Two Novel Mutations in the SI Gene Associated With Congenital Sucrase-Isomaltase Deficiency: A Case Report in China

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Background: Congenital sucrase-isomaltase deficiency (CSID) is an autosomal recessive inherited disease that leads to the maldigestion of disaccharides and is associated with mutation of the sucrase-isomaltase (SI) gene. Cases of CSID are not very prevalent in China or worldwide but are gradually being identified and reported.

Case Presentation: We report a case involving a 14-month-old male who presented with failure to thrive that had begun after food diversification and was admitted for chronic diarrhea. We used a whole-exome sequencing (WES) approach to identify mutations in this patient’s genome. WES revealed two novel heterozygous mutations in the SI gene, c.2626C > T (p.Q876*) and c.2872C > T (p.R958C), which were confirmed by Sanger DNA sequencing. With a strict sucrose- and starch-restricted diet, the patient’s diarrhea was resolved, and he began to gain weight.

Conclusions: We report a case of novel variants in the SI gene that caused CSID. This report provides valuable information for the clinical field, especially in China.

Keywords: congenital, sucrase-isomaltase deficiency, mutation, gene, case report

INTRODUCTION

Congenital sucrase-isomaltase deficiency (CSID, OMIM #222900) was first reported in 1960 by Weijers et al. (1). This deficiency has been defined as an autosomal recessive disease that is characterized by loss of sucrase or sucrase-isomaltase (SI) activities (2). Upon the ingestion of disaccharides and oligosaccharides, osmotic-fermentative diarrhea occurs due to the failure of sucrose breakdown into fructose and glucose. As a result, patients with CSID have chronic diarrhea, abdominal pain, and abdominal distension, leading to failure to thrive. The estimated prevalence of CSID in North America and Europe ranges from 0.05 to 0.2% (3), while in the Inuit population of Greenland, it ranges from 5 to 10% (4). However, the prevalence of CSID in the Chinese population is unknown (5).

Currently, the confirmation of complete or near-complete absence of sucrase and/or isomaltase activities in biopsy tissue from the small bowel is the diagnostic gold standard for CSID (6). This approach is straightforward but invasive and is difficult to implement in young patients. Lifelong sucrose restriction is an effective therapy for CSID patients (7).

At the genetic level, this condition results from compound heterozygous or homozygous mutations in the sucrase-isomaltase gene (SI, OMIM #609845), which is located on chromosome 3q26.1 (7). This locus encodes a small intestine brush-border membrane disaccharidase that is
required for the hydrolysis of some starches and sucrose. The first identification of a mutation in the SI gene associated with CSID was described by Ouwendijk et al. (8). Previous reports have shown associations of SI mutations with irritable bowel syndrome (9). Genetic testing of the SI gene for this condition is now clinically available. To date, more than 40 mutations of the SI gene that are associated with CSID have been identified (10). Here, we report a case of CSID with two novel variants of the SI gene.

**CASE PRESENTATION**

The patient was a 14-month-old male admitted to our hospital for chronic diarrhea, abdominal distention, and failure to thrive. He was the second child of healthy and non-consanguineous parents. Both his father and brother had a history of frequent episodes of diarrhea in their youth.

*Abbreviations: CSID, congenital sucrase-isomaltase deficiency; SI, sucrase-isomaltase; kg, kilogram; IgE, immunoglobulin E; ACMG, American College of Medical Genetics and Genomics.*

The patient was born at 39 weeks with a height of 50 cm, and he weighed approximately 3 kg (between the age- and sex-specific 15–25th percentile). He was breastfed at birth and showed ordinary growth until 3 months old (weight: 6 kg, at the age- and sex-specific 15–25th percentile), at which time food diversification began with goat milk, rice paste, and so on. After this dietary change for several days, he began to have seven to eight episodes per day of non-bloody watery stools and had poor weight gain. Formula changes, including deep hydrolysis formulas and amino acid formulas, were attempted without the patient showing signs of improvement. He was admitted to more than three hospitals at the ages of 6 months, 9 months, and 12 months, but treatment for a cow’s milk protein allergy did not work.

A physical examination in our hospital suggested an alert infant with a severe reduction in subcutaneous fat. He weighed 5.6 kg (below the age- and sex-specific 3rd percentile) and had not gained weight for 11 months. He could not sit, crawl, or walk by himself.

The results of a laboratory examination showed that the patient’s blood count levels, C-reactive protein levels, liver...
function, renal function and other blood or stool tests were normal. Imageology examination that included abdominal radiographs suggested intestinal motility changes without any signs of intestinal obstruction (Figure 1).

Although his parents did not consent to an invasive biopsy of small bowel tissue, they agreed to whole-exome sequencing (WES) to identify their son’s underlying genetic mutations. A genetic study was carried out after approval from the Clinical Research Ethics Committee. Informed consent was obtained. His parents also received genetic testing.

As a result, two novel heterozygous mutations, c.2626C > T (p.Q876*) (inherited from his father) and c.2872C > T (p.R958C) (inherited from his mother), in the SI gene were identified and confirmed by Sanger sequencing (Figures 2A, B), leading to the diagnosis of CSID.

This patient was given a strict sucrose- and starch-restricted diet. Without sucrose and starch, the patient’s diarrhea resolved.

**FIGURE 2** | Heterozygous SI mutations: (A) A non-sense mutation c.2626C > T (p.Q876*) and (B) missense mutation c.2872C > T (p.R958C) were identified in the patient (upper panels), while healthy control individuals had the wild-type sequence (lower panels). (C) The structure of the SI protein (NP_001032.2), depicting the functional domains, 40 reported mutations, and two mutations in this case. The mutations identified in this study are marked in red (novel), and previously reported mutations are marked in black. AA, amino acids.
## TABLE 1 | Genotypic and phenotypic features of all reported patients with CSID and Sf mutations.

| Case (reference) | Genotypic features | Clinical manifestations |
|------------------|--------------------|-------------------------|
|                  | Nt(AA) change       | Mutation type           | Zygotic type | Domain of mutation | Geographical origin | Sex (F/M) | Diarrhea | Onset of diarrhea | Failure to thrive | Enzyme activities |
|                  | (NM_001041.4)       |                        |             |                  |                    |           |         |                   |                   | Sucrase | Isomaltase |
| Present          | c.2626C > T (p.Q876*) | Non-sense              | Compound heterozygote | Isomaltase | Asia              | M         | 19/60   | +                  | 3 months          | +                  | NA | NA |
|                  | c.2872C > T (p.R958C) | Missense               | Homozygote   | Isomaltase       |                    | F         | 29/29   | +                  | 9 days            | +                  | NA | NA |
| Marcadier et al. (16) | c.273_274delAG (p.Gly92Leufs*8) | Frameshift           | Homozygote   | Stalk             | America            | F         | 19/60   | +                  |                | +                  | Reduced | Reduced |
| Gerick et al. (5) | c.315G > T (p.Trp105Cys) | Missense              | Compound heterozygote | Stalk | Europe            | NA        | 29/29   | +                  |                | +                  | Reduced | Reduced |
|                  | p.Trp931*          | Non-sense              | Homozygote   | Isomaltase       | Europe             | NA        | 28/28   | +                  |                | +                  | Reduced | Reduced |
| Spodsberg et al. (13) | c.350A > G (p.Gln117Arg) | Missense              | Homozygote   | Isomaltase       | Europe             | NA        | 28/28   | +                  |                | +                  | Reduced | Reduced |
| Gerick et al. (5) | c.416T > A (Phe139Tyr) | Missense              | NA           | Isomaltase       | Europe             | NA        | 28/28   | +                  |                | +                  | Normal | Normal |
| Capalbo et al. (17) | c.853G > T (p.Glu285*) | Non-sense              | Heterozygote | Isomaltase       | America            | F         | 28/28   | +                  |                | +                  | NA | NA |
| Capalbo et al. (17) | c.853G > T (p.Glu285*) | Non-sense              | Heterozygote | Isomaltase       | America            | M         | 28/28   | +                  |                | +                  | NA | NA |
| Gerick et al. (5) | p.Gln907Try | Missense              | NA           | Isomaltase       | Europe             | NA        | 28/28   | +                  |                | +                  | Normal | Normal |
| Jacob et al. (12) | c.1021T > C (p.Leu340Pro) | Missense              | Homozygote   | Isomaltase       | Europe             | NA        | 28/28   | +                  |                | +                  | Normal | Normal |
| Gerick et al. (5) | c.1607A > T (p.Asp536Val) | Missense              | Compound heterozygote | Isomaltase | Europe             | NA        | 28/28   | +                  |                | +                  | Reduced | Inactive |
| Sander et al. (2) | c.1648delC | Frameshift           | Compound heterozygote | Isomaltase | Europe             | M         | 28/28   | +                  |                | +                  | NA | NA |
| Sander et al. (2) | c.4099A > G (p.Arg1367Gly) | Missense              | Compound heterozygote | Isomaltase | Europe             | NA        | 28/28   | +                  |                | +                  | NA | NA |
| Sander et al. (2) | c.4099A > G (p.Arg1367Gly) | Missense              | Substrate     | Sucrase           | Europe             | NA        | 28/28   | +                  |                | +                  | Inactive | Inactive |
| Sander et al. (2) | c.4099A > G (p.Arg1367Gly) | Missense              | Compound heterozygote | Isomaltase | Europe             | NA        | 28/28   | +                  |                | +                  | Inactive | Inactive |
| Sander et al. (2) | c.4099A > G (p.Arg1367Gly) | Missense              | Compound heterozygote | Isomaltase | Europe             | NA        | 28/28   | +                  |                | +                  | Inactive | Inactive |

(Continued)
| Case (reference) | Nt(AA) change (NM_001041.4) | Mutation type | Zygotic type | Domain of mutation | Geographical origin | Sex (F/M) | Diarrhea | Onset of diarrhea | Failure to thrive | Enzyme activities | Sucrase | Isomaltase |
|------------------|-----------------------------|---------------|--------------|-------------------|-------------------|-----------|----------|-------------------|-----------------|-----------------|---------|-----------|
| Sander et al. (2) | c.1730T > G (p.Val577Gly)   | Missense      | Compound heterozygote | Europe             | M     | +      | NA    | +                     | Inactive            | Inactive       |         |           |
|                  | c.3218G > A (p.Asp1073Gly)  | Missense      | Sucrese      |                   |       |        |       |                       |                   |                |         |           |
| Capalbo et al. (17) | c.1730T > G (p.Val577Gly)   | Missense      | Heterozygote Isomaltase | America           | F(6cases) | NA     | NA     | NA     | NA     | NA      |         |           |
| Capalbo et al. (17) | c.1730T > G (p.Val577Gly)   | Missense      | Heterozygote Isomaltase | America           | M(18cases) | NA     | NA     | NA     | NA     | NA      |         |           |
| Ceyhan-Birsoy et al. (18) | c.1730T > G (p.Val577Gly)   | Missense      | NA           | Isomaltase        | America | NA     | NA     | NA     | NA     | NA      |         |           |
| Gericke et al. (6) | c.1780T > C (p.Ser594Pro)   | Missense      | NA           | Isomaltase        | Europe  | NA     | +      | NA     | +      | NA      |         |           |
| Ritz et al. (14) | c.1859T > C (p.Leu620Pro)   | Missense      | Homozygote Isomaltase | Europe            | NA     | +      | NA     | +      | Inactive | Inactive |         |           |
| Keiser et al. (15) | c.1903T > C (p.Cys635Arg)   | Missense      | Homozygote Isomaltase | Europe            | M      | +      | NA     | +      | Reduced | Reduced |         |           |
| Hou et al. (23) | c.1903delT (p.Cys646fs)     | Frameshift    | Heterozygote Isomaltase | America    | NA     | NA     | NA     | NA     | NA     | NA      |         |           |
| Sander et al. (2) | c.2080A > C (p.Trp694Pro)   | Missense      | Heterozygote Isomaltase | Europe            | NA     | +      | NA     | +      | NA      | NA      |         |           |
| Ceyhan-Birsoy et al. (18) | c.2159+2T > G   | Splicing      | NA           | Isomaltase        | America | NA     | NA     | NA     | NA     | NA      |         |           |
| Gericke et al. (6) | p.Leu741Pro            | Missense      | Compound heterozygote | Europe            | NA     | +      | NA     | +      | Inactive | Inactive |         |           |
|                  | c.5234T > G (p.Phe1745Cys) | Missense      | Sucrese      |                   |       |        |       |                       |                   |                |         |           |
| Wang et al. (21) | c.2311delA            | Frameshift    | Compound heterozygote | Asia              | F      | +      | NA     | NA     | NA     | NA      |         |           |
|                  | c.5056C > T (p.Arg1686Cys) | Missense      | Sucrese      |                   |       |        |       |                       |                   |                |         |           |
| Cheema et al. (19) | c.2401G > T (p.Glu801*)  | Non-sense     | NA           | Isomaltase        | Asia   | NA     | NA     | NA     | NA     | NA      |         |           |
| Gericke et al. (6) | c.2789A > G (p.Gln930Arg) | Missense      | Compound heterozygote | Europe            | NA     | +      | NA     | +      | Normal  | Normal  |         |           |
|                  | p.Arg1544Cys          | Missense      | Sucrese      |                   |       |        |       |                       |                   |                |         |           |
| Gericke et al. (6) | p.Trp931Arg           | Missense      | Compound heterozygote | Europe            | NA     | +      | NA     | +      | Reduced | Reduced |         |           |
|                  | p.Thr1606Ile          | Missense      | Sucrese      |                   |       |        |       |                       |                   |                |         |           |

(Continued)
| Case (reference) | Nt(AA) change (NM_001041.4) | Genotypic features | Clinical manifestations |
|-----------------|------------------------------|--------------------|------------------------|
|                 | Mutation type                | Zygotic type       | Domain of mutation     | Sex (F/M) | Diarrhea | Onset of diarrhea | Failure to thrive | Enzyme activities |
|                 |                              |                    |                        |           | 19/60    | 29/29       | 28/28         | Sucrase | Isomaltase |
| Capalbo et al. (17) | c.3186_3187delTT (p.Tyr1063fs) | Frameshift | Heterozygote Sucrase | America | F | NA | NA | NA | NA |
| Capalbo et al. (17) | c.3186_3187delTT (p.Tyr1063fs) | Frameshift | Heterozygote Sucrase | America | M (8cases) | NA | NA | NA | NA | NA |
| Sander et al. (2) | c.3218G > A (p.Gly1073Asp) | Missense | Heterozygote Sucrase | Europe | NA | + | NA | + | Inactive | Inactive |
| Capalbo et al. (17) | c.3218G > A (p.Gly1073Asp) | Missense | Heterozygote Sucrase | America | F (4cases) | NA | NA | NA | NA | NA |
| Capalbo et al. (17) | c.3218G > A (p.Gly1073Asp) | Missense | Heterozygote Sucrase | America | M (18cases) | NA | NA | NA | NA | NA |
| Ceyhan-Birsoy et al. (18) | c.3218G > A (p.Gly1073Asp) | Missense | NA | Sucrase | America | NA | NA | NA | NA | NA |
| Hou et al. (23) | c.3292C > T (p.Arg1077*) | Non-sense | Heterozygote Sucrase | America | NA | NA | NA | NA | NA |
| Hou et al. (23) | c.3266G > A (p.Trp1089*) | Non-sense | Heterozygote Sucrase | America | NA | NA | NA | NA | NA |
| Ouwendijk et al. (3) | c.3293A > C (p.Gln1098Pro) | Missense | Homozygote Sucrase | Europe | NA | + | NA | + | Inactive | Inactive |
| Capalbo et al. (17) | c.3370C > T (p.Arg1124*) | Non-sense | Heterozygote Sucrase | America | F (2cases) | NA | NA | NA | NA | NA |
| Capalbo et al. (17) | c.3370C > T (p.Arg1124*) | Non-sense | Heterozygote Sucrase | America | M (6cases) | NA | NA | NA | NA | NA |
| Gericke et al. (6) | c.3370C > T (p.Arg1124*) | Non-sense | Compound heterozygote | Europe | NA | + | NA | + | Inactive | Inactive |
| Capalbo et al. (17) | c.3586_3587delAT (p.Met1196fs) | Frameshift | Heterozygote Sucrase | America | F | NA | NA | NA | NA | NA |
| Capalbo et al. (17) | c.3586_3587delAT (p.Met1196fs) | Frameshift | Heterozygote Sucrase | America | M (2cases) | NA | NA | NA | NA | NA |
| Sander et al. (2) | c.3686G > A (p.Cys1229Tyr) | Missense | Compound heterozygote | Europe | F | + | NA | + | Inactive | Reduced |
| Sander et al. (2) | c.5234T > G (p.Phe1745Cys) | Missense | Sucrase | Inactive | Inactive |
| Naim et al. (7) | c.4427G > C (p.Gly1476Ala) | Missense | Heterozygote Sucrase | Europe | F | + | NA | + | Inactive | Reduced |
| Gericke et al. (6) | c.4592G > A (p.Cys1531Tyr) | Missense | Compound heterozygote | Europe | NA | + | NA | + | Inactive | Reduced |
| Gericke et al. (6) | c.3218G > A (p.Gly1073Asp) | Missense | Sucrase | Inactive | Inactive |

(Continued)
TABLE 1 | Continued

| Case (reference) | Nt(AA) change (NM_001041.4) | Mutationtype | Zygotictype | Domain of mutation | Geographical origin | Sex (F/M) | Diarrhea | Onset of diarrhea | Enzyme activities | Sucrase | Isomaltase |
|------------------|----------------------------|--------------|-------------|-------------------|--------------------|-----------|----------|------------------|-----------------|---------|------------|
| Haberman et al. (11) | c.4593T > G (p.Cys1531Trp) | Missense | Compound heterozygote | Sucrase | Asia | NA | NA | 28/28 | + | + |
| Capalbo et al. (17) | c.1730T > G (p.Val577Gly) | Missense | Isomaltase | NA | NA | + | + |
| Sander et al. (2) | c.5110C > T (p.Arg1704*) | Non-sense | Heterozygote | Sucrase | America | F | NA | + | + |
| Sander et al. (2) | c.5234T > G (p.Phe1745Cys) | Missense | Heterozygote | Sucrase | Europe | M | NA | + | + |
| Sander et al. (2) | c.5234T > G (p.Phe1745Cys) | Missense | Heterozygote | Sucrase | Europe | M | NA | + | + |

F, female; M, male; CSID, Congenital sucrase-isomaltase deficiency; SI, sucrase-isomaltase; +, symptomatic; NA, Not available. The red shows the current cases.

Follow-up revealed that the patient grew and that gradually caught up in weight with other children his age. Three months later (at 17 months old), he weighed 7.6 kg (below the age- and sex-specific 3rd percentile); 1 year later (at 2 years and 2 months old), he weighed 10.5 kg (below the age- and sex-specific 3rd percentile); and 3 years later (at 4 years and 2 months old), he weighed 15 kg (at the age- and sex-specific 15–25th percentile) and was 104 cm tall (at the age- and sex-specific 25–50th percentile). Furthermore, he had learned to sit, crawl, walk, and run (gradually catching up with other children his age), which he could not do before. These observations suggested that our treatment was effective.

DISCUSSION AND CONCLUSION

CSID is an inherited disease that occurs due to pathogenic variants of the SI gene (7). The phenotypes of patients are heterogeneous and vary according to onset age. Patients with an onset of CSID in infancy typically present symptoms that include diarrhea and failure to thrive, as observed in our case. Patients with an onset of CSID in childhood or adulthood present milder symptoms with only chronic diarrhea and have normal growth rates (11). According to a summary of previously reported cases (2, 6–8, 11–21), the incidence of CSID differs between females and males (19/60) (Table 1). However, in some of these cases, sex was not reported. The patients had diarrhea (29/29) and failure to thrive (28/28). However, one study reported 31 cases that were not included (22). This disease, caused by gene mutations, has been reported in Asian (3/135, 2.22%), European (26/135, 19.26%), and American (106/135, 78.52%) populations, with the majority of cases detected in Europe and America (Table 1) (including 31 cases involving American children). To date, only four patients with CSID have been reported in China, one of whom was reported to have compound heterozygous mutations in the SI gene (5, 21).

Homozygous or compound heterozygous mutations in the SI gene were found via genetic testing to have caused CSID in our patient (7). We performed WES in this patient to confirm the diagnosis of CSID. WES identified novel compound heterozygous variants (c.2626C > T and c.2872C > T) in the SI gene. The p.Q876* mutation can be interpreted as “likely pathogenic” according to the American College of Medical Genetics and Genomics (ACMG) standard, as this mutation is a null variant (pathogenic criterion PVS1) that is absent from controls (PM1) (23). The other variant, p.R958C, can also be classified as likely pathogenic, since this variant has an extremely low frequency in controls (PM1) and was detected in trans with another likely pathogenic variant (PM3). This variant was also predicted by multiple lines of prediction software to be deleterious (PM): it was predicted to be “deleterious” by PROVEAN, with a score of 6.45 (24); predicted to be “damaging” by SIFT, with a score of 0.000 (http://sift.bii.a-star.edu.sg); and predicted to be “probably damaging” by polyphen2, with a score of 1.0 (http://genetics.bwh.harvard.edu/pph2). The phenotype of the patient was also specific to the disease (PP4). In addition, residue R958 is highly conserved across various species.
(Figure 3), which indicates the functional importance of this residue. Thus, the changes in residue properties may damage the structure and function of the final product. We considered that both of these phenotypes were disease-causing mutations.

The SI gene encodes a protein of 1,827 amino acids that has four membrane-spanning regions (membrane anchor, stalk region, isomaltase domain, and sucrase domain); this protein is preferentially expressed in the small intestinal microvillus membrane, performing terminal digestion of dietary sucrose and starch (7). The two mutations in our report were located in the isomaltase domain from residues 110 to 1,007; in previous reports, there were two mutations reported in the stalk region, 19 in the isomaltase domain and 17 in the sucrase domain (Figure 2C). The first null variant p.Q876* leads to a truncated protein with only 876 amino acids. Parts of the isomaltase domain and the whole sucrase domain are missing. All of the active sites in the sucrase domain, including residues 1,231, 1,259, 1,260, 1,295, 1,335, 1,393, 1,394, 1,395, 1,484, 1,497, 1,500, 1,533, and 1,558, are missing, which might seriously disrupt the function of the enzyme sucrase-isomaltase (25). The other mutation, p.R958C, is located in the trefoil factor domain from residues 935 to 980 of the isomaltase domain (https://www.ncbi.nlm.nih.gov/protein/NP_001032.2). This domain is highly expressed by mucus-producing cells and is thought to be related to mucosal defense (26).

According to the database Human Gene Mutation Database (HGMD) Professional, 40 mutations in the SI gene have been identified as associated with CSID (Table 1). The reported mutations included missense (25/40, 62.5%), non-sense (7/40, 17.5%), and frameshift mutations (6/40, 15.0%) and mutations at the splice site (2/40, 5.0%). Three zygotic mutations have also been reported, including homozygotes (6/97, 6.19%), compound heterozygotes (15/97, 15.46%), and one case of heterozygotes (76/97, 78.35%). Because details are lacking, the data from 31 American children are not included in the above summary.

Although we did not detect sucrase and/or isomaltase activity in biopsy tissue of the small bowel, most biopsies in the reported cases revealed reduced or absent enzyme activities (sucrase and isomaltase) (Table 1). Fortunately, after 3 years of follow-up, the patient in this report gradually grew under a strict sucrose- and starch-restricted diet. Therefore, lifelong sucrose restriction is an effective therapy for patients with CSID (7).

In conclusion, the clinical manifestations, genetic results, and effective treatment support our diagnosis. Without diagnosis, the treatment would not have been appropriate, and the boy may have continued to have diarrhea and failure to thrive. If endoscopy is not allowed, genetic evaluation with WES can be used as a diagnostic tool. Due to the development of the field of genetics, we were able to describe a novel case with mutations in the SI gene that caused CSID, which provides valuable information for the clinical field, especially in China.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Shenzhen Children's Hospital. Written informed consent to participate in this study was provided by the participant’s legal guardian/next of kin.

**AUTHOR CONTRIBUTIONS**

JZ, MC, and SZ: conceptualization and writing—original draft. YZ and XQ: data collection. YZ, XQ, YC, and HC: formal analysis. SZ: funding acquisition and project administration. JZ:
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supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.731716/full#supplementary-material
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