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Clinical Short Communication

Novel biallelic missense mutations in CTC1 gene identified in a Chinese family with Coats plus syndrome

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ABSTRACT

Background: Coats plus syndrome is a recently described, very rare multisystem disorder. The clinical phenotype is wide and variable, which making the diagnosis more difficulty. The genetic study of Coats plus syndrome has been reported recently. The biallelic heterozygous mutations in CTC1 gene, encoding conserved telomere maintenance component 1, were identified in families with Coats plus from different ancestry (European, American, and African). To data, there has not been a report about genetically confirmed Coats plus syndrome from China.

Results: We firstly identify a novel biallelic heterozygous missense variants (c.775G > A p.V259M and c.2066A > G p.Y689C) of CTC1 gene in a Chinese family with Coats plus. The c.2066A > G mutation (p.Y689C) in CTC1 is a novel variant. Such variant was not found in any of the 85 healthy individuals in the same community.

Conclusion: This is the first report of a genetically confirmed case of Coats plus from China. Targeted sequencing of CTC1 gene is useful for genetic diagnosis in Coats plus and differential diagnosis for other patients with similar disease manifestations.

1. Introduction

Coats plus syndrome is a rare autosomal recessive multisystem disorder affecting brain, eye, bone and gastrointestinal tract. Coats plus is characterized primarily by extensive intracranial calcifications, leukoencephalopathy, and brain cysts, resulting in seizures, spasticity, ataxia, dystonia, and cognitive decline. Patients also have retinal telangiectasia—leading to bleedings and exudative retinopathy (Coats disease). Additional extraneurologic manifestations include pre- and post-natal growth retardation, osteopenia and a tendency to fractures, bone marrow suppression, gastrointestinal bleeding and portal hypertension. Less often, some individuals also have graying or sparse hair, skin-pigmentation changes, and nail dystrophy [1,2].

In 1998, Tolmie et al. reported 2 sisters of Scottish descent with bilateral retinal telangiectasia (Coats disease), intracranial calcification, sparse hair, and dysplastic nails [3]. In a follow-up report of the family skeletal defects with a tendency to fractures, a mixed cerebellar and extrapyramidal movement disorder and leukodystrophy were also described in the condition. So Crow et al. termed the condition Coats plus syndrome [4]. In 1996, Labrune et al. described 3 pediatric cases with a leukoencephalopathy, extensive calcifications and intracerebral cysts, without retinal abnormalities [5]. Nagae-Poetscher et al. reported 3 unrelated patients with leukoencephalopathy and brain calcifications and cysts [6]. The authors defined the disorder as LCC or Labrune syndrome. Coats plus syndrome and Labrune syndrome were initially thought to be manifestations of the same disorder spectrum, namely cerebroretinal microangiopathy with calcification and cysts (CRMCC) [7]. However, after identification of genetic basis with Coats plus syndrome and LCC, the two disorders are not allelic. It is known that CTC1 mutations have been identified in Coats plus syndrome [1,8]. The genetic basis of LCC is now known to be mutations in the SNORD118 gene [9]. Coats plus is completely distinct from LCC apart from the radiological similarities.

The molecular pathogenesis of Coats plus syndrome has been reported recently. The heterozygous mutations in CTC1 gene, encoding conserved telomere maintenance component 1, were firstly identified by whole-exome sequencing of two siblings with Coats plus syndrome [1]. Anderson et al. reported 15 different mutations in the CTC1 gene by sequencing affected proband(s) from nine of the ten families with Coats plus syndrome [1]. These mutations in CTC1 gene identified from different ancestry Coats plus patients suggest possible genetic heterogeneity. We herein firstly reported the CTC1 gene screening results from a Chinese family with Coats plus syndrome.

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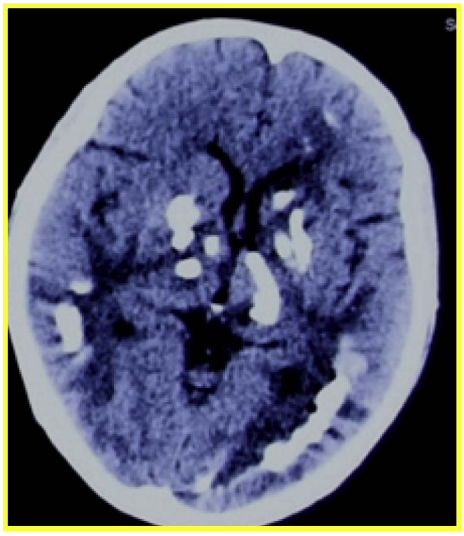

Fig. 1. Cranial CT scans showing variable and asymmetrically distributed calcifications in the deep cortex and basal ganglia.

2. Clinical reports

This 21-year-old female was born to non-consanguineous parents at preterm birth with mildly delayed development. She was referred to our hospital for evaluation of gradually progressive cognitive decline and recurrent seizures of nine years duration. At 12 years of age she developed bilateral visual difficulties and didn't receive further examination. She took oral steroid and was left with vision retaining in the left eye and light perception in the right eye. At the age of 16 years, she manifested dizziness and felt tired all the time. Blood examination demonstrated a hypochromic, microcytic anemia. She had suffered occasional seizures at this time. Her past medical history, as well as her family history, were no special notes.

On physical examination, her vitals were stable. Her neurological examination revealed mild mental retardation. There were positive Babinski sign and Hoffman sign in bilateral limbs. She had talipes cavus. A CT scan of her brain demonstrated intracranial calcification involving the thalamus, bilateral basal ganglia and cerebral white matter in parieto-occipital regions (Fig. 1). MRI of the brain revealed a diffuse infra- and supratentorial cerebral white matter hyperintensities on T2 sequences corresponding to leukencephalopathy, as well as a large cystic lesion in the right temporal lobe (Fig. 2). Ophthalmological examination showed a bilateral exudative retinopathy (Fig. 3) consistent with Coats disease. Blood tests revealed a declined hemoglobin (82 g/L) and blood platelet(58×10^9/L).Serum thyroid and parathyroid hormones, serum calcium, phosphate, and lactate levels were unremarkable. Analysis of the CSF showed normal. In summary, based on the presence of intracranial calcifications, leukencephalopathy, parenchymal brain cysts, and clinical features of bilateral Coats disease of the eye along with other extra-neurological manifestations, she was diagnosed with Coats plus syndrome.

3. Targeted sequencing of CTC1 gene and results

Coding and uncoding regions of the CTC1 gene, covering the promoter, coding exons and exon–intron junctions, were amplified by polymerase chain reaction (PCR) from genomic DNA of three individuals in the family(her parents are normal). Details of primer sequences and PCR conditions are available from the authors. The amplified PCR products were sequenced by using ABI 3100 sequencer. A Blast homology search was performed using the program BLAST2 at the National Center for Biotechnology Information Website to compare individual sequences to wild-type sequences.

We identified biallelic CTC1 variants (c.775G > A p.V259M and c.2066A > G p.Y689C) that were likely to be pathogenic in the affected individual which carried two missense variants (Fig. 5). The two identified mutations occurred in 5 and 13 of 23 exons in CTC1. Her parents tested showed appropriate heterozygosity for a single variant (Fig.4). Genotyping of family members confirmed their segregation was consistent with autosomal-recessive inheritance. The heterozygous variant identified, c.775G > A in exon 5 of the CTC1 gene, was known single nucleotide polymorphisms (SNP).Another heterozygous variant identified, c.2066A > G in exon 13 of the CTC1 gene, was a novel variant that had not been reported before. We also sequenced the variant in 50 healthy members and it was absent from 50 Chinese population controls.

Both mutations affected highly evolutionarily conserved amino acids across species from *Homo sapiens* to xenopus (Fig. 5).

4. Discussion

This is the first study to report a genetically confirmed family of Coats plus syndrome from China. Targeted sequencing of CTC1 gene identified a novel biallelic heterozygous missense variant, p.V259M on one allele and p.Y689C on the other allele, which were likely to be

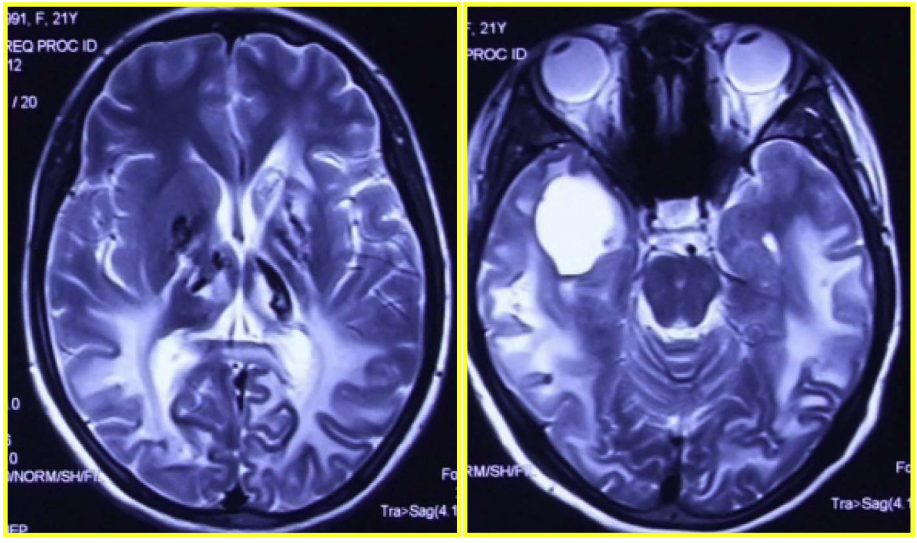

Fig. 2. Cranial T2-weighted MRI scans demonstrating diffuse involvement of the periventricular, deep and sub coertical white matter sparing the frontal white matter. The calcification is apparent as low signal areas in the thalami and basal ganglia.

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