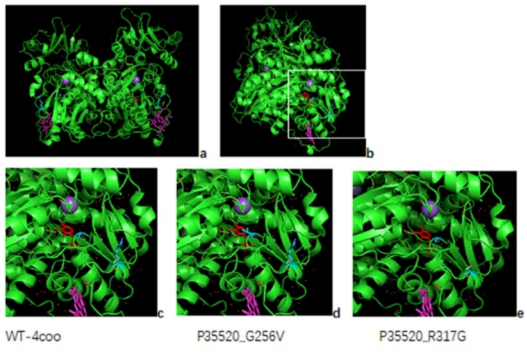

Fig. 6 Demonstration of *CBS* protein structure under changes. The ligands pyridoxal 5'-phosphate and protoporphyrin IX in the *CBS* protein were marked in red and purple, respectively (**a**). To better visualize the key residues at 256 and 317 positions, the model was laterally rotated and the G256 and R317 were marked in the mode of lines and sticks (**b**, **c**). The mutant P35520_G256V was made by replacing 256Gly with Val, which turns the residue to pyridoxal 5'-phosphate and occupied more space (**d**). The mutant P35520_R317G was made by replacing 317Arg with Gly, and thus a sharply released internal space could be seen on the relatively out layer of the model (**e**)

This change may directly influence the activity of *CBS* as pyridoxal PLP is in the reaction center. The mutant P35520_R317G was made by replacing 317Arg with Gly, and thus a sharply released internal space could be seen on the relatively outer layer of the model, which may also influence the structure and activity (Fig. 6e). Residue R317 is positioned closer to the heme (protoporphyrin IX) cofactor than G256, based on the reference structure [6]. The functional role of heme in *CBS*, though not directly catalytic, is considered regulatory and important for redox sensing and stability [9]. The mutation R317G replaces a large, basic arginine with a small, flexible glycine, creating a significant cavity on the protein surface. While neither G256 nor R317 are established as direct heme-liganding residues in the literature, our model suggests that the drastic change at R317 could potentially perturb the local environment of the heme-binding region or affect inter-domain interactions. This structural alteration is hypothesized to influence enzyme stability or regulation.

Results

This study reported a HCU patient presented with hypotonia and abnormal electromyogram. Two different sites on the *CBS* gene (c.767G > T, c.949 A > G) were identified and the former was novel to our knowledge. In silico analyses and 3D structural modeling supported the pathogenicity of the mutations.

Discussion

Homocystinuria was first reported by Carson and Neil in 1962 [10], and their follow-up studies revealed more information about this disease [11, 12]. Classical HCU (OMIM 236200) due to *CBS* deficiency is the most common form of HCU worldwide. In such patients, Hcy and methionine levels are elevated significantly in plasma and urine. The total plasma Hcy level is usually higher than 100 μmmol/L while the methionine level is higher than 50 μmmol/L [13, 14]. The Hcy and methionine levels detected in our patient exceeded this standard; therefore, a diagnosis of classic HCU was made.

Although it was not obvious in our patient, patients with classic HCU usually present with a Marfan-like appearance, such as long limbs and arachnodactyly. The most frequently reported clinical manifestations include ectopia lentis, mental retardation, skeletal abnormalities, and thrombosis [13, 15]. It was reported that ectopia lentis was found in 85% of classic HCU patients [16–19]. Ocular complaints caused by a dislocated lens, such as blurred vision and high myopia, are the earliest detected clinical symptom in 53% of cases [20], and the same was true in our case.

Compared to the common clinical manifestation of HCU, abnormal muscle tone is rare, especially in the absence of thromboembolic disease. Previous studies have revealed that some affected individuals presented with dystonia [21–23], which was usually assumed to be a sign of neurological impairment in patients with cerebrovascular thrombosis. In fact, basal ganglia injury in the MRI scan approved this suggestion [22]. However, some patients present with dystonia while their cranial imaging did not reveal any significant findings [24, 25], possibly because the basal ganglia microinfarct was undetected by MRI [26]. This phenomenon is considered primary dystonia. Muller et al. found that patients with primary dystonia had significantly higher Hcy concentrations compared to healthy controls, which suggested their inner association [27]. Neuronal excitotoxicity of Hcy was another possible contributory factor [28]. The dystonia could be improved by Hcy-lowering vitamin treatments [21], which indicated the possible correlation.

To our knowledge, this is the first report of primary hypotonia in HCU patients [6–9, 11]. The brain MRI showed no abnormality, and his electromyogram implicated myogenic damage. Although the pathophysiological mechanism is not clear, this supports the primary impairment of muscle. Moreover, it has been verified that high plasma Hcy would provoke oxidative stress and promote inflammatory response, which induces decreased muscle mass and muscle function [29, 30] and thus may explain the new clinical manifestation of hypotonia. However, no direct evidence links HCU to primary myogenic hypotonia, and more experimental studies are required to investigate the relationship between HCU and primary hypotonia. However, hypermethioninemia secondary to HCU, in this boy, may also have contributed to his hypotonia. Previous studies have reported that patients with hypermethioninemia due to congenital S-adenosylhomocysteine hydrolase enzy deficiency present with hypotonia [31–34].

The *CBS* gene is located on chromosome 21q22.3 and codes a 63-KD enzymatic protein with 551 amino acids [35]. Some mutations in *CBS* gene would lead to the deficiency of the *CBS* enzyme activity, which is essential for converting homocysteine to cysteine [36]. Pyridoxal phosphate and heme are cofactors for the biochemical activity of *CBS* protein [37–39].

So far, more than 200 *CBS* allelic variants have been reported, and the three most frequent mutations are I278T, G307S, and c.1224–2 A > C [40, 41]. A mutation of the *CBS* gene at two different sites (c.949 A > G, c.767G > T) was found in our case. The c.949 A > G variation was identified previously [42, 43] but c.767G > T was a novel site according to the Human Gene Mutation Database. As a validation, the heterozygous mutation (c.767G > T) was proved in the patient's father. The boy could be determined as having a compound heterozygous mutation according to the ClinGen Sequence

Variant Interpretation Recommendation for in trans Criterion (PM3) - Version 1.0 (https://clinicalgenome.org/working-groups/sequence-variant-interpretation/). The assumption of the two variants being in trans is unconfirmed in the absence of maternal genotype information. Consequently, the strength of the ACMG [44] criterion PM3 applied here is reduced, which should be considered when interpreting the pathogenicity of these variants.

The alignment analysis found the corresponding mutations R317G and G256V located in two evolutionarily conserved sites in the *CBS* enzyme. Furthermore, 3D structural modeling analysis revealed that the two mutations would change the distance between the subunit of the *CBS* protein and its cofactors (pyridoxal phosphate and heme). This structural variation might subsequently affect its transsulfuration activity. Overall, the pathogenicity of the mutations was predicted as likely pathogenic according to ACMG guidelines [44].

Conclusion

Overall, this study reported a new clinical manifestation of primary hypotonia in a Chinese boy with classic HCU. We detected a novel mutation of *CBS* gene in this boy. Further study was required to explore the pathophysiological mechanisms of hypotonia in HCU patients. Whether this novel mutation is associated with this new clinical manifestation is an interesting question and requires further research.

Abbreviations

ACMG	American College of Medical Genetics and Genomics
CBS	Cystathionine Beta-synthase
Hcy	Homocysteine
HCU	Homocystinuria
MRI	Magnetic Resonance Imaging
WT	Wild-type

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Authors' contributions

ZHZ and SZX contributed equally to this work and should be considered as co-first author. ZHZ wrote the paper. SZX analyzed the sequence results and completed in silico analyses. TCW, WWX collected the clinical data. CHY and BBW revised the manuscript. All authors reviewed the manuscript, and approved the final manuscript as submitted.

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Data availability

The data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of The Children's Hospital of Fudan University. Written informed consent was acquired from all participants, including the patient's father legal guardians on behalf of the patient, who is under the age of 16.

Consent for publication

Written informed consent was acquired from the father of the patient for the publication of clinical details and clinical images in this study.

Competing interests

The authors declare no competing interests.

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References

1. Sellos-Moura M, Glavin F, Lapidus D, Kristin E, Lew CR, Irwin DE. Prevalence, characteristics, and costs of diagnosed homocystinuria, elevated homocysteine, and phenylketonuria in the United States: a retrospective claims-based comparison. BMC Health Serv Res. 2020;20:183.
2. Yap S. Classical homocystinuria: vascular risk and its prevention. J Inherit Metab Dis. 2003;26:259–65.
3. Skovby F, Gaustadnes M, Mudd SH. A revisit to the natural history of homocystinuria due to cystathionine beta-synthase deficiency. Mol Genet Metab. 2010;99:1–3.
4. Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genent. 1985;37:1–31.
5. Zhang H. The Revision of WISC-IV Chinese Version. Psychol Sci. 2009;5:1177–9.
6. Meier M, et al. Structure of human cystathionine beta-synthase: a unique pyridoxal 5'-phosphate-dependent heme protein. EMBO J. 2001;20(15):3910–6.
7. Banerjee R, Zou CG. Redox regulation and reaction mechanism of human cystathionine-β-synthase: a PLP-dependent hemesensor protein. Arch Biochem Biophys. 2005;433(1):144–56.
8. Kery V, et al. Binding of pyridoxal 5'-phosphate to the heme protein human cystathionine β-synthase. Biochemistry. 1998;37(39):13461–6.
9. Taoka S, Banerjee R. Characterization of NO binding to human cystathionine β-synthase: possible implications of the effects of CO and NO binding to the human enzyme. J Inorg Biochem. 2001;87(4):245–51.
10. Carson NA, Neill DW. Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland. Arch Dis Child. 1962;37:505–13.
11. Carson NA, Cusworth DC, Dent CE, Field CM, Neill DW, Westall RG. Homocystinuria: a new inborn error of metabolism associated with mental deficiency. Arch Dis Child. 1963;38:425–36.
12. Carson NA, Dent CE, Field CM, Gaull GE. Homocystinuria: clinical and pathological review of ten cases. J Pediatr. 1965;66:565–83.
13. Morris AA, Kozich V, Santra S. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis. 2017;40:49–74. Andria G, Ben-Omran TI, Chakrapani AB, et al.
14. Sacharow SJ, Picker JD, Levy HL. Homocystinuria caused by cystathionine beta-Synthase deficiency. Seattle: GeneReviews. University of Washington; 2017.
15. Levy HL. Early development of newborn screening for HCU and current challenges. Int J Neonatal Screen. 2021;7:67.
16. Abdolrahimzadeh S, Fameli V, Mollo R, Contestabile MT, Perdicchi A, Recupero AM. Rare diseases leading to childhood glaucoma: epidemiology, pathophysiogenesis, and management. Biomed Res Int. 2015;2015:781294.
17. Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilchen B, Pyeritz RE, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet. 1985;37:1–31.
18. Boers GH, Polder TW, Cruysberg JR, Schoonderwaldt HC, Peetoom JJ, Ruyven TW, Smals AG, et al. Homocystinuria versus Marfan's syndrome: the therapeutic relevance of the differential diagnosis. Neth J Med. 1984;27:206–12.
19. Cross HE, Jensen AD. Ocular manifestations in the Marfan syndrome and homocystinuria. Am J Ophthalmol. 1973;75:405–20.
20. Gus PI, Donis KC, Marinho D. Ocular manifestations in classic homocystinuria. Ophthalmic Genet. 2021;42:71–4. Martins TF, de Souza CFM, Carloto RB, et al.
21. Rezazadeh A, Oveisgharan S, Shahidi G, Naghdi R. A case report of homocystinuria with dystonia and stroke. Child Neurol Open. 2014;1:1–3.
22. Berardelli A, Thompson PD, Zaccagnini M, Giardini O, D'Eufemia P, Massoud R, et al. Two sisters with generalized dystonia associated with homocystinuria. Mov Disord. 1991;6:163–5.
23. Sinclair AJ, Barling L, Nightingale S. Recurrent dystonia in homocystinuria: a metabolic pathogenesis. Mov Disord. 2006;21:1780–2.

24. Kempster PA, Brenton DP, Gale AN, Stern GM. Dystonia in homocystinuria. J Neurol Neurosurg Psychiatry. 1988;51:859–62.
25. Aydin S, Abuzayed B, Varlibas F, Apaydin H, Mengi M, Kucukyuruk B, et al. Treatment of homocystinuria-related dystonia with deep brain stimulation: a case report. Stereotact Funct Neurosurg. 2011;89:210–3.
26. Davous P, Rondot P. Homocystinuria and dystonia. J Neurol Neurosurg Psychiatry. 1983;46:283.
27. Muller UJ, Frick B, Winkler C, Fuchs D, Wenning GK, Poewe W, et al. Homocysteine and serum markers of immune activation in primary dystonia. Mov Disord. 2005;20:1663–7.
28. Zoccolella S, Martino D, Defazio G, Lamberti P, Livrea P. Hyperhomocysteinemia in movement disorders: Current evidence and hypotheses. Curr Vas Pharmacol. 2006;4:237–43.
29. Veeranki S, Winchester LJ, Tyagi SC. Hyperhomocysteinemia associated skeletal muscle weakness involves mitochondrial dysfunction and epigenetic modifications. Biochim Biophys Acta. 2015;1852:732–41.
30. Kim J, Kim H, Roh H, Kwon Y. Causes of hyperhomocysteinemia and its pathological significance. Arch Pharm Res. 2018;41:372–83.
31. Baric I, Fumic K, Glenn B, Cuk M, Schulze A, Finkelstein JD, James SJ, et al. S-adenosylhomocysteine hydrolase deficiency in a human: a genetic disorder of methionine metabolism. Proc Natl Acad Sci U S A. 2004;101(12):4234–9.
32. Barić I, Cuk M, Fumić K, Vugrek O, Allen RH, Glenn B, et al. S-Adenosylhomocysteine hydrolase deficiency: a second patient, the younger brother of the index patient, and outcomes during therapy. J Inherit Metab Dis. 2005;28(6):885–902.
33. Shakiba M, Mahjoub F, Fazilaty H, Rezagholizadeh F, Shakiba A, Ziadlou M, et al. Adenosine kinase deficiency with neurodevelopemental delay and recurrent hepatic dysfunction: A case report. Adv Rare Dis. 2016;3:2.
34. Bas H, Cilingir O, Tekin N, Saylisoy S, Durak Aras B, Uzay E, Erzurumluoglu Gokalp E, Artan S. A Turkish patient with novel AHCY variants and presumed diagnosis of S-adenosylhomocysteine hydrolase deficiency. Am J Med Genet A. 2020;182(4):740–5.
35. Kraus JP, Oliveriusova J, Sokolova J, Kraus E, Vlcek C, de Franchis R, et al. The human cystathionine beta-synthase (*CBS*) gene: complete sequence, alternative splicing, and polymorphisms. Genomics. 1998;52:312–24.
36. Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 2: homocystinuria, organic acidurias, and urea cycle disorders. Arch Neurol. 2010;67:148–53.
37. Miles EW, Kraus JP. Cystathionine beta-synthase: structure, function, regulation, and location of homocystinuria-causing mutations. J Biol Chem. 2004;279:29871–4.
38. Banerjee R, Evande R, Kabil O, Ojha S, Taoka S. Reaction mechanism and regulation of cystathionine beta-synthase. Biochim Biophys Acta. 2003;1647:30–5.
39. Majtan T, Singh LR, Wang L, Kruger WD, Kraus JP. Active cystathionine beta-synthase can be expressed in heme-free systems in the presence of metal-substituted porphyrins or a chemical chaperone. J Biol Chem. 2008;283:34588–95.
40. Kruger WD, Wang L, Jhee KH, Singh RH, Elsas LN. Cystathionine beta-synthase deficiency in Georgia (USA): correlation of clinical and biochemical phenotype with genotype. Hum Mutat. 2003;22:434–41.
41. Kaur R, Attri SV, Saini AG, Sankhyan N, Singh S, Faruq M, et al. Seven novel genetic variants in a North Indian cohort with classical homocystinuria. Sci Rep. 2020;10:17299.
42. Shang K, Li H, Luo X. Cerebral venous sinus thrombosis due to hyperhomocysteinemia with cystathionine-β-synthase (*CBS*) gene mutation: a case report. Med (Baltim). 2019;98:e14349.
43. Yi C, He J, Xu J, Zhang X, Huang J. Homocystinuria in a family with novel cystathionine beta synthase Gene mutations. Clin Lab. 2021;67:402-5.
44. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.

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