Received: 18 April 2023 | Revised: 29 July 2023 | Accepted: 22 August 2023

DOI: 10.1002/mgg3.2281

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

Clinical analysis of Gabriele-de Vries caused by *YY1* mutations and literature review

Jingjing Yang[1] | **Chaonan Yu**[1] | **Nan Lyn**[1] | **Lei Liu**[2] | **Dongxiao Li**[2] | **Qing Shang**[1]

[1]Department of Pediatric Rehabilitation Medicine, Children's Hospital Affiliated to Zhengzhou University, Zhengzhou, China

[2]Henan Neurodevelopment Engineering Research Center for Children, Henan Key Laboratory of Children's Genetics and Metabolic Diseases, Children's Hospital Affiliated to Zhengzhou University, Zhengzhou, China

Correspondence
Qing Shang, Department of Pediatric Rehabilitation Medicine, Children's Hospital Affiliated to Zhengzhou University, Zhengzhou, 450018, China.
Email: sqing1965@163.com

Abstract

Background: Gabriele-de Vries syndrome is a rare autosomal dominant genetic disease characterized by global development delay/intellectual disability, delayed language development, feeding difficulties, and distinctive facial dysmorphism. It is caused by pathogenic variants in *YY1*.

Methods: The current report describes a female patient with motor delay and a facial dysmorphism phenotype. We identified pathogenic mutations in the patient by whole-exome sequencing and confirmed them by Sanger sequencing.

Results: A novel heterozygous frameshift mutation NM_003403.5:c.458_476del (p. V153fs*97) in the *YY1* gene was detected in the proband. Finally, we provide a case-based review of the clinical features associated with Gabriele-de Vries syndrome. A total of 28 patients with genetic abnormalities and clinical phenotypes have been reported in the literature thus far.

Conclusions: The mutation site is reported for the first time, and its discovery would expand the mutation spectrum of the *YY1* gene. The main clinical manifestations of Gabriele-de Vries syndrome are developmental delay/intellectual disability, craniofacial dysplasia, intrauterine growth delay, low birth weight, feeding difficulties, and rare congenital malformations. Genetic tests are crucial techniques for its diagnosis because of its nonspecific clinical manifestations.

KEYWORDS

developmental delay/intellectual disability, Gabriele-de Vries syndrome, literature review, whole-exome sequencing, *YY1*

1 | BACKGROUND

Gabriele-de Vries syndrome (GADEVS) (OMIM 617557) is a rare autosomal dominant neurodevelopmental disorder caused by mutations in the *YY1* gene (OMIM 600013). It was first reported by Gabriele et al. (2017) and is characterized by craniofacial deformities (generalized facial asymmetry, broad forehead, downslanted palpebral fissure, strabismus), low birth weight, feeding difficulties, varying degrees of developmental delay/intellectual

disability, delayed speech and language development, behavioral phenotype (attention deficit/hyperactivity disorder, anxiety and autistic behavior, and schizoaffective disorder), neurological abnormalities (dystonia, abnormal gait, and tremor), congenital malformations, etc. After a literature review, 28 cases of Gabriele-de Vries syndrome were reported.

Herein, we reported a girl suffering from GADEVS carrying a novel heterozygous frameshift mutation (c.458_476del, p. V153fs*97) in exon 1 of the *YY1* gene. Our findings expand the genetic spectrum of *YY1* and improve clinicians' understanding of the disease.

2 | METHODS

2.1 | Patient and ethical compliance

This study has been approved by the institutional review board of Children's Hospital Affiliated to Zhengzhou University, Zhengzhou, China. And informed consent was obtained for all participants.

2.2 | Whole-exome sequencing and sanger sequencing

2.2.1 | Library preparation

We took a Trio-WES strategy to identify the causal variants from the family trios. In brief, genomic DNA was extracted, hybridized, and enriched.

Firstly, 1 μg genomic DNA was extracted from 200 μL peripheral blood, using a Qiagen DNA Blood Midi/Mini kit (Qiagen GmbH) following the manufacturer's protocol. A quantity of 50 nanogram DNA was interrupted to 200 bp around by fragmentation enzymes. The DNA fragments were then end-repaired, and the 3'end was added one A base. Secondly, the DNA fragments were ligated with barcoded sequencing adaptors, and fragments about 320 bp were collected by XP beads. After PCR amplification, the DNA fragments were hybridized and captured by NanoWES according to the manufacturer's Protocol. The hybrid products were eluted and collected, and then subjected to PCR amplification and the purification. Next, the libraries were quantified by qPCR and size distribution were determined.

Finally, Novaseq6000 platform (Illumina), with 150 bp pair-end sequencing mode, was used for sequencing the genomic DNA of the family. Raw image files were processed using CASAVA v1.82 for base calling and generating raw data.

2.2.2 | Data analysis

The sequencing reads were aligned to the human reference genome (hg19/GRCh37) using Burrows–Wheeler Aligner tool and PCR duplicates were removed by using Picard v1.57 (https://picard.sourceforge.net/). Variant annotation and interpretation were conducted by ANNOVAR and the plenty of Variants Annotation Interpretation System. Annotation databases mainly included:

1. human population databases, such as gnomAD (https://gnomad.broadinstitute.org/), the 1000 Genome Project (https://browser.1000genomes.org), Berrybig data population database and dbSNP (https://www.ncbi.nlm.nih.gov/snp);
2. in silico prediction algorithms, such as SIFT (https://sift.jcvi.org), FATHMM (https://fathmm.biocompute.org.uk), MutationAssessor (https://mutationassessor.org), CADD (https://cadd.gs.washington.edu), and SPIDEX;
3. disease and phenotype databases, such as OMIM (https://www.omim.org), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar), HGMD (https://www.hgmd.org), and HPO (https://hpo.jax.org/app/).

According to the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines (Richards et al., 2015), the identified sequence variant was further interpreted and classified. Variants with minor allele frequencies (MAF) <1% in exonic region or with splicing impact were taken for deep interpretation considering ACMG category, evidence of pathogenicity, and clinical synopsis and inheritance model of the associated disease. Potentially pathogenic mutations relevant to the proband's phenotype were prioritized and confirmed by Sanger sequencing.

2.3 | Bioinformatic predictions and 3D modeling of protein structure

MutationTaster (https://www. mutationtaster.org/) was used to predict the effects of variants on protein structure and function. A 3D model of the YY1 protein was constructed using AlphaFold2.

3 | RESULTS

3.1 | Clinical findings

The proband was the second child from normal nonconsanguineous parents without a known family history of

inherited disease, and the first child was a healthy girl with normal growth and neurodevelopment (Figure 1). The proband was a 22-month-old girl who was delivered at 37 weeks by cesarean section due to the nuchal cord. She had a birth weight of 2450 g (−2 SD), a head circumference of 33 cm (−1 SD) and a birth length of 48 cm (−1 SD). She was admitted to the Rehabilitation Center of Children's Hospital Affiliated to Zhengzhou University for the first time in March 2022 due to developmental delay. She manifested morphological features, such as broad forehead and slender fingers, low birth weight, motor retardation, and delayed language development. What is more, brain magnetic resonance imaging showed a plump bilateral ventricle, thin callosum and demyelinating changes (Figure 2). Her head circumference was 46 cm (−1 SD), weight was 9.8 kg (−1 SD) and height was 81 cm (−1 SD) at 22 months old. The proband was developmentally delayed from infancy, raised her head at 3 months old, turned over at 5 months old, sat up alone at 9 months old, and crawled at 11 months old. Currently, she cannot walk alone smoothly and has poor balance ability. In addition, she occasionally could speak "father, mother, grandpa, grandma" and understand simple instructions. The Gesell Developmental Schedules showed a gross motor quotient of 64, fine motor quotient of 59, adaptive behavior quotient of 68, language quotient of 59, and personal-social behavior quotient of 73, which suggests that she was diagnosed with mild global developmental delay. The clinical details and genotype of the child are shown in Tables 1 and 2.

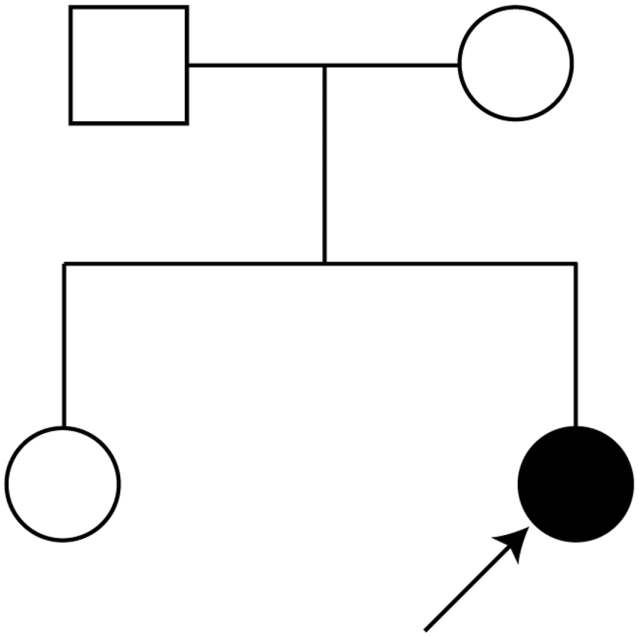

FIGURE 1 Pedigree of the family.

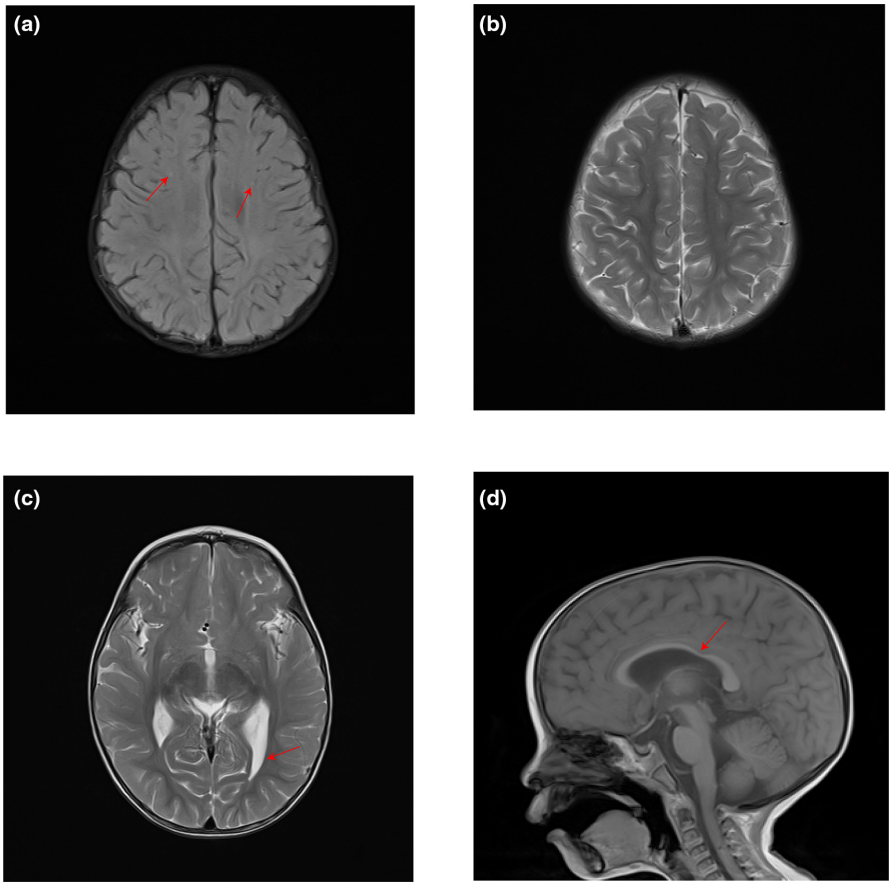

FIGURE 2 Brain MRI plain scan and enhancement: (a) T2WI- lipid inhibition sequence: Subcortical multiple small flake abnormal hyperintensity (red arrow); (b) T2WI-TSE: Deepening cerebral sulci of the bilateral frontal–parietal lobes; (c) T2WI-TSE: plump bilateral ventricle (red arrow); (d) thin callosum (red arrow).

TABLE 1 Comparison of the clinical features of individuals with *YY1* variants reported by other groups with our proband.

	Proband (*N* = 1)	Gabriele et al (*N* = 10)	Cherik et al. (*N* = 10)	Morales-Rosado et al. (*N* = 1)	Maria Teresa et al. (*N* = 1)	Surya et al. (*N* = 1)	Giovanna et al. (*N* = 1)	Li Tan et al. (*N* = 1)	Suely Rodrigues et al. (*N* = 1)	Nenad Koruga et al. (*N* = 1)	Hossein et al. (*N* = 1)	Frequency (*N* = 29)
Growth												
Birth weight in g (≤2SD)	−	3/9	2/10	NA	−	−	NA	−	+	+	−	7/26
Nervous system												
Motor delay	+	10/10	8/10	+	__	+	+	+	+	+	+	26/29
Delayed speech and Language development	+	10/10	10/10	+	+	+	+	NA	+	+	+	28/28
Intellectual disability	−	9/9	9/10	+	−	+	+	NA	+	−	+	23/27
Behavioral abnormality	−	5/9	10/10	+	+	−	−	−	−	NA	+	18/27
Abnormal movement	−	5/9	3/10	−	+	+	−	−	NA	NA	+	11/26
Abnormal Brain MRI	+	5/9	4/7	+	−	NA	NA	NA	−	+	+	11/22
Musculature												
Hypotonia	+	3/10	4/10	−	+	+	+	−	+	NA	+	13/28
Head and neck												
Broad forehead	+	10/10	9/10	+	+	+	+	−	−	−	+	25/29
Facial asymmetry	−	7/10	3/10	−	+	−	−	+	−	−	+	13/29
Broad nasal tip	−	8/10	8/10	+	+	−	−	−	−	−	−	18/29
Thick lower lip vermilion	−	8/10	2/10	+	+	−	+	−	−	−	−	13/29
Pointed chin	−	4/10	3/10	−	−	+	−	+	+	+	−	11/29
Ear abnormality	−	9/9	10/10	+	+	−	−	−	+	−	+	23/28
Miscellaneous												
Cardiac abnormalities	−	2/8	1/9	+	NA	−	−	+	NA	NA	−	5/23
Feeding difficulties	−	9/10	10/10	+	−	−	NA	NA	+	NA	+	22/26
Recurrent infections	−	1/9	2/10	NA	+	NA	NA	NA	NA	NA	+	5/22
Eye abnormalities	+	6/10	9/9	NA	−	NA	−	NA	NA	−	+	17/24
Skeletal abnormalities	+	6/9	9/9	+	+	+	−	NA	+	+	+	22/26

Abbreviations: NA, not applicable/not available; +: feature present; −: feature absent.

TABLE 2 Comparison of the genotype of individuals with *YY1* variants reported by other groups with our proband.

Individual ID	Sex	Genotype	Exon
Individual-1[a]	F	c.958C > T(p.His320Tyr)	4
Individual-2[a]	M	c.1015A > C(p.Lys339Gln)	4
Individual-3[a]	M	c.1097T > C(p.Leu366Pro)	5
Individual-4[a]	F	c.1096C > G(p.Leu366Val)	5
Individual-5[a]	M	c.1138G > T(p.Asp380Tyr)	5
Individual-6[b]	F	c.1007A > G(p.Glu336Gly)	4
Individual-7[b]	F	c.1112G > A(p.Arg371His)	5
Individual-8[b]	F	c.1001T > C(p.Phe334Ser)	4
Individual-9[b]	M	c.1067C > T(p.Thr356Met)	5
Individual-10[b]	M	(p.Val374Gly)	5
Individual-11[b]	M	(p.His320Arg)	4
Individual-12[b]	M	c.1124G > A(p.Arg375Gln)	5
Individual-13[b]	M	c.908G > T(p.Cys303Phe)	4
Individual-14[c]	F	c.907T > C(p.Cys303Arg)	4
Individual-15[d]	F	c.1124G > A(p.Arg375Gln)	5
Individual-16[e]	F	c.1106A > G(p.Asn369Ser)	5
Individual-17[a]	F	c.385delG(p.Asp129Ilefs*127)	1
Individual-18[a]	M	c.1173delT(p.Asn391Lysfs*10)	5
Individual-19[b]	F	c.1151-1154dup(p.Pro386Valfs*7)	5
Individual-20[b]	M	c.690dup(p.Asp231Argfs*3)	2
Individual-21[f]	F	c.860-864delTTAAAA(p.Ile287Argfs*3)	3
Individual-22[g]	F	c.690delA(p.Glu231Ilefs*25)	2
Individual-23[k]	M	c.1118-1119delAT(p.His373Argfs*18)	5
Individual-24[m]	M	c.690delA(p.Glu231Ilefs*25)	2
Individual-25[n]	M	c.1A > C(p.Met?)	1
Individual-26[a]	F	c.1030C > T(p.Gln344*)	4
Individual-27[a]	F	c.535A > T(p.Lys179*)	1
Individual-28[a]	M	c.1174-1176del(p.Lys393del)	5
Individual-29	F	c.458_476del (p. V153fs*97)	1

Note: Individuals marked by (a) are individuals already described in Gabriele et al. Individuals marked by (b) are individuals already described in Cherik et al. Individual marked by (c) is individual already described in Maria Teresa et al. Individual marked by (d) is individual already described in Li Tan et al. Individual marked by (e) is individual already described in Suely Rodrigues et al. Individual marked by (f) is individual already described in Morales-Rosado et al. Individual marked by (g) is individual already described in Surya et al. Individual marked by (k) is individual already described in Giovanna et al. Individual marked by (m) is individual already described in Hossein et al. Individual marked by (n) is individual already described in Nenad Koruga et al.

Abbreviations: F, female; M, male.

3.2 | Genetic findings

High-throughput sequencing revealed a mutation NM_003403 in exon 1 of the proband's *YY1* gene: c.458_476del (p.V153fs*97) (Figure 3). This mutation was a frameshift mutation, which would cause changes in the open reading frame of the gene, resulting in protein truncation and affecting protein function. Notably, it was a haploinsufficient gene, and there were several pathogenic reports of truncation mutation downstream (PVS1-Strong). In addition, Sanger sequencing showed that the parents and sister of the proband were all wild-type (Figure 4); thus, this mutation was a new mutation in the proband (PS2). Finally, the variant c.458_476del (p.V153fs*97) was not found in the HGMD, dbSNP, ExAC, gnomAD, and ClinVar (PM2). According to the classification Standards and Guidelines of ACMG genetic variation, this variation was rated as a pathogenic variation (PVS1_Strong+PS2 + PM2). It was submitted to the ClinVar (cession number: SCV003842269) database.

The position of the amino acid that is affected by the mutation in the proband is highly conserved in different species (Figure 5). AlphaFold2 software was used to predict the 3D structures of the mutant YY1 protein (Figure 6).

4 | DISCUSSION

Gabriele-de Vries syndrome is a rare autosomal dominant genetic disease (Morales-Rosado et al., 2018) caused by *YY1* gene mutations. The *YY1* gene, located in the q32 region of chromosome 14 (14q32.2), contains five exons and encodes a zinc finger protein transcription factor composed of 414 amino acids. The YY1 protein is composed of the histidine-rich domain at the N-terminus, the GK domain, the REPO domain, and the C2H2 zinc finger domain at the C-terminus (Vissers et al., 2010). Among them, the N-terminus of the YY1 protein binds to cofactors, such as general TF, YY1AP, HATs, PRMT1, INO80, and the BAF complex to mediate transcriptional activation, whereas it binds to cofactors such as the SMAD family, HDACs and multicomb family proteins to mediate transcriptional inhibition (Verheul et al., 2020). This protein belongs to the GLI-Kruppel family with transcriptional regulation, which can participate in the regulation of the cell cycle, such as cell proliferation, differentiation, and apoptosis, through activation and inhibition of gene expression (Atchison et al., 2011; Morales-Rosado et al., 2018). In addition, the YY1 protein can participate in neuronal differentiation to promote nervous system development (Dos Santos et al., 2022) and promote the formation of peripheral myelin (Zorzi et al., 2021). In conclusion, the YY1 protein, as a transcription regulator universally expressed in mammals, plays a role in regulatory pathways and developmental stages of multiple cell types (Khamirani et al., 2022).

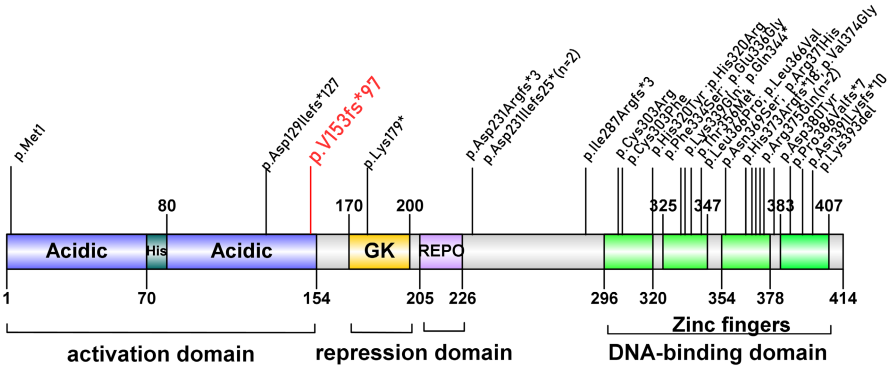

FIGURE 3 Schematic diagram of human YY1 protein structure, summarizing the 29 *YY1* pathogenic/likely pathogenic sequence variants described in the literature, with the p.V153fs*97 highlighted.

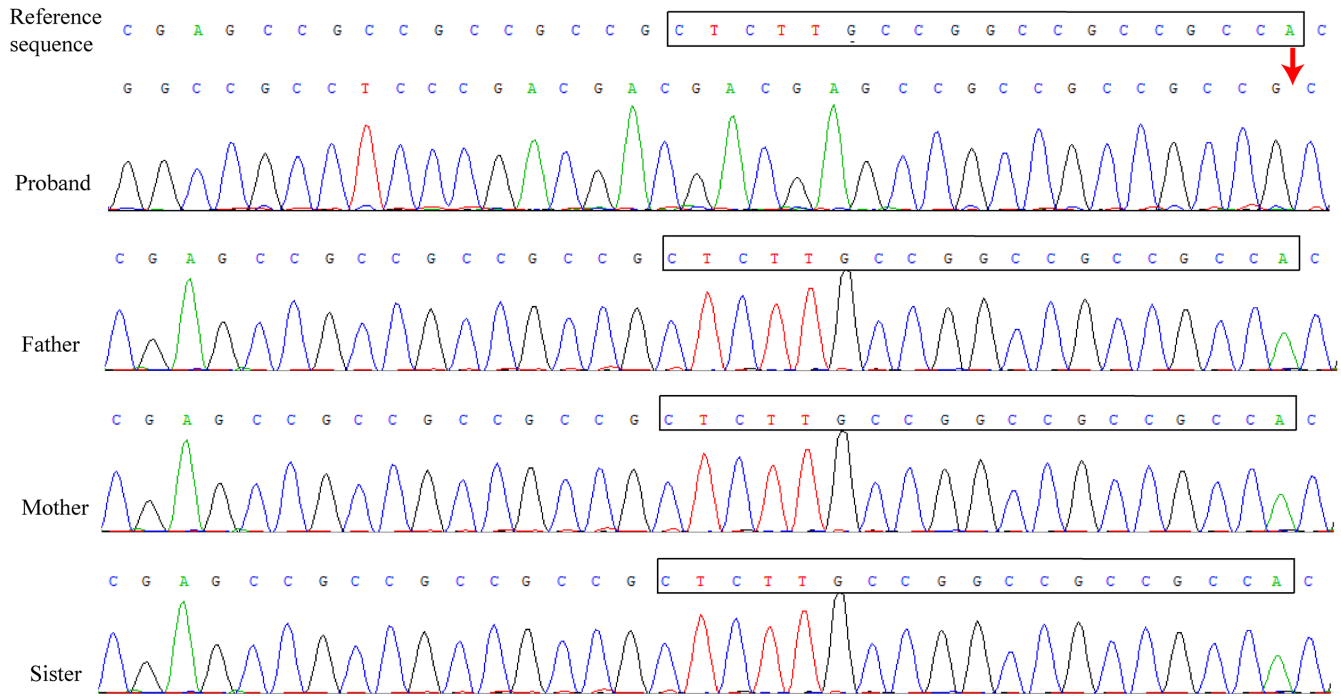

FIGURE 4 Sanger sequencing chromatograms of *YY1* indicating that the frameshift variant c.212G > A (p. Gly71Glu) is a novel mutation.

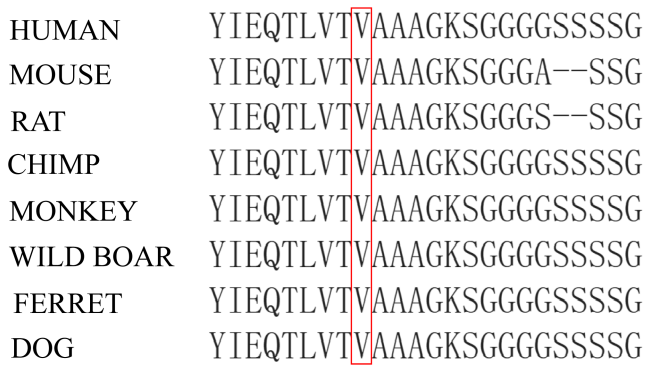

FIGURE 5 The mutation in the proband is highly conserved in different species.

Herein, a new heterozygous mutation in the *YY1* gene was detected in the peripheral blood samples of a child with developmental delay: c.458_476del (p. V153fs*97), and the locus of this mutation was wild-type in both her parents and elder sister. The frameshift mutation resulted in the conversion of valine to alanine at position 153, resulting in a change in the reading frame of the protein triplet codon after this spot, thereby prematurely terminating the peptide chain at position 249. This mutation resulted in protein truncation and altered protein structure, thereby affecting the physiological function of the protein. Nonsense-mediated mRNA decay is a cellular monitoring mechanism that degrades transcripts containing premature translation-stop codons, avoiding the large

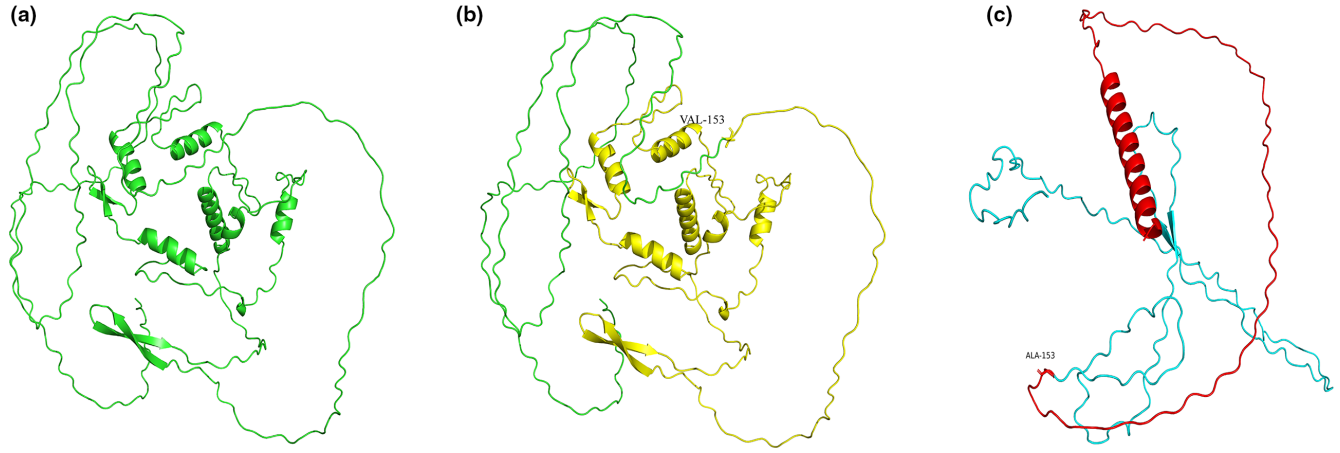

FIGURE 6 3D structure modeling (a) YY1 protein structure before mutation; (b): The marked position of the mutation start point – the 153rd position valine VAL on the normal protein structure diagram, the green part is the protein structure before the mutation start point, and the yellow part is the protein structure after the mutation start. (c): The new protein structure formed after the mutation. This variant causes a frameshift leading to premature truncation of the protein 97 amino acids downstream of codon 153, thereby resulting in a transcript, which is either too short to form a biologically active protein or undergoes nonsense-mediated decay.

expression of truncated proteins affecting the function of wild-type proteins and avoiding strong dominant negative effects. The studies of Donohoe (Donohoe et al., 1999) and Gabriele (Gabriele et al., 2017) both indicated proved that haploinsufficiency of the *YY1* gene was the main genetic basis of this syndrome. Haploinsufficiency of the *YY1* gene can result in extensive loss of H3K28 acetylation, which makes the H3K27 substrate available for PrC2-mediated methylation, thereby inhibiting gene expression (Dong et al., 2022).

The mutation types in the *YY1* gene of 29 patients were reviewed, including 16 missense mutations, nine frameshift mutations, two nonsense mutations, one 3-bp deletion and one mutation located in initiation codon. Notably, the mutant bases of 13 patients were located in exon 5, and those of 8 patients were in exon 4, which suggests that these exons might be mutation hotspots of *YY1*. Dramatically, the de novo mutation reported in this child involves the relatively rare exon 1, and only four cases have been reported in the last few years.

Analyzing the clinical symptoms of 29 patients with Gabriele de Vries syndrome caused by *YY1* gene mutation (Balakrishnan & Ranganath, 2021; Carminho-Rodrigues et al., 2020; Dos Santos et al., 2022; Khamirani et al., 2022; Koruga et al., 2023; Morales-Rosado et al., 2018; Tan et al., 2021), we discovered that craniofacial deformities were common in all patients. The most common feature is a broad forehead. In addition, there are some malformations in the external ear, including a simple ear, a posteriorly rotated ear, a low-set ear, and protruding ears. In this study, the proband showed a broad forehead without auricle deformity or facial asymmetry, which may be related to their own genetic factors. Approximately, 90% of patients have varying degrees of motor retardation and intellectual disability (Cherik et al., 2022). Animal experiments on mice showed that knockout of the *YY1* gene at the early stage of cortical development increased the apoptosis rate of neuroepithelial cells (NECs) and neural precursor cells (NPCs) and led the cell to stay in the G1/S phase (Martins Peçanha et al., 2022), which led to neurodevelopmental defects by affecting the development of neurons. This is consistent with the case of motor retardation as the first manifestation. Approximately, half of the patients had other neurological symptoms, such as hypotonia, abnormal movement, abnormal gait, and rare febrile convulsions. A variety of patients manifested nonspecific morphologic abnormalities of the central nervous system (CNS), including delayed myelination, frontal gliosis, cortical dysplasia, focal areas of encephalomalacia, lateral ventricular dilatation, white matter atrophy, and agenesis or agenesis of the corpus callosum. The proband also had similar morphologic abnormalities, bilateral dilatation of the lateral ventricles, demyelination changes, subcortical abnormal signal, and abnormalities of the corpus callosum.

Almost all patients had mild to severe language delay. In this study, the proband presented with mild language retardation, while Carminho-Rodrigues et al. (2020) reported a 21-year-old female patient with severe language communication disorder. Behavioral problems such as attention deficit hyperactivity disorder and autism spectrum disorder have been reported in three cases. This may be related to the fact that *YY1* can bind to some target genes related to neurodevelopmental disorders, such as *GTF2I*, *KANSL1*, *MED12*, *ZBTB20*, *NSD1*, and other target genes related to autism spectrum disorders, such as *NRXN2* (Gabriele et al., 2017). The child in this study is so young that we

could not observe her behavioral abnormalities; therefore, long-term follow-up is extremely necessary. YY1 protein is not only involved in the whole process of neuronal cell development but also in the regulation of muscle, cardiopulmonary development, and intestinal stem cell development, which may explain the clinical phenotypes of some patients with esophageal atresia, patent foramen ovale, atrial septal defect, etc. In this case, no gastrointestinal symptoms or abnormal cardiac color echocardiography were found.

The proband had related clinical manifestations of Gabriele-de Vries syndrome, such as motor delay, delay speech and language development, broad forehead, micrognathia, long fingers, low birth weight, and global development delay. She has not shown serious clinical symptoms. Compared with the other three individuals with exon 1 mutation, the proband did not show non-neurological manifestations such as hypothyroidism and feeding difficulties.

Patients with Gabriele-de Vries syndrome caused by the *YY1* gene mutation have various clinical manifestations, varying severity of disease, and lack specific diagnostic methods. For patients with highly suspected genetic disease, a whole-exon gene test can be performed as soon as possible to confirm the diagnosis, which can provide help for clinical treatment and genetic counseling to better judge the prognosis of patients. There is no specific treatment for this disease, but symptomatic treatment and comprehensive rehabilitation therapy can improve the quality of life of children. Neurodevelopmental assessment, especially early assessment of gross and fine motor function and language, is necessary for this disease. Early detection can lead to early intervention in rehabilitation training. Since only one patient with Gabriele-de Vries syndrome was reported in this study, there are some certain limitations, and more sample cases, family studies and in-depth gene function studies are needed to further explore the genetic mechanism and diagnosis and treatment experience of this disease. As the number of reported cases increases, further studies are expected to improve the understanding of the association between genotype and phenotype of the disease. Further functional studies of these variants may also improve our understanding of the disease and its pathogenesis.

In summary, the *YY1* gene c.458_476del (p. V153fs*97) found in this study was a new mutation reported for the first time. This discovery expanded the mutation spectrum of the *YY1* gene and enriched the mutation database of Gabriele-de Vries syndrome, which is of great significance for the study of Gabriele-de Vries syndrome. At the same time, it enriches the clinician's understanding of the disease.

AUTHOR CONTRIBUTIONS

Jingjing Yang: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review and editing. Chaonan Yu: Formal analysis, Methodology, Supervision, Writing – review and editing. Nan Lyn: Clinical data collection, Investigation, Project administration, Validation, Visualization, Supervision. Lei Liu: Formal analysis, Methodology, Supervision. Dongxiao Li: Formal analysis, Methodology, Supervision, Writing - review and editing. Qing Shang: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review and editing.

ACKNOWLEDGMENTS

We are grateful to the family for their participation in this study. We also thank the doctors and nurses who contributed to this study at Children's Hospital Affiliated to Zhengzhou University.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest related to the publication of this study.

DATA AVAILABILITY STATEMENT

Data will be made available on request.

ETHICS APPROVAL STATEMENT AND PATIENT CONSENT STATEMENT

The ethics approval was given by the institutional review board of Children's Hospital Affiliated to Zhengzhou University. A written consent was obtained from our patient's parents.

ORCID

Jingjing Yang https://orcid.org/0009-0005-3982-0465

REFERENCES

Atchison, M., Basu, A., Zaprazna, K., & Papasani, M. (2011). Mechanisms of yin Yang 1 in oncogenesis: The importance of indirect effects. *Critical Reviews in Oncogenesis*, *16*(3–4), 143–161. https://doi.org/10.1615/critrevoncog.v16.i3-4.20

Balakrishnan, S., & Ranganath, P. (2021). Report of an unusual association of hydrosyringomyelia with Gabriele-de Vries syndrome in an Asian-Indian patient. *Clinical Dysmorphology*, *30*(4), 204–206. https://doi.org/10.1097/mcd.0000000000000385

Carminho-Rodrigues, M. T., Steel, D., Sousa, S. B., Brandt, G., Guipponi, M., Laurent, S., Fokstuen, S., Moren, A., Zacharia, A., Dirren, E., Oliveira, R., Kurian, M. A., Burkhard, P. R., & Bally, J. F. (2020). Complex movement disorder in a patient with heterozygous YY1 mutation (Gabriele-de Vries syndrome). *American Journal of Medical Genetics. Part A*, *182*(9), 2129–2132. https://doi.org/10.1002/ajmg.a.61731

Cherik, F., Reilly, J., Kerkhof, J., Levy, M., McConkey, H., Barat-Houari, M., Butler, K. M., Coubes, C., Lee, J. A., le Guyader, G., Louie, R. J., Patterson, W. G., Tedder, M. L., Bak, M., Hammer, T. B., Craigen, W., Démurger, F., Dubourg, C., Fradin, M., … Genevieve, D. (2022). DNA methylation episignature in

Gabriele-de Vries syndrome. *Genetics in Medicine*, *24*(4), 905–914. https://doi.org/10.1016/j.gim.2021.12.003

Dong, X., Guo, R., Ji, T., Zhang, J., Xu, J., Li, Y., Sheng, Y., Wang, Y., Fang, K., Wen, Y., Liu, B., Hu, G., Deng, H., & Yao, H. (2022). YY1 safeguard multidimensional epigenetic landscape associated with extended pluripotency. *Nucleic Acids Research*, *50*(21), 12019–12038. https://doi.org/10.1093/nar/gkac230

Donohoe, M. E., Zhang, X., McGinnis, L., Biggers, J., Li, E., & Shi, Y. (1999). Targeted disruption of mouse yin Yang 1 transcription factor results in peri-implantation lethality. *Molecular and Cellular Biology*, *19*(10), 7237–7244. https://doi.org/10.1128/mcb.19.10.7237

Dos Santos, S. R., Piergiorge, R. M., Rocha, J., Abdala, B. B., Gonçalves, A. P., Pimentel, M. M. G., & Santos-Rebouças, C. B. (2022). A de novo YY1 missense variant expanding the Gabriele-de Vries syndrome phenotype and affecting X-chromosome inactivation. *Metabolic Brain Disease*, *37*(7), 2431–2440. https://doi.org/10.1007/s11011-022-01024-2

Gabriele, M., Vulto-van Silfhout, A. T., Germain, P. L., Vitriolo, A., Kumar, R., Douglas, E., Haan, E., Kosaki, K., Takenouchi, T., Rauch, A., Steindl, K., Frengen, E., Misceo, D., Pedurupillay, C. R. J., Stromme, P., Rosenfeld, J. A., Shao, Y., Craigen, W. J., Schaaf, C. P., … de Vries, B. B. A. (2017). YY1 Haploinsufficiency causes an intellectual disability syndrome featuring transcriptional and chromatin dysfunction. *American Journal of Human Genetics*, *100*(6), 907–925. https://doi.org/10.1016/j.ajhg.2017.05.006

Khamirani, H. J., Zoghi, S., Namdar, Z. M., Kamal, N., Dianatpour, M., Tabei, S. M. B., Mohammadi, S., Dehghanian, F., Farbod, Z., & Dastgheib, S. A. (2022). Clinical features of patients with yin Yang 1 deficiency causing Gabriele-de Vries syndrome: A new case and review of the literature. *Annals of Human Genetics*, *86*(1), 52–62. https://doi.org/10.1111/ahg.12448

Koruga, N., Pušeljić, S., Babić, M., Ćuk, M., Cvitković Roić, A., Vrtarić, V., Soldo Koruga, A., Rončević, A., Tomac, V., Rotim, T., Turk, T., Kretić, D., Pušeljić, N., Nađ, R., & Serdarušić, I. (2023). First reported case of Gabriele-de Vries syndrome with spinal Dysraphism. *Children (Basel)*, *10*(4), 623. https://doi.org/10.3390/children10040623

Martins Peçanha, F. L., Jaafar, R., Werneck-de-Castro, J. P., Apostolopolou, C. C., Bhushan, A., & Bernal-Mizrachi, E. (2022). The transcription factor YY1 is essential for Normal DNA repair and cell cycle in human and mouse β-cells. *Diabetes*, *71*(8), 1694–1705. https://doi.org/10.2337/db21-0908

Morales-Rosado, J. A., Kaiwar, C., Smith, B. E., Klee, E. W., & Dhamija, R. (2018). A case of YY1-associated syndromic learning disability or Gabriele-de Vries syndrome with myasthenia gravis. *American Journal of Medical Genetics. Part A*, *176*(12), 2846–2849. https://doi.org/10.1002/ajmg.a.40626

Richards, S., Aziz, N., Bale, S., Bick, D., das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L., & ACMG Laboratory Quality Assurance Committee. (2015). 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. *Genetics in Medicine*, *17*(5), 405–424. https://doi.org/10.1038/gim.2015.30

Tan, L., Li, Y., Liu, F., Huang, Y., Luo, S., Zhao, P., Gu, W., Lin, J., Zhou, A., & He, X. (2021). A 9-month-old Chinese patient with Gabriele-de Vries syndrome due to novel germline mutation in the YY1 gene. *Molecular Genetics & Genomic Medicine*, *9*(2), e1582. https://doi.org/10.1002/mgg3.1582

Verheul, T. C. J., van Hijfte, L., Perenthaler, E., & Barakat, T. S. (2020). The why of YY1: Mechanisms of transcriptional regulation by yin Yang 1. *Frontiers in Cell and Development Biology*, *8*, 592164. https://doi.org/10.3389/fcell.2020.592164

Vissers, L. E., de Ligt, J., Gilissen, C., Janssen, I., Steehouwer, M., de Vries, P., van Lier, B., Arts, P., Wieskamp, N., del Rosario, M., van Bon, B. V. M., Hoischen, A., de Vries, B. B. A., Brunner, H. G., & Veltman, J. A. (2010). A de novo paradigm for mental retardation. *Nature Genetics*, *42*(12), 1109–1112. https://doi.org/10.1038/ng.712

Wang, W., Qiao, S., Li, G., Cheng, J., Yang, C., Zhong, C., Stovall, D. B., Shi, J., Teng, C., Li, D., & Sui, G. (2022). A histidine cluster determines YY1-compartmentalized coactivators and chromatin elements in phase-separated enhancer clusters. *Nucleic Acids Research*, *50*(9), 4917–4937. https://doi.org/10.1093/nar/gkac233

Zorzi, G., Keller Sarmiento, I. J., Danti, F. R., Bustos, B. I., Invernizzi, F., Panteghini, C., Reale, C., Garavaglia, B., Chiapparini, L., Lubbe, S. J., Nardocci, N., & Mencacci, N. E. (2021). YY1-related dystonia: Clinical aspects and long-term response to deep brain stimulation. *Movement Disorders*, *36*(6), 1461–1462. https://doi.org/10.1002/mds.28547

How to cite this article: Yang, J., Yu, C., Lyn, N., Liu, L., Li, D., & Shang, Q. (2024). Clinical analysis of Gabriele-de Vries caused by *YY1* mutations and literature review. *Molecular Genetics & Genomic Medicine*, *12*, e2281. https://doi.org/10.1002/mgg3.2281