

## ORIGINAL ARTICLE

# A 9-month-old Chinese patient with Gabriele-de Vries syndrome due to novel germline mutation in the *YY1* gene

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## Abstract

**Background:** Gabriele-de Vries syndrome (GADEVs), also known as *YY1* haploinsufficiency syndrome, is a very rare autosomal dominant neurodevelopmental disorder (NDD) due to *YY1* mutation characterized by mild-to-profound developmental delay (DD)/intellectual disability (ID), a wide spectrum of functional and morphologic abnormalities, and intrauterine growth restriction or low birth weight and feeding difficulties are common in the patients. However, NDDs, such as language development disorder and ID, could hardly be assessed in patients younger than 2 years old.

**Methods:** We describe a 9-month-old female with DD, failure to thrive, and facial dysmorphism. Genetic analysis was conducted by whole exome sequencing (WES) and confirmed by Sanger sequencing.

**Results:** In addition to DD and dysmorphic facial features, this patient had urinary tract infection, acute pyelonephritis, bilateral vesicoureteral reflux (grade III), gastroesophageal reflux, and malnutrition. She was found to have foramen ovale or atrial septal defect, and enlarged left lateral ventricle in the brain. After performing WES, a novel heterozygous mutation NM\_003403.5:c.1124G>A, p.Arg375Gln in the *YY1* gene was identified.

**Conclusion:** Our findings suggest that genetic tests are critical technique for diagnosis of GADEVs, especially in patients with early-childhood, unexplained developmental or growth disorders, thus, the prevalence of GADEVs may be underestimated.

Li Tan, Ying Li and Fan Liu have equally contributed.

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The clinical features and identified *YY1* mutation in our patient expand the spectra of phenotypes and genotypes of GADEVs, respectively.

#### KEYWORDS

Gabriele-de Vries syndrome, haploinsufficiency, intellectual disability, neurodevelopmental disorder, *YY1* gene

## 1 | BACKGROUND

Gabriele-de Vries syndrome (GADEVs, OMIM 617557) is a newly recognized neurodevelopmental disorder (NDD) characterized by mild-to-profound developmental delay (DD) and/or intellectual disability (ID), facial dysmorphism, and various congenital abnormalities (Vries, 2019). This disorder, first delineated by Gabriele M, Testa G, and Vries B, is caused by the deletion of or pathogenic variant in *Yin Yang* (*YY1*) gene (OMIM 600013) (Gabriele et al., 2017). *YY1* gene, located on chromosome 14q32.2, encodes a ubiquitously expressed zinc finger transcription factor YY1, and YY1 is involved in the regulation of multiple cellular processes including differentiation, DNA repair, autophagy, cell proliferation, and apoptosis by activating or repressing gene expression depending on interacting partners, promoter context, and chromatin structure (Figiel & Górecki, 2017). Complete ablation of *YY1* gene in mice results in peri-implantation lethality, whereas *YY1* heterozygous mice display DD, neurulation defects, and brain abnormalities (Donohoe et al., 1999), suggesting *Yin Yang 1* may have a crucial role in early embryogenesis and neurodevelopment.

YY1, first discovered in early 1990s as a DNA-binding protein, consists of highly conserved 414 amino acids and has several defined functional domains. The N-terminal residues (1–69 or 1–100) are defined as responsible for transcriptional activation, whereas residues 170–226 have been reported to be involved in transcriptional repression (Yang et al., 1996) (Bushmeyer et al., 1995). The C-terminal residues 295–414 are DNA-binding domains, including four zinc fingers (Sarvagalla et al., 2019). To date, only 25 patients with GADEVs have been reported, and all these patients carried loss-of-function mutations or missense mutations in the zinc fingers of *YY1* gene, or a deletion encompassing *YY1* and other neighboring genes (Gabriele et al., 2017; Morales-Rosado et al., 2018; Vissers et al., 2010). However, there is no report about *YY1*-associated syndrome in China.

Herein, we reported a Chinese girl with DD, dysmorphic facial features, and congenital abnormalities, carrying a novel de novo missense mutation (c.1124G>A, p.Arg-375Gln) in the exon 5 of *YY1* gene (NM\_003403.5) identified by whole exome sequencing (WES).

## 2 | METHODS

### 2.1 | Study subjects

A 9-month-old girl was admitted because of DD, failure to thrive, and facial dysmorphism. Peripheral venous blood was withdrawn from the patient and both parents after obtaining written consent. This study has been approved by the institutional review board of Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology (WCH 2019011).

### 2.2 | Whole exome sequencing

Genomic DNA was extracted from peripheral blood for genetic analysis. For WES, the genomic DNA was subjected to sonication, hybrid capturing with xGen Exome Research Panel v1.0 (Integrated DNA Technologies, Inc.), and target enrichment. Captured DNA was amplified and paired-end sequenced on the Illumina NovaSeq 6000 platform (Illumina). After raw data were processed, paired-end alignment to the human reference genome (hg19) and variant detection were conducted using GATK 3.8 (<http://www.broadinstitute.org/gatk>). Variant annotation was obtained using ANNOVAR (version 2017-07-16) and variants were filtered against the 1000 genomes project database, dbSNP, ESP, GnomAD, and inhouse database. The clinical effects of variants identified were classified into five categories according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Kalia et al., 2016). PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph/>), SIFT (<http://www.Blocks.fhcrc.org/sift/SIFT.html>), and MutationTaster (<http://www.mutationtaster.org/>) were performed to predict the possible effects of the variants identified. Possible pathogenic genes were identified from the screened deleterious variants combining disease correlation and clinical phenotypes.

### 2.3 | Sanger sequencing

Polymerase chain reaction (PCR) was performed to amplify *YY1* (NM\_003403.5) fragment using the primers as following: *YY1*-F (5'-TCCCTTAGGTGTGTAGGATTCATT

-3') and *YY1*-R (5'-CTGTTCTCTAGCAAAGCAGTGAG-3'). Amplification was performed in a 25  $\mu$ l system with an annealing temperature of 60°C. The PCR products were sequenced with ABI 3730XL (Thermo Fisher Scientific Inc.) and analyzed by DNASTAR 5.0 software (DNASTAR, Inc.).

## 2.4 | Sequential analysis and structural modeling

BioEdit sequence alignment editor was used for sequence study (<http://www.mbio.ncsu.edu/bioedit/bioedit.html>). Structural modeling was performed as described previously (Gabriele et al., 2017). In brief, the 3D coordinates of the YY1 zinc domain structure were obtained from the Protein Data Bank (PDB: 1UBD 43) (<http://www.rcsb.org/pdb/home/home.do>), and the structures were visualized using PyMOL software (<http://www.pymol.org/>).

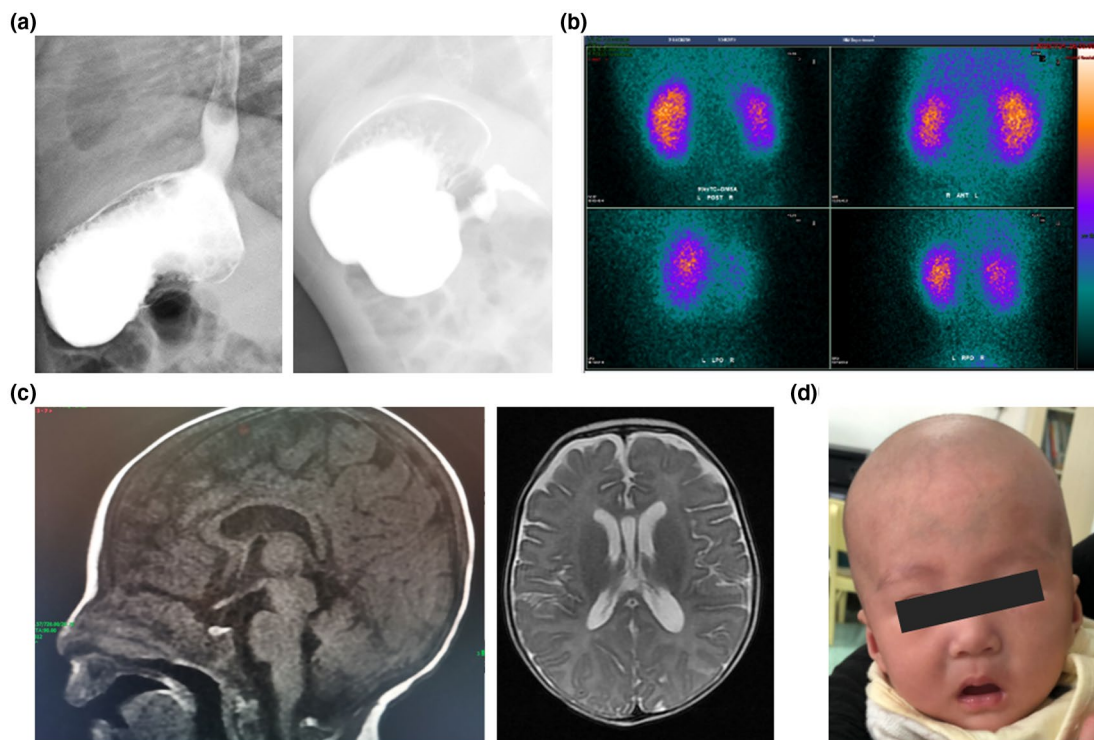
## 3 | RESULTS

### 3.1 | Clinical finding

The proband is the second child from normal nonconsanguineous parents without known family history of inherited

disease, and the first child is a healthy boy with normal growth and neurodevelopment. This girl was born by cesarean delivery at 39 weeks of gestation after uneventful pregnancy. Her newborn measurements were within normal range (weight of 2.8 kg, length of 49 cm, and head circumference of 34 cm), and no obvious congenital anomaly was observed. She was admitted to the hospital at the age of 2 months because of fever (39.2°C) and urinary tract infection. Physical examination indicated that she failed to thrive with lower weight (3.8 kg, <3rd) and length (54 cm, <3rd). Her subcutaneous fat was thin. Laboratory urinary sediment examination showed abnormal numbers of WBC (white blood cells) (10,659/ $\mu$ l), RBC (179/ $\mu$ l), and protein cast (7/ $\mu$ l). Blood routine examination was normal. Ultrasound sonography for heart revealed slight blood left-to-right shunting, suggesting foramen ovale or atrial septal defect in the patient.

The angiography of digestive tract found gastroesophageal reflux and intermittent pyloric spasm (Figure 1a). Renal ultrasound scanning did not show obvious change in position, size, and morphology. 99mTc-DMSA static renal scintigraphy showed abnormal appearance of right kidney, with overall lower uptake compared with left one (40.58% vs. 59.42%), and lower uptake (54% and 47%) in two areas (0.8 cm  $\times$  0.9 cm and 0.6 cm  $\times$  1.0 cm), respectively, compared with normal, and the examination of left kidney showed normal (Figure 1b). In addition, excretion urography



**FIGURE 1** Clinical and imaging features of the patient. (a) Gastroesophageal reflux and intermittent pyloric obstruction observed by radiography. (b) 99mTc-DMSA static renal scintigraphy showed abnormal appearance of right kidney, with lower uptake compared with left one. (c) Brain MR images showed the enlarged left lateral ventricle observed in the patient at the age of 2 months old. (d) The dysmorphic facial features, including mild facial asymmetry, fullness of upper eyelids, bulbous nose, malar fattening, and pointed chin

found vesicoureteral reflux (III) in the right (Figure 1b). The brain MRI suggested enlarged left lateral ventricle (Figure 1c). This girl was diagnosed with acute pyelonephritis, bilateral vesicoureteral reflux (grade III), gastroesophageal reflux, and malnutrition. She was discharged after 10 days of anti-infection treatment. After 2 months, she was re-admitted due to acute pyelonephritis, received similar treatment, and released after 1 week.

Around the age of 5 months, she was unable to raise her head steadily without support, and she had a weight of 4.5 kg (<3rd) and a length of 65 cm (<50th), with a thin subcutaneous fat. Dysmorphic facial features were observed, including mild facial asymmetry, malar fattening, sparse hair and eyebrows, fullness of upper eyelids, bulbous nose, low-set ears, long philtrum, and pointed chin (Figure 1d). Blood and urine routine test and other laboratory examination for thyroid, liver, and renal functions resulted in normal range. Echocardiography, EEG, and audiological examination were normal. This patient was discharged after 2-week rehabilitation in hospital for family reasons. A follow-up by phone at age of 9 months revealed DD; the baby was not able to crawl and not sit independently.

### 3.2 | WES identified *YY1* as the candidate pathogenic gene

Using WES, a total of 51.1 million clean reads were obtained, with average sequencing depth of 109.52X and 99.02% of whole exome target region covered at least 20X. A total number of 86448 variants (SNVs and Indels) were detected in this trio-WES. There were 21,843 wild-type variations in the proband, 18,728 variations in the intron deep region (>30 bp), 3632 variations with allele frequencies (dbSNP/1000G/GnomAD/ESP/in house) less than 0.2 or allele depths less than 4X, and 39 variations with insertions greater than 50 bp. The variations were further analyzed according to ACMG standards and guidelines. As a result, 42116 benign variations, 522 likely benign variations, 1834 uncertain significance variations, 45 likely pathogenic variations, and 6 pathogenic variations were obtained (Table S1).

Furthermore, 619 variations were annotated in OMIM disease database associated with pathogenic or likely pathogenic or uncertain significance variations, in which a total of 34 variations were in line with the family separation according to genetic rules, such as autosomal recessive, autosomal dominant, X-linked dominant patterns, and genomic imprinting, and one variation could explain the clinical characteristics of the patient. All these genetic variants were screened by pathogenicity, mode of inheritance, and clinical phenotypes (Table 1). As a result, we identified a de novo heterozygous missense mutation (c.1124G>A, p.Arg-375Gln) in the exon 5 of *YY1* gene (NM\_003403.5), which

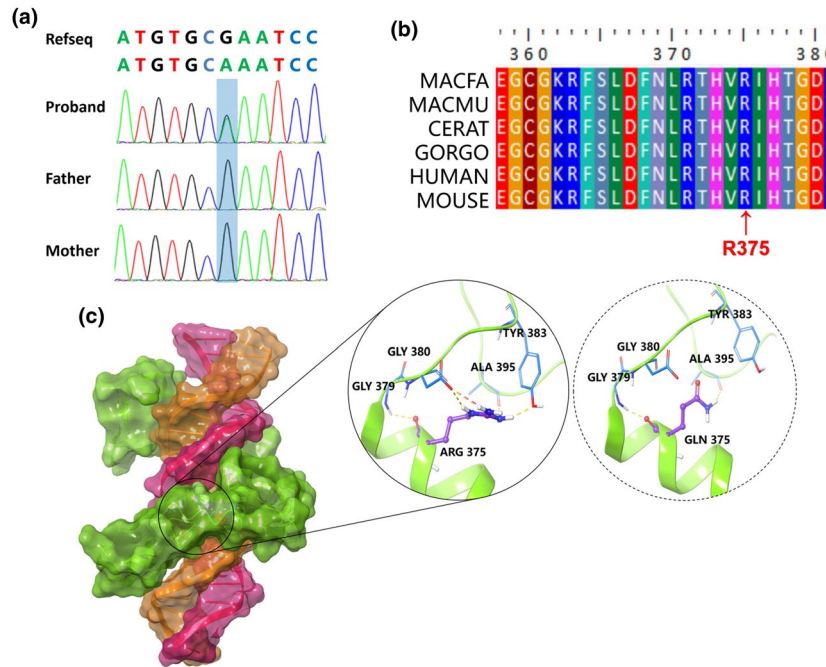
was confirmed by Sanger sequencing and from the paternal allele by allele co-segregation analysis (Figure 2a). This variant was not listed in dbSNP, HGMD, Decipher, 1000 Genomes project, or ClinVar, and it is a novel germline mutation. The prediction of function of this missense mutation with online software (SIFT, PolyPhen-2, MutationTaster, CADD, and PROVEAN) was damaging or probably damaging. According to ACMG guidelines (Richards et al., 2015), this variant was classified as likely pathogenic.

### 3.3 | Sequential analysis and Structural modeling

The point mutation sites are relatively conserved among different species (Figure 2b). As this variant is located within the third zinc finger domain of *YY1*, to further explore the possible impact of the substitution, we applied 3D structure modeling to see the interaction between different atoms using PDB and PyMol (Figure 2c). The H atom of the guanidyl group of the side chain of ARG-375 forms hydrogen bonds with the CO of ASP 380, the CO of TYR-383,

**TABLE 1** The sequencing parameters of NGS and the number of variants filtered at different levels of a hierarchy

Sequencing parameters of NGS	
The percentage of target sequencing coverage (Q20)	99.02%
The average depth for WES	109.52X
Total clean reads	51,169,414
Number of variants at different levels of hierarchy	
Total variants from trio whole exome and partial intron sequencing	86,448
First round of filtering criteria (variants were excluded using filtering criteria)	
Proband wild-type	21,843
Intron >30 bp	18,728
Variant Allele frequencies <0.2 or allele depths <4X	3632
Indel >50 bp	39
Classified according to 2015 ACMG guidelines	
Benign	42,116
Likely benign	522
Uncertain significance	1834
Likely pathogenic	45
Pathogenic	6
Second round of filtering criteria	
Pathogenic/Like pathogenic/Uncertain of variants with OMIM database	619
Co-segregation analysis	34
Variants related to the patient's clinical phenotype	1



**FIGURE 2** Sanger sequencing, sequential analysis, and 3D structure modeling. (a) The mutation, c.1124G>A, identified in *YY1* (NM\_003403.5) in the proband but not found in her parents, the mutation in red was found in our patient. (b) Amino acid alignment showed that *YY1*, including the point mutation sites (red arrows), is highly conserved among species, MACAF *Macaca fascicularis*, MACMU *Macaca mulatta*, CERAT *Cercocebus atys*, GORGO *Gorilla gorilla gorilla*, HUMAN *Homo sapiens*, MOUSE *Mus musculus*. (c) The H atom of the guanidyl group of the side chain of ARG-375 forms hydrogen bonds with the CO of ASP 380, the CO of TYR-383, and the CO of the amide skeleton of ALA 395; the N atom forms salt bridge with the CO of ASP 380. In addition, the O atom of the CO backbone of ARG 375 forms a hydrogen bond with the H atom of the amide backbone of GLY 379. When ARG 375 mutates into GLN, the interaction between GLN375 and nearby amino acids is reduced

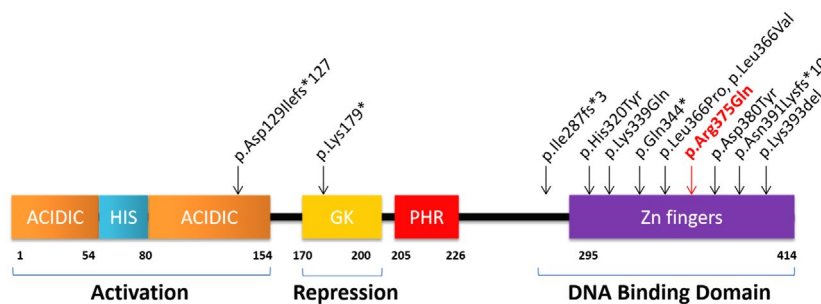
and the CO of the amide skeleton of ALA 395; the N atom forms salt bridge with the CO of ASP 380. In addition, the O atom of the CO backbone of ARG 375 forms a hydrogen bond with the H atom of the amide backbone of GLY 379. It can be seen that ARG375 forms an important interaction with nearby amino acids, which stabilizes the complex of protein and DNA. When ARG 375 mutates into GLN, the interaction between GLN375 and nearby amino acids is reduced, which may have uncertain effect on the stability of protein and DNA complexes. Collectively, structural modeling data demonstrated that the variant may play a role in the etiology and diagnosis of our case.

## 4 | DISCUSSION

*YY1* was first identified in 1991, representing Chinese word, as it was known as a dual function transcription factor to regulate transcriptional repression (Yin) and activation (Yang) of many genes (Sarvagalla et al., 2019). *YY1* was involved in diverse cellular processing and diseases, including cancer, by direct binding to the corresponding gene promoter or indirectly through association with chromatin remodeling proteins and histone modifiers. Many somatic

mutations in *YY1* gene were found in various cancers, which are listed in COSMIC (<https://cancer.sanger.ac.uk/cosmic>). Among these mutations, a recurrent mutation, T372R, was frequently found in insulinomas (10%-30%), especially in Asian populations (Cao et al., 2013; Lichtenauer et al., 2015).

In 2010, the first germline mutation (c.1138G>T p.Asp-380Tyr) in *YY1* gene was reported in a 3-year-old boy with intrauterine growth retardation, moderate ID, and dysmorphic features (Vissers et al., 2010). In 2017, *YY1*-associated syndrome was characterized in 23 patients by direct Sanger sequencing for *YY1* mutations or by exome sequencing, respectively, for 500 individuals and for 14,969 individuals with unexplained ID from Japan, Swiss, Norway, and USA (Gabriele et al., 2017). After sequencing, in addition to 13 microdeletions, they identified 10 germline *YY1* gene mutations, including five missense mutations [c.958C>T (p.His320Tyr), c.1015A>C (p.Lys339Gln), c.1097T>C (p.Leu366Pro), c.1096C>G (p.Leu366Val), and c.1138G>T (p.Asp380Tyr)], two frameshift mutations [c.1173del (p.Asn391Lysfs\*10) and c.385del (p.Asp129Ilefs\*127)], two nonsense mutations [c.1030C>T (p.Gln344\*) and c.535A>T (p.Lys179\*)], and one 3 bp-deletion (c.1174\_1176del, p.Lys393del). Recently, Morales-Rosado JA et al. (Morales-Rosado et al., 2018) identified a truncating mutation, c.860\_864del, p.Ile287Argfs\*3,



**FIGURE 3** Schematic diagrams showing the structure of YY1 protein. Mutations associated with GADEVS were shown

in the *YY1* gene in a 25-year-old female with learning disability, autoimmune myasthenia gravis, facial dysmorphism, and delayed motor development, which indicates the underestimation of *YY1* defects in patients with variable NDDs. Most of these mutations identified are situated in zinc fingers, which is a DNA-binding domain (Figure 3). So far, most mutations identified in *YY1*-associated syndrome are located within zinc fingers or repression domain, and a few truncated mutations were reported in N-terminal domain, but no missense mutation appears at the N-terminal, and our patient is the first reported case. The missense mutation identified in our patient, c.1124G>A, p.Arg375Gln, is highly conserve across species and located within the third zinc finger. Previous study showed that the variant, c.1138G>T (p.Asp380Tyr), could disrupt the hydrogen bonds with surrounding residues, thus affecting the structure of YY1 and its interaction with cofactors, while the change of amino acid at the 366 residue lowered the steric hindrance and increased the surface-accessible area of the Phe368 side chain (Gabriele et al., 2017).

Our prediction by 3D modeling showed that the H on the guanidyl group and the carbonyl O atom of the backbone of Arg 375 interact with nearby amino acids, which is important to maintain the stability of protein and DNA complexes. The substitution of Arg with Gln at the 375 side chain could impair the interaction, and probably disrupting DNA binding to its interacting partner. The mutation in silico disrupts the hydrogen bonds with surrounding residues, and appears to impair the stability of protein structure. As this has been already observed for other pathological *YY1* mutations, suggesting a similar disruptive mechanism. However, further study is needed to investigate the detailed molecular mechanism.

Our patient presented with development delay, growth retardation, and facial dysmorphism, which matches those patients with pathogenic mutations in *YY1* gene. Our patient showed vesicoureteral reflux (III), gastroesophageal reflux, and intermittent pyloric spasm, which could attribute to the dysplasia connective tissue involved and had not been reported previously, instead, two patients with *YY1*-associated syndrome had hydronephrosis, and one with ureteropelvic junction, and one with esophageal atresia (Gabriele et al.,

2017). It could be due to vesicoureteral reflux, our patient had recurrent infections (acute pyelonephritis), and only one patient with *YY1* mutation (c.1097T>C, p.Leu366Pro) also had recurrent infection (Gabriele et al., 2017); however, the information about the organ involved was not available. Enlarged left lateral ventricle in brain was found in our patient, consistent with imaging findings from one patient reported previously with a 3 bp-deletion mutation (c.1174\_1176del, p.Lys393del) (Gabriele et al., 2017). Cardiac abnormalities were found in three patients (Gabriele et al., 2017; Morales-Rosado et al., 2018), and one of them had congenital myopathy (Morales-Rosado et al., 2018); however, no obvious abnormality was detected in our patient at the age of 5 months.

## 5 | CONCLUSION

We identified a de novo missense mutation in *YY1* gene in a Chinese patient with similar clinical phenotypes to GADEVS, and this variant is classified as likely pathogenic according to ACMG standards and guidelines. This is the first time to report a patient with *YY1*-associated syndrome in China, and this report expanded the clinical phenotype and mutation spectrum of *YY1*. In order to clarify the detailed molecular mechanism of this variant, further study should be considered.

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## CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

Study concepts: Xuelian He, Aifen Zhou, and Jun Lin. Study design: Li Tan, Aifen Zhou, and Jun Lin. Literature research: Ying

Li and Fan Liu. Clinical information collection: Jun Lin, Fan Liu, and Ying Li. Data acquisition: Ying Li, Fan liu, Yufeng Huang, Sukun Luo, and Weiyue Gu. Data analysis/interpretation: Ying Li, Fan Liu, Peiwei Zhao, and Weiyue Gu. Manuscript preparation: Xuelian He and Li Tan. Manuscript editing: Xuelian He. Manuscript revision/review: Aifen Zhou and Jun Lin. Manuscript final version approval: Aifen Zhou and Jun Lin.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethics approval was given by the institutional review board of Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology (WCH 2019011).

## PATIENT CONSENT FOR PUBLICATION

A written consent was obtained from our patient's parents.

## DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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## REFERENCES

- Bushmeyer, S., Park, K., & Atchison, M. L. (1995). Characterization of functional domains within the multifunctional transcription factor, YY1. *Journal of Biological Chemistry*, *270*(50), 30213–30220. <https://doi.org/10.1074/jbc.270.50.30213>.
- Cao, Y., Gao, Z., Li, L., Jiang, X., Shan, A., Cai, J., Peng, Y., Li, Y., Jiang, X., Huang, X., Wang, J., Wei, Q., Qin, G., Zhao, J., Jin, X., Liu, L. I., Li, Y., Wang, W., Wang, J., & Ning, G. (2013). 'Whole exome sequencing of insulinoma reveals recurrent T372R mutations in YY1'. *Nature Communications*, *4*, 1–6. <https://doi.org/10.1038/ncomms3810>
- De Vries, B. B. A. (2019) Gabriele-de Vries Syndrome Summary Genetic counseling. pp. 1–15.
- Donohoe, M. E., Zhang, X., McGinnis, L., Biggers, J., Li, E. N., & 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>
- Figiel, M., & Górecki, A. (2017). Physical interaction of human Yin Yang 1 protein with DNA. *Critical Reviews in Oncogenesis*, *22* (1–2), 75–97. <https://doi.org/10.1615/CritRevOncog.2017020976>
- 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>
- Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C., Evans, J. P., Herman, G. E., Hufnagel, S. B., Klein, T. E., Korf, B. R., McKelvey, K. D., Ormond, K. E., Richards, C. S., Vlangos, C. N., Watson, M., Martin, C. L., Miller, D. T. (2016). ACMG Statement Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. IOP Publishing, (November). <https://doi.org/10.1038/gim.2016.190>
- Lichtenauer, U. D., Di Dalmazi, G., Slater, E. P., Wieland, T., Kuebart, A., Schmittfull, A., Schwarzmayr, T., Diener, S., Wiese, D., Thasler, W. E., Reincke, M., Meitinger, T., Schott, M., Fassnacht, M., Bartsch, D. K., Strom, T. M., & Beuschlein, F. (2015). Frequency and clinical correlates of somatic Ying Yang 1 mutations in sporadic insulinomas. *Journal of Clinical Endocrinology and Metabolism*, *100*(5), E776–E782. <https://doi.org/10.1210/jc.2015-1100>
- 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., & Rehms, H. L. (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>
- Sarvagalla, S., Kolapalli, S. P., & Vallabhapurapu, S. (2019). The Two Sides of YY1 in cancer: A friend and a foe. *Frontiers in Oncology*, *9*(November), 10–13. <https://doi.org/10.3389/fonc.2019.01230>
- Visser, L. E. L. M., de Ligt, J., Gilissen, C., Janssen, I., Stehouwer, M., de Vries, P., van Lier, B., Arts, P., Wieskamp, N., del Rosario, M., van Bon, B. W. M., Hoischen, A., de Vries, B. B. A., Brunner, H. G., & Veltman, J. A. (2010). A de novo paradigm for mental retardation. *Nature Genetics*. *Nature Publishing Group*, *42*(12), 1109–1112. <https://doi.org/10.1038/ng.712>
- Yang, W.-M., Inouye, C., Zeng, Y., Bearss, D., & Seto, E. (1996). Transcriptional repression by YY1 is mediated by interaction with a mammalian homolog of the yeast global regulator RPD3. *Proceedings of the National Academy of Sciences*, *93*(23), 12845–12850. <https://doi.org/10.1073/pnas.93.23.12845>

## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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