Temtamy syndrome caused by a new *C12orf57* variant in a Chinese boy, including pedigree analysis and literature review

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Abstract. Temtamy syndrome is an extremely rare disorder caused by chromosome 12 open reading frame 57 (*C12orf57*) pathogenic variants. The present study reported a boy with Temtamy syndrome displaying global developmental delay, epilepsy and dysmorphic facial appearance. Whole-exome sequencing was performed to identify a novel homozygous pathogenic variant of *C12orf57* (c.3G >C, p.Met1IIe), and the affected protein structure and function were predicted to be pathogenic. Additionally, clinical features of the other reported 56 patients with *C12orf57* pathogenic variants were reviewed and compared. This study highlighted that *C12orf57* pathogenic variants are mainly associated with global developmental delay, epilepsy and dysmorphic facial appearances. The clinical features were in accordance with the previously reported cases, except for those with recurrent infection, but without corpus callosum abnormalities. The present study reported the first Asian case to the best of our knowledge with Temtamy syndrome, and the novel *C12orf57* pathogenic variant has not reported in any ethnic groups previously. The present study expanded the spectrum of *C12orf57* pathogenic variants as well as the ethnic backgrounds of the affected patients.

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Introduction

Temtamy syndrome (MIM no. 218340) is a rare disorder which was first described in 1991 and then published a full formal report in 1996, where three siblings affected appeared to have inherited an autosomal recessive gene (1,2). It is characterized with mental retardation and multiple congenital anomaly, with symptoms including variable craniofacial dysmorphism, ocular coloboma, seizures and abnormalities in the corpus callosum and thalamus (1-3). Of note, the chromosome 12 open reading frame 57 (*C12orf57*) encodes a 126-amino acid cytoplasmic protein of unknown function was reported to be required for human corpus callosum development (3,4). In 2013, pathogenic variants of *C12orf57* were first reported to cause Temtamy syndrome (3,4). At the present time, only seven pathogenic variants have been illustrated (1-6). Those of Middle Eastern descent are particularly susceptible to *C12orf57* pathogenic variants, with 54/56 (96.4%) of all the reported patients from Middle Eastern countries, predominantly Saudi Arabia (3-7).

The present study reported the first East Asian patient with global developmental delay and epilepsy caused by a novel homozygous *C12orf57* pathogenic variant, and presented a brief review of all the previously published cases.

Patients and methods

Patients. Ethics approval for this study was obtained through the Institutional Review Board of Children's Hospital of Chongqing Medical University. Written informed consent was obtained from the parents of the patient for the publication of this case report and accompanying images.

The present case is of a boy born to first-cousin consanguineous Chinese parents of Hui nationality at 40 weeks and 5 days of gestation, gravida 2 para 2. The boy was born by normal delivery with a birth weight of 3,510 g, while the birth length and head circumference were unknown. His elder sister is 7 years old and healthy as of October 2019.

The patient was admitted to the Neurology ward at the Children's Hospital of Chongqing Medical University (May 2018) at the age of 8 months and 28 days because of four tonic-clonic seizures in 10 days, as well as pneumonia which had lasted for 1 week. All of the available clinical characteristics of the patient, along with the aforementioned auxiliary examination results are summarized in the present study.

Whole-exome sequencing and bioinformatics analysis. Based on the hg19/GRCh37 reference, whole-exome sequencing was performed on the proband and the parents at Beijing Mygenostics Co., Ltd. Several online databases containing data from different ethnic groups were used as follows: Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/); 1000 genome Project variants database (http://www.1000genomes.or/); Esp6500siv2_all (http://evs.gs.washington.edu/EVS/), Inhouse databases (http://192.168.0.69/db/inhouse/); Exome Variant Server (version 0.0.30;http://evs.gs.washington.edu/EVS/); ExAC (http://exac.broadinstitute.org/); dbSNP (version 2.0; http://www.ncbi.nlm.nih.gov/projects/SNP/); and Clinvar (https://www.ncbi.nlm.nih.gov/clinvar/). The variants were selected according to the following five-step process, to select the potential pathogenic variants in the downstream analysis: i) Mutation reads >10 and mutation ratio ≥30%; ii) following removal of the mutation from the search, the frequency showed more than 0.1% in the 1,000 Genomes, ESP6500, ExAC and Inhouse databases; iii) if the mutations existed in the In Normal database (MyGenostics), they were dropped; iv) removal of synonymous mutations or mutations in intronic region, since they were considered non-pathogenic; and v) after i), ii) and iii), if the mutations were in introns or were synonymous and reported in HGMD, they were included. All remaining variants were considered pathogenic. Finally, seven homozygous mutations were identified. Combined with the phenotype of the child, only the *C12orf57* variant was confirmed as pathogenic. The *C12orf57* pathogenic variant was screened using Sanger sequencing to amplify exon 1 (chr12-7053287) of *C12orf57* (NM_138425). The segregation of the identified pathogenic variant was investigated in all the family members (Fig. 2A and B). The prediction of mutations was assessed using software, including Polyphen2_HVAR_score, Polyphen2_HVAR_pred, PolyPhen_2_Predict and PolyPhen_2 (April 2010; http://genetics.bwh.harvard.edu/pph2/); MutationTaster, Mutation Taster_Predict (April 2009; http://www.mutationtaster.org/ChrPos.html); SIFT,SIFT_Predict (http://sift.jcvi.org/); LRT_score, LRT_pred (November 2009; http://www.genetics.wustl.edu/jflab/lrt_query.html); CADD_raw, CADD_phred (version 1.3; http://cadd.gs.washington.edu/).

Literature review. PubMed and Wanfang (http://www.wanfangdata.com.cn/index.html) databases were searched to retrieve studies using the keywords '*C12orf57*', from inception to March 2019. The publication language was restricted to English and Chinese.

Results

Clinical manifestation. On admission, the patient was unable to hold his head at 6 months, and was unable to sit up straight at 10 months. Hospitalization had occurred three times because of severe pneumonia. Also, abnormal dysmorphic features (Figs. 1A and Video S1), such as frontal bossing, low-set ears, depressed nasal bridge, ocular hypertelorism, micrognathia and single transverse palmar crease were observed. Referring to the World Health Organization Anthro guidelines, the patient was 7 kg (Z-score=-2.17 SD) in weight and 65 cm (Z-score=-2.75 SD) in length; the head circumference was 45 cm (Z-score=0.02 SD).

An atrial septum defect (4.5 mm) was found by color Doppler ultrasonography (Fig. 1B). The magnetic resonance imaging (MRI) scans showed slightly expanded lateral ventricles and increased extra-axial spaces (Fig. 1C and D). The interictal electroencephalography showed sporadic spike-slow wave during waking. Any abnormalities of the eyes were not detected during the ophthalmological consultation. Furthermore, this patient was administered oxcarbazepine (8-15 mg/kg/day) and anti-infection therapy (ceftazidime 100 mg/kg/day (intravenous infusion) for 5 days, followed by cefixime 5 mg/kg/day (oral administration) for 5 days. After 2 weeks, the patient was discharged and transferred to a local hospital for the recovery phase management.

During the 1-year follow-up, the patient was seizure-free for 1 month after the oxcarbazepine (26 mg/kg/day) was administered, and could only sit up straight for <30 sec at the age of 14 months. While there were still another six hospitalizations for pneumonia, only two had occurred in the previous 6 months and the patient had recovered easily. The atrial septum defect was not observed by color Doppler ultrasonography at the age of 19 months.

Genetic analysis. Exome sequencing revealed a homozygous pathogenic variant, c.3G>C (p.Met1Ile), that was confirmed by Sanger sequencing. Furthermore, the pathogenic variant was segregated according to a strictly recessive model with full penetrance. The parents were tested as possible heterozygous carriers. A total of four heterozygous carriers of the *C12orf57* pathogenic variant were detected; the patient's parents and their second degree relatives inherited the pathogenic variants from their grandparents (Fig. 2A and B).

C12orf57 encodes a protein that is evolutionarily conserved across representative species (Fig. 2C), according to HomoloGene (https://www.ncbi.nlm.nih.gov/homologene/). The actual *in silico* results are as follows: SIFT_score (0); SIFT_pred (D); Polyphen2_HDIV_score (0.072); Polyphen2_HDIV_pred (B); Polyphen2_HVAR_score (0.008); Polyphen2_HVAR_pred (B); LRT_score (0); LRT_pred (D); CADD_raw (3.109); CADD_phred (22.5); Pathogenic variant Taster_score (1); Pathogenic variant Taster_pred (D). As a result, most of the *in silico* results predicted this biallelic missense pathogenic variant to be deleterious, wherein the pathogenic variant is localized at the start codon, abolishing the translation of *C12orf57*.

Literature review. Temtamy syndrome is not easy to distinguish clinically from other syndromes with similar phenotypes. As such, the present study only summarized cases with *C12orf57* mutations. A total of 56 cases with *C12orf57* pathogenic variants (Fig. S1) have been reported (3-7). All the cases were early onset, and the clinical features are summarized in Table I.

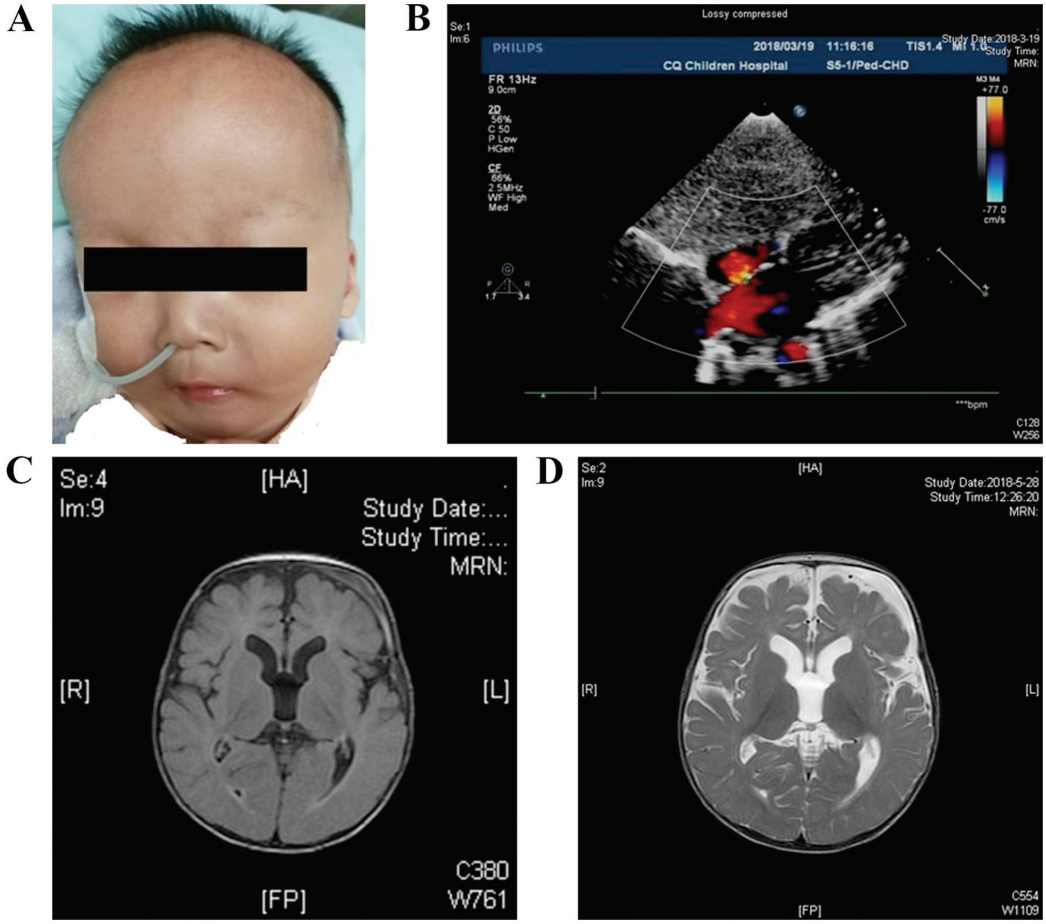

Figure 1. (A) Photograph of the patient (9 months), facial dysmorphism including frontal bossing, low set ears, depressed nasal bridge, ocular hypertelorism, and micrognathia. (B) The atrial septum defect (red arrow, 4.5 mm) was detected through color Doppler ultrasonography. Magnetic resonance imaging (C) T1 and (D) T2 axial slices showed widened bilateral lateral ventricles and increased extracellular spaces.

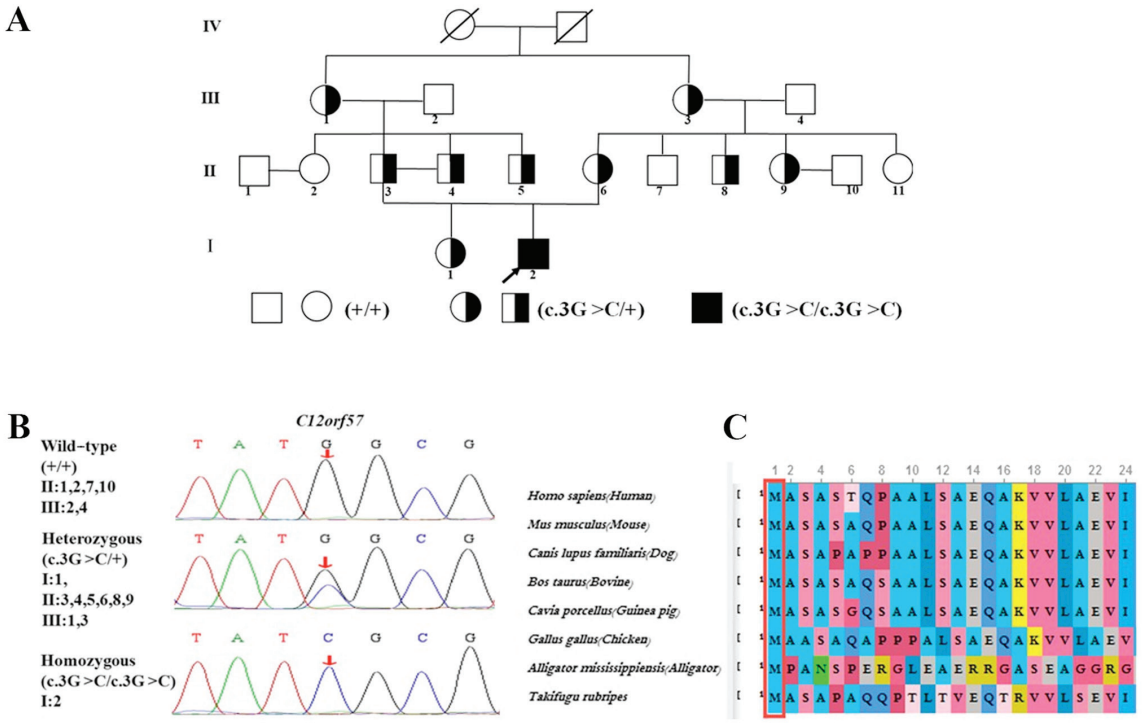

Figure 2. (A) Pedigree of the family. (B) The DNA sequencing showed that a novel *C12orf57* pathogenic variant (c.3G>C, red arrows) co-segregates with the phenotype in the proband and the family members. (C) The *C12orf57* missense pathogenic variant, as shown by the red arrow in (B) is localized in a highly conserved amino acid sequence among representative species.

Table I. Chromosome 12 open reading frame 57 pathogenic variants and phenotypes of all the affected cases from the literature and the current report.

Characteristic	The present case	Literature (n=56)	Total, %
Basic characteristics			
Early onset	1	56	100
Consanguineous	1	49	87.7
Ethnic origin			
Saudi Arabia		25	43.9
Kuwait		9	15.8
United Arab Emirates		9	15.8
Libya		4	7.0
Palestine		4	7.0
Oman		3	5.3
Germany		2	3.5
China	1		1.8
Genetics			
c.1A>G, p.(Met1?)		45	78.9
c.3G>C, p.(Met1I)	1		1.8
c.53-2A>G		3	5.3
c.184C>T, p.(Gln62*)		2	3.5
c.-3_2delinsG		2	3.5
c.43C>T, p.(Gln15*)		2	3.5
c.229+2T>C		1	1.8
c.152T>A, p.(Leu51Gln)		1	1.8
Phenotype			
Neurological findings			
Developmental delay	1	56/56	100
Seizures	1	41/56	73.7
Absent speech	N/A	41/55	74.5
Generalized hypotonia	1	40/56	71.9
Delayed speech	1	20/55	37.5
Autistic behavior	N/A	40/55	72.7
Spasticity	0	20/56	35.1
Dysmorphic features			
Dysmorphic faces	1	36/55	66.1
Microphthalmia	1	9/55	14.3
Ophthalmology			
Ocular anomalies	0	26/55	46.4
Coloboma	0	8/55	14.5
Congenital heart disease			
Atria septal defect	1	16/55	30.4
Ventricular septal defect	0	2/19	10.0
Pulmonic stenosis	0	3/26	11.1
Brain imaging			
Abnormal corpus callosum	0	34/54	61.8
Abnormal thalamic size	0	20/51	38.5
Abnormal septum pellucidum	0	19/50	37.3
Abnormal white matter	0	19/50	37.3
Abnormal anterior commissure	0	11/51	21.2
Ventriculomegaly	1	17/50	35.3
Others			
Recurrent pneumonia	1	N/A	

N/A, not available.

Discussion

Temtamy syndrome is an extremely rare disorder, and only a limited number of studies have been conducted (1-7). The present study reports the first East Asian patient with a novel *C12orf57* homozygous pathogenic variant; all other heterozygous carriers in the family were clinically healthy. The inheritance pattern of this pedigree was in accordance with autosomal recessive inheritance with complete penetrance.

Pathogenic variants in *C12orf57* were first reported to cause Temtamy syndrome in 2013 (3-5), and the affected individuals were recently described to have variable phenotypes beyond this syndrome (5). The c.1A>G pathogenic variant in the *C12orf57* start codon has been reported as the most frequent pathogenic variant (45/56, 80.3%). Interestingly, the pathogenic variant in this start codon can severely reduce the protein levels, suggesting a loss of function as the mechanism of action behind the disease. Moreover, the pathogenic variant (c.3G>C) in the current case was located at the same start codon of *C12orf57*, but at different bases. This suggests that the c.3G>C pathogenic variant may affect the protein expression level and may lead to the occurrence of disease. Bioinformatics analysis indicated that the aforementioned pathogenic variant is the most likely mechanism of action behind the pathogenesis. Since the parents of the patient are first-cousin consanguineous relatives, whether the patient had other additional homozygous pathogenic variants was investigated, but no positive results were obtained.

All the patients with *C12orf57* pathogenic variants identified in the literature review exhibited global developmental delay in concurrence with hypotonia. Compared to the previously reported cases of epilepsy (73.2%), relatively refractory (37.5%) and low frequency of seizure-free (15.6%), as found in the literature review, the seizures in the current case were controlled. No recurrence of seizures occurred after the patient was medicated with oxcarbazepine. Although the dysmorphic features are not distinctly recognized among patients with *C12orf57* pathogenic variants, the current case had many similar dysmorphic facial features (65.5%), including frontal bossing, low set and posteriorly rotated ears, depressed nasal bridge, hypertelorism, micrognathia, up-slanted palpebral fissures and microphthalmia, but without epicanthal folds. Previously reported abnormalities of the eyes (such as chorioretinal coloboma), iris or optic nerve were not found in this present case. *C12orf57* was once reported to cause colobomatous microphthalmia, which seems to be invariably associated with profound global developmental delay, seizures and defects of the corpus callosum, but these cases were later summarized to be Temtamy syndrome by the same research group (4,5). This present study identified colobomatous microphthalmia to be a clear sign of this syndrome.

Abnormalities of the corpus callosum were included in the classical characteristics of this disease and may be observed in approximately two-thirds of patients with *C12orf57* pathogenic variants. However, no similar corpus callosum changes were demonstrated and MRI scanning of the brain revealed only slight cerebral dysplasia in the present case. Reportedly, atrial septum defects are the most frequent congenital heart defect, which was also observed in the present case, at 4.5 mm.

Additionally, the present patient was particularly susceptible to infection, developing severe pneumonia every 2-3 months leading to hospitalization for several weeks. No similar recurrent pneumonia has been mentioned in the previous studies. During the follow-up, the recurrent infections were less frequent in the latter 6 months; therefore, it is considered that the recurrent infections may be partly associated with the atrial spectrum defects, which was not detected at previous visits. Therefore, additional cases could substantiate the findings if recurrent infection is a feature of patients with *C12orf57* pathogenic variants. Currently, the patient is 20 months old and no more new outcomes have been observed. Follow-up observations are needed to confirm the presence of further phenotypes.

The present study has some limitations. Detailed information on reported cases of pathogenic *C12orf57* pathogenic variants is limited (for example, familial aggregation, life expectancy and type of seizures). Furthermore, the phenotype-genotype correlation cannot be confirmed since the majority (45/57) of the reported cases had the same pathogenic variant, c.1A>G, p.(Met1?), and the other different genetic variants were only observed in one or two cases.

In conclusion, a novel homozygous *C12orf57* pathogenic variant (c.3G>C) was identified in a patient with developmental delay, epilepsy and dysmorphic facial appearance. The *C12orf57* pathogenic variant site has not been published previously, and this was the first reported East Asian case with Temtamy syndrome to the best of our knowledge. The present results expanded the spectrum of *C12orf57* pathogenic variants, as well as the ethnic backgrounds of the affected cases.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YW, YL and ML carried out the diagnosis and treatment of the case, collected the data, and performed literature review. MZ designed and supervised the study. XZ, SL, LJ and XL were involved in the management of the patient and approved the final version of the manuscript.

Ethics approval and consent to participate

The ethics approval for this study was obtained through the Institutional Review Board of Children's Hospital of Chongqing Medical University (Chongqing, China; no. 2018-64).

Patient consent for publication

The parents provided consent for the case report and for images of the patient's face to be published for educational purposes.

Competing interests

The authors declare that they have no competing interests.

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