

The first CDC42 variant (p.Arg68Gln) associated with Takenouchi-Kosaki syndrome in Asia: a case report and literature review

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Case Report

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Abstract

This study reports the first Asian pediatric patient harboring the de novo heterozygous *CDC42* variant (c.203G > A, p.Arg68Gln), a globally ultrarare variant with limited clinical and genetic data. The proband presents with typical manifestations of Takenouchi-Kosaki syndrome (TKS), a rare multisystem neurodevelopmental disorder, including severe growth retardation, characteristic craniofacial dysmorphism, persistent thrombocytopenia and progressive sensorineural hearing loss. Recombinant human growth hormone (rhGH) therapy was initiated for the proband. A literature review is performed to further understand this rare variant and improve its clinical recognition. This case fills the ethnic data gap for the *CDC42* p.Arg68Gln variant, enriches its clinical and genetic spectrum, and provides evidence for the early clinical identification, individualized management and targeted genetic counseling.

Background

Cell division cycle 42 (*CDC42*) gene, a vital small GTPase belonging to the Rho family, functions as a central molecular switch in the physiological regulatory network of the human body[1]. It precisely modulates a series of core cellular life activities through the dynamic cycling between the GTP-bound active and inactive state, coupled with specific binding and interactions with over 45 downstream effector proteins[2, 3]. The functional homeostasis of *CDC42* is essential for maintaining multiple critical biological processes during embryonic development, including tissue and organ morphogenesis, cell proliferation and differentiation, cytoskeleton remodeling, cell migration, and apoptosis[4, 5]. Particularly, *CDC42* plays an indispensable regulatory role in embryonic development, morphogenesis, and functional maturation of the nervous system, hematopoietic system, craniofacial skeleton, and multiple vital organs throughout the body[6].

Pathogenic variants in *CDC42* directly alter the amino acid sequence and three-dimensional structure of the encoded protein, disrupting GTP-GDP cycle homeostasis and binding affinity with downstream effector proteins. These alterations subsequently impair cellular signal transduction, perturbing normal embryonic tissue and organ development and ultimately resulting in multiple clinical manifestations, including neurodevelopmental abnormalities, growth retardation, immunodeficiency, and thrombocytopenia[7, 8]. According to differences in variant locations in protein structural domains, distinct functional impairment mechanisms, and clinical phenotypic characteristics, *CDC42* variants can be categorized into three types: Type I includes three variants located in the *CDC42* switch II domain (p. Tyr64Cys, p. Arg66Gly, and p. Arg68Gln). These variants are predicted to impair GTPase catalytic activity and signal transmission ability, which may further disturb platelet activation and present with platelet abnormalities primarily[6, 9, 10]. Type II mainly occurs at the nucleotide-binding pocket site (Ala159) of *CDC42* or adjacent regions (Cys81 and Ser83). These alterations impair GTP-binding affinity and GTP hydrolysis activity, resulting in constitutive hyperactivity of GTPase[6]. This abnormal activation may disturb the survival, proliferation, actin cytoskeleton remodeling and migration of neural crest-derived cells, ultimately leading to severe and typical craniofacial malformations[11–13]. Type III includes I21T, Y23C and E171K variants, which locate in amino acid residues critical for the interaction between *CDC42* and effector proteins containing the *CDC42*/Rac-interacting binding motif. Clinically, this type exhibits phenotypes highly reminiscent of Noonan syndrome[6, 7, 14].

To date, no de novo missense variant of *CDC42* Type I p.Arg68Gln has been documented in Asian populations. The phenotypic spectrum associated with this rare variant remains poorly defined and incompletely elucidated.

Takenouchi-Kosaki syndrome (TKS) is a rare congenital multisystem developmental disorder caused by de novo pathogenic *CDC42* variants, clinically characterized by macrothrombocytopenia, distinctive craniofacial dysmorphism, growth retardation, lymphatic abnormalities and variable neurodevelopmental delays[8].

On this basis, this study reports the first Asian pediatric patient of TKS carrying the de novo *CDC42* p.Arg68Gln variant. By correlating genetic characteristics with multimodal clinical manifestations, our findings enrich the clinical and genetic repository of the *CDC42* p.Arg68Gln variant, fill the ethnic data gap and provide critical references for early clinical recognition, management and targeted genetic counseling.

Case Presentation

The proband was delivered via cesarean section at term, and the mother had gestational hypertension during pregnancy. The patient had a birth weight of 2500 g and a birth length of 50 cm, and was diagnosed with congenital deafness and congenital atrial septal defect (Fig. 1). She presented with significant developmental delay, including crawling at 1 year of age and independent walking at 2.5 years of age, accompanied by intellectual disability. Her academic performance and motor skills were markedly impaired. Her elder sister and brother had normal growth and development consistent with typical peers. The paternal height was 169 cm and the maternal height was 156 cm. The family had no relevant hereditary or chronic disease history. The patient underwent cochlear implantation at the age of 6 years and 10 months.

She presented to the pediatric department at 11 years of age due to short stature, with a height of 123.7 cm (– 3.47 SD). Her annual growth rate was unknown. Physical examination revealed characteristic facial dysmorphic features, including hypertelorism, depressed nasal bridge, widened nasal alar, high-arched palate, micrognathia, malocclusion, and thick lips, as well as low-set ears, slender fingers and camptodactyly. Laboratory tests showed a reduced IGF-1 level of 174.7 ng/mL (– 2.0 SD). Routine blood tests indicated thrombocytopenia, with a platelet count of $88 \times 10^9/L$ and a slightly elevated platelet-large cell ratio (P-LCR). Breast ultrasound indicated normal pubertal development. Brain MRI confirmed a right-sided cochlear implant. ECG revealed sinus arrhythmia. Spinal X-ray showed mild lumbar dextroscoliosis. No remarkable abnormalities were identified in other examinations, including biochemistry, liver function, cortisol, corticotropin, tumor markers, fasting insulin, infection screening, and urine analysis.

In the exploration of the genetic etiology underlying the patient's short stature and developmental deformities, whole-exome sequencing (WES) was performed. A missense variant within the coding region of the *CDC42* gene (c.203G > A, p.Arg68Gln) was prioritized for further analysis, with a REVEL prediction score of 0.827 (PP3). This missense variant was absent from the large population frequency database gnomAD v2.1.1 (PM2) and was confirmed

to be de novo via Sanger sequencing. To date, only two individuals harboring this variant have been reported, with clinical phenotypes similar to the proband. Functional studies have demonstrated that the p.Arg68Gln variant disrupts the switch II domain of *CDC42*, causing GTPase activity dysregulation and impaired effector binding, thereby affecting cell migration, proliferation, and development (PM6+PS3_Supporting)[15]. According to the American College of Medical Genetics and Genomics (ACMG) criteria[16], this variant was classified as likely pathogenic (PP3 + PM2+PM6+PS3_Supporting).

Two heterozygous variants were identified in the *GJB2* gene (c.235del, p.Leu79Cysfs*3; c.109G > A, p.Val37Ile). These variants were confirmed to be strongly associated with hearing loss and were categorized as pathogenic variants[15, 17–22].

After thorough exclusion of contraindications and obtaining informed consent from the patient's guardians, recombinant human growth hormone (rhGH) therapy was initiated for the proband. Regular follow-up was scheduled to assess growth and developmental outcomes, monitor drug safety, and evaluate serial platelet counts.

Discussion and conclusions

The present study comprehensively delineate the clinical profiles and genetic molecular characteristics of a pediatric patient affected by TKS, a rare neurodevelopmental genetic disorder harboring the pathogenic rare missense variant c.203G > A (p.Arg68Gln) in the *CDC42* gene. To our knowledge, this case is among the limited number of globally reported individuals carrying this specific variant.

TKS, first described in 2015, may exhibits severe developmental delay, dysmorphic facial features, camptodactyly, sensorineural deafness, neurodevelopmental delay and multiple hematological abnormalities including macrothrombocytopenia, lymphopenia, anemia and leukopenia[8, 23–25]. Genetically, the *CDC42* missense variant (c.191A > G p.Tyr64Cys) represents the most prevalent variant in TKS cohorts, while other Type I variants in *CDC42* have only been sporadically documented in clinical practice[8]. The *CDC42* variant (c.203G > A, p.Arg68Gln) identified in the proband is classified as a Type I pathogenic variant, providing a robust genetic foundation for the confirmed TKS diagnosis. Previous research have verified that substitution of Arg68 with Gln significantly disrupts the physiological activation-inactivation cycle of the *CDC42* GTPase[26]. Such functional aberration may impairs intrinsic GTPase catalytic activity and further disturbs multiple downstream physiological processes, encompassing hematopoiesis, neurodevelopment, auditory function, and immune homeostasis[6, 24, 26–28].

Currently, only two cases carrying the identical *CDC42* variant (c.203G > A, p.Arg68Gln) have been reported worldwide, with their baseline information and phenotypic features summarized in Table 1[6, 29]. Comparative analysis reveals that all affected patients present consistent clinical manifestations, including thrombocytopenia, typical craniofacial and somatic dysmorphic features (broad nasal bridge, low-set ears, flared nostrils and mandibular prognathism), short stature, and sensorineural hearing loss (Fig. 2). The high phenotypic consistency across affected individuals fully conforms to the typical clinical manifestations of TKS, demonstrating that the *CDC42* p.Arg68Gln variant may confer a genetic predisposition to the canonical TKS clinical phenotype.

Table 1
Clinical manifestations and treatment of individuals of CDC42 p.Arg68Gln variant

Reference	Patients	Hematological Manifestations	Neurological Manifestations	Growth and Development	Other Manifestations	Dysmorphic Features	Therap
Case 1 Martinelli et al. 2018	Male, age unreported	Macrothrombocytopenia	Sensorineural hearing loss, cognitive deficit. The brain MRI revealed mildly prominent periventricular white matter signal intensities (predominantly posteriorly), ventriculomegaly and increased extra-axial space.	Last evaluation at 4 years old: weight 13 Kg (< 3rd percentile, -2.4 SD), height 93 cm (< 3rd percentile, -2.29 SD) and occipitofrontal circumference 49 cm (< 3rd percentile)	Hypertrophic cardiomyopathy, congenital pulmonary emphysema, OSAS, recurrent maculopapular rash, gastrointestinal bleeding, periodic fever, polyserositis and splenomegaly	Sparse hair with whorls, prominent forehead, epicanthal folds, wide nasal bridge, flared nostrils with a broad nasal tip, long philtrum, an under developed midface, thick ears and a webbed appearance of the neck	Cortic
Case 2 Stubbs et al. 2021	Male, 17 years old	Chronic macrothrombocytopenia	Asymptomatic external hydrocephalus, bilateral sensorineural hearing loss	Global developmental delay, short stature	Recurrent inguinal hernia, OSAS, congenital lobar emphysema (left lower lobectomy was performed)	Biparietal prominence, high forehead, upslanting palpebral fissures, low-set ears with thick helices, a long and smooth philtrum, a thin upper lip, midface hypoplasia, and mandibular prognathia. limited abduction of the shoulders, limited extension of the elbows, camptodactyly of the 5th digits, decreased rotation of the hips, severe thoracic dextroscoliosis and a leg length discrepancy	Surgical of teth cord syndro periop Corticc
Case 3 Current case	Female, 11 years old	Thrombocytopenia	Sensorineural hearing loss, weakened academic performance. Cranial MRI was limited due to severe artifacts from the cochlear implant.	Global developmental delay, short stature: height 123.7 cm (< 3rd percentile, -3.47 SD)	Congenital atrial septal defect	Hypertelorism, depressed nasal bridge, widened nasal alar, high arched palate, micrognathia, malocclusion, thick lips, lowset ears, slender fingers, camptodactyly, mild right lumbar scoliosis	Short-a growth hormoi

Additionally, previously reported cases exhibited heterogeneous and life-threatening multisystem complications beyond typical phenotypic characteristics. Specifically, one patient presented with hydrocephalus and congenital lobar emphysema, indicating that *CDC42* dysfunction may disturb the normal embryonic development and differentiation of neuroepithelial tissues and pulmonary mesenchyme[29]. Another case presented with necrotizing enterocolitis, pancytopenia, and hemophagocytic lymphohistiocytosis (HLH)-like manifestations, suggesting this pathogenic variant may trigger excessive inflammation and phagocytic activation in hematopoietic stem cells and immunocyte[6]. Collectively, these severe multisystem complications underscore the necessity of long-term standardized systematic monitoring of immune, respiratory, and hematological functions for lifelong clinical follow-up and personalized management of TKS patients harboring this specific variant.

With regard to the hematological phenotype of the present proband, the patient exhibited thrombocytopenia accompanied by a mild elevation in the proportion of large platelets, without any clinical manifestation of spontaneous bleeding. Given that the exact bleeding risk threshold of thrombocytopenia in TKS remains undefined and no unified clinical consensus has been established, regular dynamic monitoring of platelet count and hemoglobin concentration is highly recommended during long-term follow-up, with close surveillance for potential occult bleeding events such as mucosal hemorrhage and gastrointestinal bleeding.

Beyond the pathogenic *CDC42* variant, the proband also carried susceptibility variants in the deafness-associated *GJB2* gene, indicating that her sensorineural hearing loss likely arose from the synergistic pathogenic interaction between *CDC42* and *GJB2* variants[30].

Severe persistent growth retardation constituted the most prominent clinical concern for the proband, whose height was significantly below the age-matched normal reference range and had induced notable psychological anxiety and low self-esteem. Therefore, timely and targeted clinical intervention for growth retardation is both medically essential and psychologically necessary. At present, no standardized clinical guidelines or approved therapeutic indications are available for short stature associated with *CDC42* pathogenic variants. In comparison, short stature caused by *PTPN11* variants has been well recognized as a standard indication for rhGH replacement therapy[31]. Notably, both *CDC42* and *PTPN11* participate in the regulation of the MAPK signaling pathway, which plays an indispensable regulatory role in skeletal growth and bone development[32–35]. In view of the shared core signaling regulatory mechanism and the significant psychosocial burden induced by long-term severe short stature in the proband, off-label rhGH treatment was cautiously attempted after thorough exclusion of all contraindications. Regular follow-up will be continuously conducted to systematically evaluate the growth-promoting efficacy and safety profile. This exploratory clinical practice is expected to accumulate preliminary real-world clinical evidence for the off-label application of rhGH in pediatric patients with *CDC42*-related growth retardation, and provide a practical reference for the standardized clinical management of this type of variant. However, long-term follow-up data in the future are still required for validation.

In conclusion, this study reports the first Asian patient with TKS harboring the *CDC42* p.Arg68Gln variant. It enriches the Asian genetic spectrum of TKS and provides valuable evidence for clinical diagnosis, genetic counseling and individualized management of this rare disorder and variant. Further larger-sample investigations are required to elucidate the underlying mechanisms of genotype-phenotype correlations.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

XXL collected data, conceptualized the study, did the literature research, wrote the manuscript, and proof read the manuscript. YYS and JCX collected the medical data, proof read and commented on the manuscript. HL was the main treating physician of the patient, got the consent from the parents, followed up the patient. Thank all authors for the contributions above.

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Data availability

The datasets for this article are not publicly available due to concerns regarding participant/patients anonymity. Requests to access the datasets should be directed to the corresponding author. The parents disagree to publish the patient's appearance picture.

Ethics approval and consent to participate

The ethics approval of The First Affiliated Hospital of Guangzhou University of Chinese Medicine was obtained (JY2026-054). Written informed consent was provided by parents of the child for publication of this manuscript.

Consent for publication

Written informed consent for publication of this case report was obtained

from the child's parents.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

References

1. Murphy NP, Mott HR, Owen D. Progress in the therapeutic inhibition of Cdc42 signalling. *BIOCHEM SOC T*. 2021;49:1443–56.
2. Brakebusch C. Rho GTPase Signaling in Health and Disease: A Complex Signaling Network. *CELLS-BASEL*. 2021;10:401.
3. Heasman SJ, Ridley AJ. Mammalian Rho GTPases:: new insights into their functions from in vivo studies. *NAT REV MOL CELL BIO*. 2008;9:690–701.

4. Etienne-Manneville S, Hall A. Rho GTPases in cell biology. *Nature*. 2002;420:629–35.
5. Nagahama R, Yamada A, Tanaka J, et al. Rho GTPase protein Cdc42 is critical for postnatal cartilage development. *BIOCHEM BIOPH RES CO*. 2016;470:813–7.
6. Martinelli S, Krumbach OHF, Pantaleoni F, et al. Functional Dysregulation of CDC42 Causes Diverse Developmental Phenotypes. *AM J HUM GENET*. 2018;102:309–20.
7. Yasumi T. CDC42 missense mutations and human diseases: from neurodevelopmental disorders to autoinflammation. *J Biochem*. 2025;178:73–8.
8. Caragli V, Genovese E, Parretta S, Pellegrino M, Ciorba A. Auditory and Language Abilities in Children with Takenouchi-Kosaki Syndrome: A Systematic Review. *GENES-BASEL*. 2024;15:974.
9. Comer SP. Turning Platelets Off and On: Role of RhoGAPs and RhoGEFs in Platelet Activity. *FRONT CARDIOVASC MED*. 2022;8:820945.
10. Vainchenker W, Arkoun B, Basso-Valentina F, et al. Role of Rho-GTPases in megakaryopoiesis. *Small GTPases*. 2021;12:399–415.
11. Oshima-Nakayama M, Yamada A, Kurosawa T, et al. Cdc42 is crucial for facial and palatal formation during craniofacial development. *BONE REP*. 2016;5:1–6.
12. Liu Y, Jin Y, Li J, et al. Inactivation of Cdc42 in neural crest cells causes craniofacial and cardiovascular morphogenesis defects. *DEV BIOL*. 2013;383:239–52.
13. Fuchs S, Herzog D, Sumara G, et al. Stage-specific control of neural crest stem cell proliferation by the small rho GTPases Cdc42 and Rac1. *Cell Stem Cell*. 2009;4:236–47.
14. Pirone DM, Carter DE, Burbelo PD. Evolutionary expansion of CRIB-containing Cdc42 effector proteins. *Trends Genet*. 2001;17:370–3.
15. Lin Y, Chen C, Lee C, Lin H, Hsu Y. Mutation Spectrum of GJB2 in Taiwanese Patients with Sensorineural Hearing Loss: Prevalence, Pathogenicity, and Clinical Implications. *Int J Mol Sci*. 2025;26:8213.
16. Richards S, Aziz N, Bale S, 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 medicine: official J Am Coll Med Genet*. 2015;17:405–24.
17. Shen J, Oza AM, Del Castillo I, et al. Consensus interpretation of the p.Met34Thr and p.Val37Ile variants in GJB2 by the ClinGen Hearing Loss Expert Panel. *Genet medicine: official J Am Coll Med Genet*. 2019;21:2442–52.
18. Dai P, Yu F, Han B, et al. GJB2 mutation spectrum in 2,063 Chinese patients with nonsyndromic hearing impairment. *J TRANSL MED*. 2009;7:26.
19. Lin Y, Lin H, Tsai C, Hsu Y. GJB2 mutation spectrum in the Taiwanese population and genotype-phenotype comparisons in patients with hearing loss carrying GJB2 c.109G > A and c.235delC mutations. *Hear RES*. 2022;413:108135.
20. Snoeckx RL, Huygen PLM, Feldmann D, et al. GJB2 mutations and degree of hearing loss: a multicenter study. *AM J HUM GENET*. 2005;77:945–57.
21. Xiong Y, Chen M, Wang H, et al. Mutation analysis of GJB2, SLC26A4, GJB3 and mtDNA12SrRNA genes in 251 non-syndromic hearing loss patients in Fujian, China. *INT J PEDIATR OTORHI*. 2024;176:111777.
22. Abe S, Usami S, Shinkawa H, Kelley PM, Kimberling WJ. Prevalent connexin 26 gene (GJB2) mutations in Japanese. *J MED GENET*. 2000;37:41–3.
23. Motokawa M, Watanabe S, Nakatomi A, et al. A hot-spot mutation in CDC42 (p.Tyr64Cys) and novel phenotypes in the third patient with Takenouchi-Kosaki syndrome. *J HUM GENET*. 2018;63:387–90.
24. Flynn K, Feben C, Lamola L, et al. Ending a diagnostic odyssey-The first case of Takenouchi-Kosaki syndrome in an African patient. *CLIN CASE REP*. 2021;9:2144–8.
25. Takenouchi T, Kosaki R, Niizuma T, Hata K, Kosaki K. Macrothrombocytopenia and developmental delay with a de novo CDC42 mutation: Yet another locus for thrombocytopenia and developmental delay. *Am J Med Genet: A*. 2015;167A:2822–5.
26. Jahid S, Ortega JA, Vuong LM, et al. Structure-based design of CDC42 effector interaction inhibitors for the treatment of cancer. *CELL REP*. 2022;39:110641.
27. Mosaddeghzadeh N, Ahmadian MR. The RHO Family GTPases: Mechanisms of Regulation and Signaling. *CELLS-BASEL*. 2021;10:1831.
28. Fu J, Liu B, Zhang H, et al. The role of cell division control protein 42 in tumor and non-tumor diseases: A systematic review. *J CANCER*. 2022;13:800–14.
29. Stubbs L, Grimes A, Forbes L, et al. Immune-Mediated Chronic Macrothrombocytopenia, Musculoskeletal Abnormalities, and Dysmorphic Features in a Patient with Takenouchi-Kosaki Syndrome. *J Clin Immunol*. 2021;41(Suppl):S135–41.
30. Morris JA, Gonzalez T, Blanton SH, Angeli SI, Liu XZ. GJB2-Related Hearing Loss: Genotype-Phenotype Correlations, Natural History, and Emerging Therapeutic Strategies. *Int J Mol Sci*. 2026;27:491.
31. Danowitz M, Grimberg A. Clinical Indications for Growth Hormone Therapy. *Adv Pediatr*. 2022;69:203–17.
32. Fattah M, Raman MM, Reiss AL, Green T. PTPN11 Mutations in the Ras-MAPK Signaling Pathway Affect Human White Matter Microstructure. *Cerebral cortex (New York, N.Y.: 1991)* 2021;31:1489–1499.
33. Suzuki W, Yamada A, Aizawa R, et al. Cdc42 is critical for cartilage development during endochondral ossification. *Endocrinology*. 2015;156:314–22.
34. Wang JR, Wang CJ, Xu CY, et al. Signaling Cascades Governing Cdc42-Mediated Chondrogenic Differentiation and Mesenchymal Condensation. *Genetics*. 2016;202:1055–69.
35. Yang W, Lefebvre V. PTPN11 in cartilage development, adult homeostasis, and diseases. *BONE RES*. 2025;13:53.

Figures

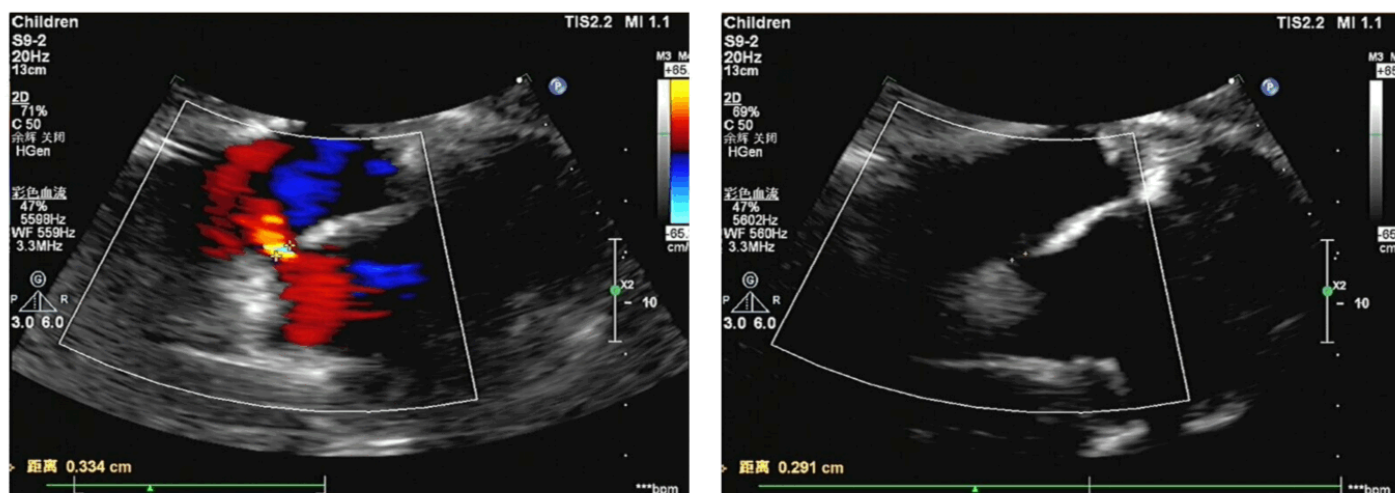


Figure 1

Echocardiogram revealed congenital atrial septal defect

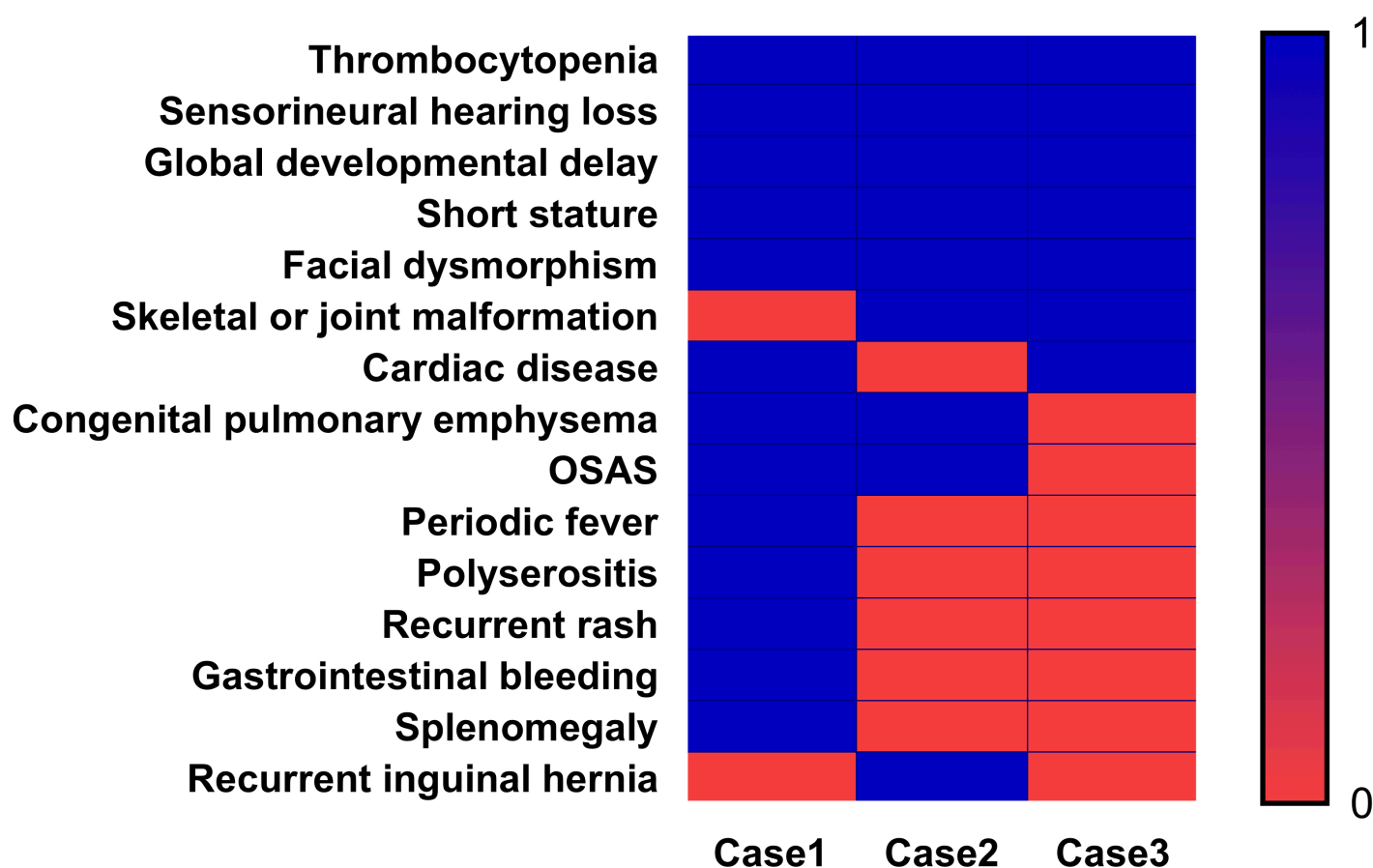


Figure 2
Heatmap of clinical manifestations in patients with *CDC42* p.Arg68Gln variant (Value 1 indicates the presence of a phenotype, and 0 indicates absence)

Supplementary Files

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