Novel Synonymous and Frameshift Variants in the TRIP12 Gene Identified in 2 Chinese Patients With Intellectual Disability

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Abstract

Background and Objectives
Clark-Baraitser syndrome is characterized by intellectual disability with or without autism spectrum disorders, speech delay, motor delay, behavioral abnormalities, and facial dysmorphism. It is caused by a heterozygous pathogenic variant in the thyroid hormone receptor interactor 12 (TRIP12) gene. However, loss of function and haploinsufficiency are the pathogenic mechanisms behind the TRIP12-related disorder.

Methods
We conducted an exome sequencing analysis for 2 unrelated patients with moderate intellectual disability, speech delay, and motor delay.

Results
We identified 2 de novo TRIP12 mutations in these 2 patients. One patient had a frameshift duplication, whereas the other had a synonymous variant. Both patients presented with common features of the syndrome, but clinical heterogeneity has been also observed between them. For the synonymous variant, reverse transcription PCR in RNA extracted from leukocytes demonstrated the presence of a truncated messenger RNA (mRNA) transcript that skipped exon 12. This transcript escapes degradation at the mRNA level. To assess the effect of the synonymous substitute on TRIP12 proteolytic activity, the expression of 9 known responsive genes at the mRNA level was measured, of which 3 genes were upregulated at least 2-fold in the patient.

Discussion
We reported 2 patients with Clark-Baraitser syndrome caused by novel synonymous and frameshift variants in the TRIP12 gene, and our study expands the mutation spectrum of the TRIP12 gene. This study will help to improve our understanding of variable phenotypic presentations in TRIP12-related disorders.
Intellectual disability (ID) is the most common neuro-developmental disorder and affects approximately 1%–3% of the general population across the world. The etiology of ID can be the result of a variety of genetic and environmental factors. The genetic causes are heterogeneous and include both chromosomal and monogenic etiologies. To date, at least 1,394 genes have been reported to be associated with ID.

The thyroid hormone receptor interactor 12 (TRIP12) gene (MIM# 604506) is referenced as a causative gene that is associated with autosomal dominant mental retardation 49 (MIM# 617752), which is also known as Clark-Baraitser syndrome. This syndrome is characterized by ID, with or without autism spectrum disorders (ASDs), speech delay, motor delay, behavioral abnormalities, and facial dysmorphism. Detailed characterization has been performed on a total of 24 patients with ID associated with TRIP12 variants. Almost 100 pathogenic variants, which include large fragment deletions, indels, and single nucleotide variations, have been documented in the Leiden Open Variation Database, ClinVar, or the Human Gene Mutation Database databases. Apart from the large fragment deletions that span the entire gene or a partial region of the gene, most pathogenic variations in the coding region of the TRIP12 gene are loss of function. These variations include 21 nonsense mutations, 29 frameshift insertions/deletions, 13 splice site mutations, and 10 missense mutations (eTable 1, links.lww.com/NXG/A544).

Here, we studied 2 patients with de novo TRIP12 variants: a frameshift duplication (c.2959dupT) and a synonymous mutation (NM_004238.2: c.1842G>A). The synonymous sequence variant affects messenger RNA (mRNA) splicing in the TRIP12 gene. Both patients presented with common features, which included ID, speech delay, motor delay, and behavioral abnormalities, but neither showed autism or obvious facial deformities. However, clinical heterogeneity was also observed between the 2 patients.

**Methods**

**Standard Protocol, Approvals, Registrations, and Patient Consents**

The patients and healthy controls were from Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region. The work was approved by the local ethics committee. Written informed consent was obtained from all patients or their relatives.

**Exome Sequencing**

Genomic DNA from the peripheral blood lymphocytes of the patients and their family numbers was extracted with a LabAid DNA kit (Zeesan Biotech Co., Ltd, Xiamen, China). The DNA concentration and purity were determined using a NanoDrop ND-2000 ultraviolet spectrophotometer and software (Thermo Fisher Scientific, Waltham, MA). For exome sequencing, the library was prepared using an Agilent SureSelect Human All Exon V6 Kit (Agilent Technologies, Santa Clara, CA). The complete libraries were then sequenced on a HiSeq2500 system (Illumina, San Diego, CA). Sequence alignment and variant calling against the human GRCh37 reference genome were performed using BWA and the Genome Analysis Toolkit (GATK HaplotypeCaller). The analysis of copy number variants (CNVs) was processed on an in-house pipeline, and CNVs of significant interest were further visually inspected using the Integrative Genomics Viewer. Single nucleotide variants and indels were filtered and prioritized with TGex software (LifeMap Sciences, Alameda, CA). All operations were performed according to the manufacturer’s instructions.

**Sanger Sequencing**

All the potential candidate variants were confirmed by Sanger sequencing for the patients and informative family members. The potential causative mutation regions and flanking sequences were amplified by PCR (see eTable 2, links.lww.com/NXG/A544, for primer sequences). PCR amplifications were conducted in a total volume of 30 μL with 2U Taq DNA polymerase (Takara Biotechnology, Dalian, China). The purified PCR products were sequenced directly with the same amplification primers using an ABI 3130 genetic analyzer (Applied Biosystems, Foster City, CA).

**Sequence Variant Classification**

The clinical significance of the sequence variants was interpreted according to American College of Medical Genetics and Genomics–Association for Molecular Pathology (ACMG/AMP) guidelines.

**RNA Extraction and Reverse Transcription**

Fresh peripheral blood samples were collected from patients and cohort controls into tubes containing EDTA-K2. Total RNA was extracted by TRIzol reagent (Invitrogen, Carlsbad, CA) following the manufacturer’s instruction. The quality of RNA was analyzed with agarose gel electrophoresis and NanoDrop ND-2000 (Thermo Fisher Scientific). After being quantified, 1 μg mRNA was immediately reverse transcribed
into complementary DNA (cDNA) using a First-strand cDNA Synthesis Kit (Takara Biotechnology, Dalian, China).

**cDNA Sequencing**
The cDNA amplifications were performed using LA Taq polymerase (Takara Biotechnology). The reaction cycle parameters were optimized for each fragment (eTable 2, links.lww.com/NXG/A544). PCR products were resolved on a 1.5% agarose gel and sequenced on an ABI 3130 genetic analyzer (Applied Biosystems) after purification.

**3D Model Analysis**
Three-dimensional models were established to predict the effect of conformational change associated with the mutation using SWISS-MODEL10 based on the crystal structure of Iwa5 (Protein Data Bank accession number).11

**RT-qPCR**
Expression levels were measured by quantitative real-time PCR using the FastStart Universal SYBR Green Master (Roche Diagnostics GmbH, Mannheim, Germany) on a CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA). GAPDH expression was used as an internal control. Gene-specific primers used for reverse transcription–quantitative PCR (RT-qPCR) are listed in eTable 2 (links.lww.com/NXG/A544). Sample was run in triplicate for each assay, and the relative gene expression levels were calculated using the comparative 2–ΔΔCT method.12

**Data Availability**
All data generated during this study are included in this published article and its supplementary information files.

**Results**

**Clinical Descriptions**
Patient 1 was a 13-year-old Chinese boy who was the only child of nonconsanguineous healthy parents (eFigure 1, links.lww.com/NXG/A544). No family history of genetic disease or any pregnancy complications were recorded. At around 1 year of age, global developmental delay was evident. The child had delayed motor milestones and was not able to walk by himself until age 2 years. He also had retardation of his language development and began to speak around 1 year of age, globally delayed, and lost the ability to understand and generate meaningful language and could only understand and execute simple instructions. He did not show autistic behavioral tendencies, but he presented with behavioral abnormalities, which included restlessness, paranoia, mood swings, nail biting, and poor eye contact. The child had ID and was unable to take care of himself. No obvious abnormality was detected by brain or cervical MRIs, EMG, or abdominal ultrasound examination.

**Genetic Analysis**
Using exome sequencing analysis of patient 1, a total of 1,216 variants were identified in coding regions and splice sites, after filtering out minor allele frequencies (MAFs) of >3% from our local and commercial databases. The latter included the Genome Aggregation Database, Exome Sequencing Project, and 1000 Genomes databases. Through clinical phenotype analysis, candidate heterozygous variants in 4 autosomal dominant genes (CHD2, TRIP12, KAT6A, and TRAF7) were selected, with subsequent validation performed through Sanger sequencing of samples obtained from his parents. The c.3047A>C CHD2 variant and c.1942G>A TRAF7 variant were inherited from the unaffected mother, and the c.3670_3672delAAG variant in the KAT6A gene was inherited from his unaffected father. The c.2959dupT variant in the TRIP12 gene (NM_004238.3) was absent in both parents (eFigure 2, links.lww.com/NXG/A544), and paternity was confirmed by short tandem repeat (STR) genotyping. The variant was not listed in any of the general population databases, such as the Single Nucleotide Polymorphism Database, 1000 Genomes Project, and Exome Aggregation Consortium. The duplication in exon 20 was expected to generate a frameshift mutation and create a premature termination at codon 998 (p.Ser987fs*11). The variant is classified as pathogenic, in accordance with the ACMG/AMP guidelines (PV5I+PS2+PM2_supporting).
Through exome sequencing analysis of patient 2, a total of 945 variants were selected in protein coding regions and splice sites, after filtering out MAF of >3% in local and commercial databases. After clinical phenotype analysis, 6 heterozygous candidate variants in autosomal dominant genes (*RAI1*, *AHDC1*, *CDON*, *TRIP12*, *SCN9A*, and *KCNT2*) were of special interest, with subsequent validation by Sanger sequencing of all family members. The *RAI1* (c.3839A>G), *AHDC1* (c.838C>T), *CDON* (c.172C>A), and *SCN9A* (c.3700T>A) variants were inherited from the unaffected mother, whereas the c.2689-1G>A variant in the *KCNT2* gene (NM_001287820.1) was inherited from his unaffected father. A synonymous variant, c.1842G>A, of the *TRIP12* gene (NM_004238.3) was absent in both parents (Figure 1A). The paternity was confirmed by STR genotyping. The variant was not listed in any control databases. The single-base substitution did not alter the original amino acid code but could potentially affect precursor mRNA splicing as nucleotide c.1842 is the last base of exon 12. Reverse transcription PCR analysis on total RNA isolated from leukocytes demonstrated the presence of a truncated mRNA transcript that skipped exon 12 (Figure 1, B and C), which led to an in-frame deletion of 54 amino acids (r.1681_1842del; p.Gly561_Glu614del). The *TRIP12* mRNA expression level in the patient, as measured by RT-qPCR, was not decreased when compared with the normal controls (Figure 2). However, the expression of 3 known responsive genes (*PARP1*, *SOX6*, and *SMARCE1*) was upregulated more than 2-fold when compared with the controls (Figure 2). The synonymous substitution is classified as pathogenic according to the ACMG/AMP guidelines (PS2+PS3+PM2_supporting).

**Discussion**

The ubiquitin pathway is part of the ubiquitin-mediated proteolysis process, which is a major pathway for protein degradation and participates in a series of physiologic cellular functions. These include cell cycle progression, differentiation, and homeostasis. Ubiquitination is catalyzed by a cascade of enzymatic reactions that include ubiquitin activation (E1), conjugation (E2), and ligation (E3). Dysregulation of the ubiquitin pathway has been associated with diverse pathologic disorders.

The *TRIP12* gene is located at locus q36.3 of chromosome 2 and is almost 168 kb in length. To date, at least 26 different splicing variants of *TRIP12* mRNA have been identified in human cells and their lengths range from 9,065 to 10,492 nucleotides. Many studies use the 1992 amino acid isoform of *TRIP12* (NP_004229.1) as a reference. However, a single nucleotide deletion in the intron region (rs155365558) has been described as a frameshift variation in the dbSNP database, which uses the 2067 amino acid isoform (NP_001335252.1) as the reference. This deletion is located in the coding region of the other transcripts. The differences in alternative transcripts should be taken into account when interpreting the functional effects of variations. Alternative exon utilization of the *TRIP12* gene leads to the generation of 14 different protein isoforms, and the long isoforms comprise...
a catalytic HECT domain (homologous to the E6-AP carboxyl terminus), a WWE domain (tryptophan-tryptophan-glutamate), an ARM domain (armadillo/β-catenin-like repeats), and an IDR domain (intrinsically disordered region).\textsuperscript{16-19} The TRIP12 protein is an E3 ubiquitin-protein ligase and plays a critical role in several essential cellular processes, such as cell cycle progression, DNA damage repair, chromatin remodeling, and cell differentiation.\textsuperscript{20}

As a member of the ubiquitin-proteasome pathway, TRIP12 is integral to cell survival and numerous normal functions of the nervous system.\textsuperscript{21,22} Compromised function of this protein contributes to the pathogenesis of multiple human diseases, such as cancer and neurodevelopmental disorders.\textsuperscript{14} To date, more than 400 \textit{TRIP12} mutations have been detected in tumor tissues from different patients with cancer.\textsuperscript{23,24} Germline \textit{TRIP12} loss-of-function mutations and whole gene deletions are associated with developmental delay, ID, and ASD.\textsuperscript{6,25-27} In addition to loss-of-function variants distributed throughout the gene, 10 missense mutations have also been reported (eTable 1, links.lww.com/NXG/A544). Of interest, 8 of them are located at the HECT domain. This may reflect the functional importance of the TRIP12 HECT domain, which is required for the ubiquitin ligase activity and the mammalian ubiquitin fusion degradation pathway.\textsuperscript{23} In this study, we identified 2 novel \textit{TRIP12} variants in 2 Chinese patients with ID, motor delay, and speech delay.

As has been reported, patients with the \textit{TRIP12} mutation showed ID/developmental delay and speech delay.\textsuperscript{4,6} The majority of patients also present with motor delay (66%), autistic behaviors (71%), and other behavioral anomalies (75%).\textsuperscript{8} Both of our patients also showed moderate ID, without autistic features, moderate to severe speech delay, motor delay, and distinct behavioral abnormalities. They both started walking at age 2 years, but patient 2 still had hypotonia, whereas no obvious muscular abnormalities were observed in patient 1. Neither of the patients had short stature, although patient 1 had a previously low level of growth hormone. According to previous reports, nearly half of patients (41%) have a diagnosis of obesity, but neither of our patients was overweight. Epilepsy was only present in patient 2. Results from MRI of the brain revealed no obvious structural abnormalities, and they had no obvious facial abnormalities. Significantly, patient 2 was prone to recurrent episodes of hypoglycemia, particularly during the night, without abnormalities in thyroid, liver, or kidney function or insulin levels. It is not known whether this abnormality is associated with the \textit{TRIP12} mutation. In summary, both of our patients exhibited the core phenotypical features of \textit{TRIP12}-related disease, such as ID with behavioral abnormalities and speech delay. They also presented with some of the variable phenotypes, such as motor delay and seizures.

A novel frameshift variant in \textit{TRIP12} was identified in patient 1. This variant caused premature termination of the coding sequence and probably leads to degradation of mutant mRNA by nonsense-mediated decay.\textsuperscript{28} This was consistent with previous reports that heterozygous loss-of-function mutations of \textit{TRIP12} are responsible for Clark-Baraitser syndrome.\textsuperscript{6,25-27} Patient 2 had a de novo synonymous variant, c.1842G>A, in the \textit{TRIP12} gene, which did not cause a change in the amino acid sequence. Given that the variant was located at the last base of exon 12, the substitution may affect RNA splicing. Then, reverse transcription PCR in RNA extracted from leukocytes of the patient demonstrated the presence of a
truncated mRNA transcript that skipped exon 12. However, the truncated mRNA would not cause a frameshift or premature termination codon. Agarose gel electrophoresis of the RT-PCR amplicon from the patient showed 2 bands (normal band and a shorter abnormal band) with similar in brightness (Figure 1B). The TRIP12 mRNA expression level in the patient, as measured by RT-qPCR, was not decreased when compared with the normal controls (Figure 2). The results suggested that the mRNA would escape degradation due to the abnormal splicing caused by the variant.

Exon 12 (NM_004238.3) is present in all known human TRIP12 transcripts, which indicates that it is essential for gene function. This exon encodes amino acids 561 to 614 of the TRIP12 protein, and multiple sequence alignments using Clustal X revealed that the protein sequence is highly conserved among mammalian species and some nonmammalian species (Figure 3A). In the EBI database, most of these residues also appear to be conserved (Figure 3B). The 54-amino-acid sequence is located in the middle part of the ARM domain (residues 437–715, NP_004229.1), which consists of imperfect tandem repeats of 42 hydrophobic amino acids. The ARM repeat-containing proteins are involved in diverse cellular functions, such as cell adhesion, cell signal transduction, cytoskeleton functions, nuclear trafficking, cell proliferation, differentiation, and ubiquitination process. Successive ARM repeats can form a super helix of helices, and the structure is thought to be a protein-protein interaction motif.18 As TRIP12 has not yet established its complete 3D structure, we predicted the crystal structure of its ARM repeats based on the crystal structure of 1wa5 (Figure 4A). Compared with wild-type protein, the truncated protein reduced part of alpha-helices (Figure 4B), which is crucial for protein function.18 Deletion of the 54 amino acids in this domain would disrupt the spatial structure of the protein, and the mutant protein may lose or change physiologic functions, such as E3 ligase activity in the ubiquitin pathway, which is essential for the development and plasticity of the CNS.21,22 However, it is not known whether the aberrant transcript would be translated into a truncated protein.

It is known that, by regulating the stability and promoting the proteolysis, TRIP12 acts on 9 protein substrates: ASXL1, CDKN2A, NAE1, PARP1, PTF1A, RNF168, SOX6, SMARCE1, and USP7.29 These proteins play important roles in a variety of biological and/or pathologic processes.29 Genetic mutation is the main cause of reduced or eliminated enzyme activity, and TRIP12 dysfunction may result in inhibition of proteolytic activity. To assess the effect of the synonymous variant on TRIP12 enzymatic activity, we measured the expression of the known responsive genes at the mRNA level by quantitative RT-PCR, using gene-specific primers. Of the 9 substrate genes, we failed to detect PTF1A, presumably due to a low level of expression. Among the remaining genes, 3 (PARP1, SOX6, and SMARCE1) were upregulated more than 2-fold when compared with the controls (Figure 2). The p values were not calculated as there was only 1 valid data point in each case. The expression levels of the other genes in the patient were not significantly different from those of the control group, although 2 genes (NAE1 and RNF168) were expressed at relatively low levels (Figure 2).

The PARP1 gene encodes a chromatin-associated enzyme, poly (ADP-ribosyl) transferase, which modifies various nuclear proteins.30 The modification is involved in the regulation of important cellular processes, such as differentiation, proliferation, tumor transformation, and the recovery of the cell from DNA damage.30 Thus, the protein has been linked to brain development and tumor suppression, and it is considered to be an attractive cancer target. The TRIP12 protein is a

![Figure 3](Image)

(A) Multispecies alignment of the amino acid sequences surrounding the missing part (p.Gly561_Glu614). The red box represents the missed 54 residues. (B) Residue conservation of the protein from the EBI database. TRIP12 = thyroid hormone receptor interactor 12.
PAR-targeted ubiquitin ligase and controls PARP1 turnover. Elevated PARP1 abundance can be attributed to down-regulation of TRIP12 in patients with breast and ovarian cancer. However, the PARP1 mRNA levels were only mildly affected by TRIP12 loss, and the authors suggested that TRIP12 mainly regulates PARP1 at the protein level. In this study, the PARP1 mRNA level was elevated in the patient with the TRIP12 variant. Intriguingly, TRIP12 interacts with PARylated PARP1 via its WWE domain, rather than the ARM domain. This indicates that the variation may affect the spatial structure of the entire protein and disrupt its function or stability.

The SOX6 (SRY-box transcription factor 6) gene is a member of the SOX gene family, which encodes transcription factors containing the highly conserved high-mobility group (HMG) domains that bind to the minor groove of DNA. The protein can cooperatively activate gene expression and plays a critical role in the differentiation of cortical interneurons, dopaminergic neurons in the substantia nigra and oligodendrocyte development. The transcriptional activator is crucial for normal development of the CNS, chondrogenesis, and maintenance of cardiac and skeletal muscle cells. In mammals, TRIP12 binds to SOX6 protein and induces its ubiquitination. A TRIP12 knockdown in muscle cells results in an increase in SOX6 protein levels. In our patient, SOX6 expression is upregulated by the TRIP12 variant at the mRNA level, which was consistent with the aforementioned changes in protein expression level.

The SMARCE1 gene, also known as BAF57, encodes a subunit of the switch/sucrose nonfermenting (SWI/SNF) complex, which is a chromatin remodeling complex that mainly functions primarily through nucleosome mobilization. The SMARCE1 protein is required for transcriptional activation of genes that are normally repressed by chromatin, and germline

Figure 4 Cartoon Model of the TRIP12 Protein Structure (the ARM Domain, Residues 400–800) by PyMOL Based on the Structure of Protein Data Bank ID Code 1wa5

(A) Wild type. (B) Mutant TRIP12 protein. TRIP12 = thyroid hormone receptor interactor 12.

Figure 5 Mutation Spectrum of the TRIP12 Gene

The schematic genomic structure of the TRIP12 gene and the corresponding encoded protein domains are drawn to scale. Frameshift mutations are depicted by blue triangles (solid, insertion; hollow, deletion). The novel variant (c.2959dupT) in patient 1 is highlighted in red. Splicing mutations are marked by purple diamonds. Nonsense mutations are represented by black squares. Missense mutations are indicated by gray dots. The synonymous variant in this study is labeled with an asterisk. TRIP12 = thyroid hormone receptor interactor 12.
mutations are associated with the development of clear cell meningiomas and Coffin-Siris syndrome. The TRIP12 protein is the major E3 ubiquitin ligase for SMARCE1 ubiquitination, which leads to the degradation of its unbound form. The TRIP12-mediated degradation of SMARCE1 may affect the expression and function of SWI/SNF subunits and consequently disturb the expression patterns of downstream genes. Thus, TRIP12 may be involved in chromatin remodeling by controlling the integrity of the SWI/SNF complex. In our patient, the SMARCE1 expression is upregulated at the mRNA level. This indicated that the variant diminishes the ubiquitin hydrolase activity of TRIP12. It has also been reported that upregulated SMARCE1 is associated with the development and function of the nervous system.

To date, a variety of mutation types have been identified in the TRIP12 gene. These include nonsense mutations, missense mutations, splicing mutations, small deletions or insertions, gross deletions or insertions, and complex rearrangements. Here, in addition to a frameshift TRIP12 mutation, we identified a novel synonymous mutation in a patient with ID. The study expands the mutation spectrum of the TRIP12 gene (Figure 5). Although synonymous variants do not affect the protein amino acid sequence, they may influence the thermodynamic stability of mRNA secondary structures, which affects mRNA splicing or affects translation efficiency and kinetics. In genetic analyses for disease-causing mutations, synonymous substitutions should not be filtered out directly, particularly for low-frequency synonymous mutations. The cDNA analysis was valuable for identifying the effects of suspicious synonymous variants on mRNA transcript splicing.

In summary, we investigated 2 patients with Clark-Baraitser syndrome. Both patients presented with common features and also showed some clinical heterogeneity. Besides a frameshift insertion, a novel synonymous mutation that led to aberrant mRNA splicing was identified in the TRIP12 gene. In the patient with the synonymous mutation, the truncated mRNA transcript lacked exon 12 and escaped degradation at the mRNA level. The expression levels of 3 known responsive genes were upregulated in this patient. This study will help to improve our understanding of variable phenotypic presentations in TRIP12-related disorders and highlights the importance of the interpretation of synonymous mutations for accurate diagnosis and genetic counseling of inherited conditions.

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### Appendix (continued)

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### References


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