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Case report

Novel *SIL1* nonstop mutation in a Chinese consanguineous family with Marinesco-Sjögren syndrome and Dandy-Walker syndrome

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ABSTRACT

Marinesco-Sjögren syndrome (MSS) is a rare autosomal recessive disorder, which is characterized by congenital cataracts, cerebellar ataxia, progressive muscle weakness, and delayed psychomotor development. *SIL1*, which is located at 5q31.2, is the only gene known to cause MSS. Dandy-Walker syndrome (DWS) is defined by hypoplasia, upward rotation of the cerebellar vermis, and cystic dilation of the fourth ventricle; however, its genetic pathogeny remains unclear. Here, we report a Chinese consanguineous family with MSS and DWS. Whole exome sequencing identified a novel nonstop mutation in *SIL1*. Sanger sequencing revealed that the mutation was segregated in this family according to a recessive mode of inheritance. We found that the mutation changed a stop codon (TGA) to an arginine codon (CGA), and no in-frame termination codon in the 3′ untranslated region (UTR) of *SIL1* could be found. The mRNA levels of *SIL1* were decreased by 56.6% and 37.5% in immortalized lymphoblasts of the patients respectively; the protein levels of *SIL1* were substantially decreased. This case study is the first report on Chinese MSS patients, MSS complicated by DWS, and a nonstop mutation in *SIL1*. Our findings imply the pathogenetic association between DWS and MSS.

1. Introduction

Marinesco-Sjögren syndrome (MSS; OMIM 248800), as a form of autosomal recessive cerebellar ataxia, is characterized by congenital cataracts, cerebellar ataxia, progressive muscle weakness due to myopathy, and delayed psychomotor development. Other minor features, such as short stature, hypergonadotropic hypogonadism, and skeletal deformities due to muscle weakness, can also be observed in MSS patients. Mutated *SIL1* is the only known genetic etiology of MSS [1]. Dandy-Walker Syndrome (DWS; OMIM 220200) is defined by hypoplasia and upward rotation of the cerebellar vermis and cystic dilation of the fourth ventricle [2]. Patients with DWS often have motor deficits, such as delayed motor development, hypotonia, and ataxia; approximately 50% have mental retardation, and some have hydrocephalus. DWS is a heterogeneous disorder, genetic pathogeny of which remains unclear. Here, we describe a consanguineous family with MSS and DWS, and identify a nonstop mutation in *SIL1*.

2. Case report

There are two patients in this family: II-1 is 15 years old and II-2 is 10 years old (Fig. 1). Both of them were born uneventfully. Cataract was found in both siblings at 3 years of age. The physical development of both siblings was delayed. When they were referred to us, II-1's weight was 52 kg (10th–25th percentile) and height was 150 cm (0th–3th percentile) and II-2's weight was 20 kg (0th–3th percentile) and height was 114 cm (0th–3th percentile). Both patients had mild mental retardation, hypotonia, ataxia, dysarthria, and strabismus. There are no skeletal deformities other than cubitus valgus in II-1. Brain magnetic resonance imaging of both the siblings demonstrated Dandy-Walker variant deformity (Fig. 2). Cytogenetic analysis on patient II-2 showed a normal karyotype. Disease-causing genomic copy number variations were not detected in either patient by single nucleotide polymorphism (SNP) arrays, but loss of heterozygosity (LOH) was detected at a 13.6-Mb region located on 5p31.2–33.1 of both patients.

3. Molecular studies

The Committee for Ethical Issues on Gene Analysis and Prenatal Diagnosis, Central South University approved this study and informed consent was obtained for each parent of the patients described. We

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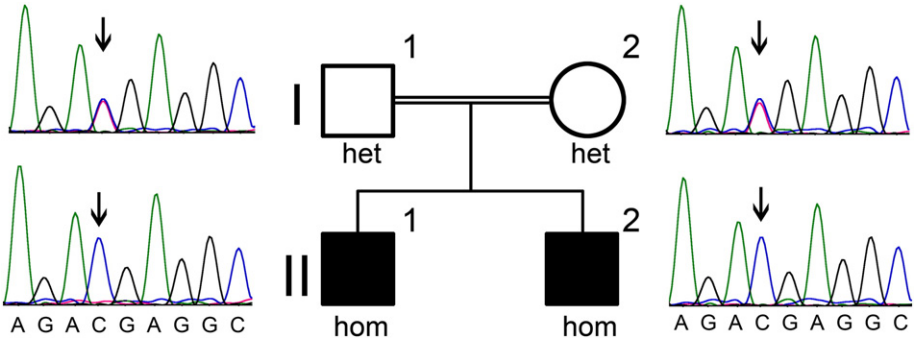

Fig. 1. Familial pedigree and *SIL1* mutation The affected status is indicated by filled symbols in pedigree, and the allele status is given below. Sanger sequencing chromatograms show the heterozygous mutation at chr5: 138,282,808 A > G in unaffected parents and homozygous mutation in affected sibs.

performed whole exome sequencing (WES) on the patients and their parents. WES and data analysis were carried out as previously described [3], with sufficient CCDS coverages (95%–97%, for depth ≥ 8). Candidate mutations were confirmed by Sanger sequencing. We identified a non-stop mutation (chr5: 138,282,808 A > G) in the *SIL1* gene co-separated within this family; both patients were homozygous, whereas both parents were heterozygous (Fig. 1). This mutation was not listed in any public database (dbSNP, ESP6500, ExAC, HGMD). This mutation turned the terminator codon (TGA) to an arginine codon (CGA). There is no in-frame terminator codon in *SIL1* 3′ UTR according to human reference genome sequence (UCSC Genome Browser assembly GRCh38/hg38). We scanned *SIL1* 3′ UTR in the patients by Sanger sequencing, and found no variation (data not shown), thus we confirmed the mutated mRNA of *SIL1* had no substitutive terminator codon in the 3′ UTR.

Further, we studied the outcome of this mutation on gene expression. We extracted RNA and protein from immortalized lymphoblasts of the patients and their age- and gender-matched controls. RNA and protein extraction, reverse transcription, Real-time PCR and Western Blotting were carried out as previously described [4,5]. The following antibodies were used: mouse monoclonal anti-*SIL1* clone 1F9 (Origene Technologies; dilution 1:1000), mouse monoclonal anti-β-Actin antibody (Sigma; dilution 1:10,000) and goat anti-mouse IgG (Jackson;

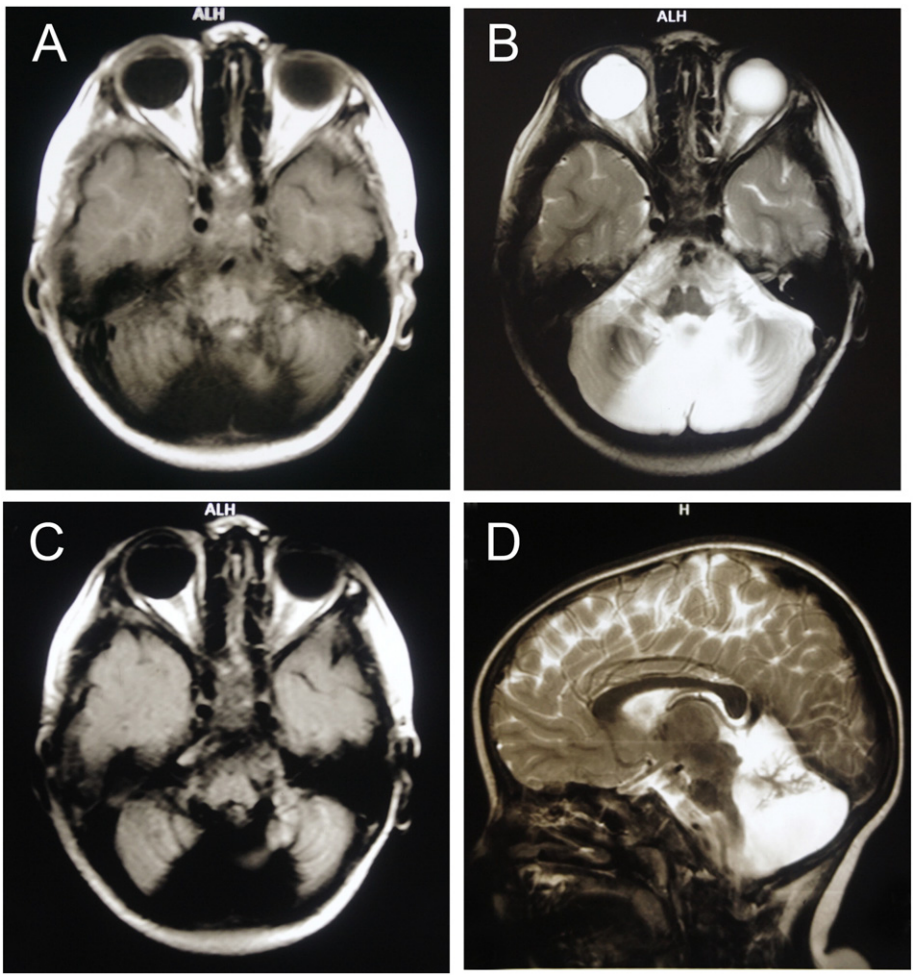

Fig. 2. Brain MRI imaging of II-1 Brain MRI features of II-1 demonstrate cerebellar vermis hypoplasia, cerebellar atrophy and fourth ventricle enlargement, the appearance of which is consistent with a Dandy walker variant deformity. A. Axial T1 section; B. Axial T2 section; C. Axial Flair section; D. Sagittal T2 section.