CLINICAL REPORT

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Coffin-Siris Syndrome: Phenotypic Evolution of a Novel *SMARCA4* Mutation

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Coffin-Siris Syndrome (CSS) is an intellectual disability disorder caused by mutation of components of the SWI/SNF chromatin-remodeling complex. We describe the evolution of the phenotypic features for a male patient with CSS from birth to age 7 years and 9 months and by review of reported CSS patients, we expand the phenotype to include neonatal and infantile hypertonia and upper airway obstruction. The propositus had a novel de novo heterozygous missense mutation in exon 17 of *SMARCA4* (NM_001128849.1:c.2434C>T (NP_001122321.1:p.Leu812Phe)). This is the first reported mutation within motif Ia of the SMARCA4 SNF2 domain. In summary, *SMARCA4*-associated CSS is a pleiotropic disorder in which the pathognomic clinical features evolve and for which the few reported individuals do not demonstrate a clear genotype–phenotype correlation.

Key words: chromatin remodeling; intellectual disability; scoliosis; expressivity; choanal stenosis

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INTRODUCTION

CSS is caused by mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, *ARID1A*, and *ARID1B* [Tsurusaki et al., 2012; Schrier Vergano et al., 2013]. Each encodes a component of the SWI/SNF complex, which modulates eukaryotic gene expression and DNA repair via nucleosome remodeling [Sudarsanam and Winston, 2000; Park et al., 2006]. In vitro studies have shown that the SWI/SNF complex disrupts nucleosome structure at promoter sites to allow the binding of transcription factors [Kingston et al., 1996; Romero and Sanchez-Cespedes, 2013].

By modulating or buffering gene expression, the SWI/SNF complex contributes to cellular differentiation. Formation of an organism from a single zygote is achieved by stepwise changes in gene expression throughout development and occurs in response to cell autonomous and cell non-autonomous mechanisms [Mikkelsen et al., 2007; Meissner et al., 2008; Bernstein et al., 2012]. The loss of functional SWI/SNF will therefore alter modulation of gene expression and predispose to pathological gene expression changes and consequently the pleiotropic manifestations of CSS [Raj et al., 2010].

Besides CSS, mutations of the SWI/SNF complex are also associated with cancer and Nicolaides-Baraitser Syndrome (NBS) [Santen et al., 2012]. NBS arises from mutations in *SMARCA2*, which encodes another SWI/SNF complex component. Although characterized by facial features and developmental delay similar to CSS, individuals with NBS can be distinguished by the absence of hypoplastic fifth fingernails and distal phalanges and by prominent finger joints, sparse hair, and more frequent internal organ malformations [Sousa et al., 2009].

The genotype–phenotype correlation for the broad spectrum of features and the different disorders associated with dysfunction of the SWI/SNF complex are incompletely understood. We review therefore the reported phenotypic characteristics of CSS and expand the phenotypic spectrum to include infantile hypertonia, transient vocal cord paralysis, and upper airway obstruction for individuals with mutations of *SMARCA4*.

CLINICAL REPORT

Following an uncomplicated pregnancy, the propositus was born at 41 weeks of gestation to a non-consanguineous couple of Northern

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European ancestry. There was no family history of intellectual disability or congenital malformations. He had a birth weight of 3.06 kg (20th centile), length of 50.5 cm (58th centile), and head circumference of 34 cm (19th centile). He had respiratory distress and required mechanical ventilation for the first few days of life. At 2 days of age, microlaryngobronchoscopy and nasolaryngoscopy identified laryngomalacia, a shortened left aryepiglottic fold and vocal cords fixed in the abducted position; reevaluation at 21 days revealed vocal cord granulomas, laryngeal erythema and edema and mobile vocal cords. He also had several dysmorphic features (Fig. 1) including short palpebral fissures, blepharophimosis, micrognathia, short midface with malar hypoplasia, deviated nasal septum, cryptorchidism, fisting of the right hand, left knee contracture, distal fifth finger and toe phalanx hypoplasia, long broad toes, and hypoplasia of all toenails. Additional findings included an absent left brainstem auditory evoked response (BAER) and partial agenesis of the corpus callosum but no other brain malformations (Fig. 2).

During the first year of life, the propositus manifested global developmental delay (GDD) and multiple medical problems. These problems included gastroesophageal reflux, uncoordinated swallowing, continued upper airway obstruction, laryngomalacia, muscular hypertonia with fisting of the hands and scissoring of the legs, growth restriction treated with gastrostomy tube (G-tube) feeding, hearing loss, and right cryptorchidism. When examined at 12 months of age, his height, weight, and head circumference were 71.1 cm (5th centile), 9.1 kg (13th centile), and 43.5 cm (1st centile), respectively. Besides microcephaly and hypertonic posturing, his dysmorphisms included brachycephaly, plagiocephaly, frontal bossing with bitemporal narrowing, bilateral supraorbital ridge hypoplasia, malar hypoplasia, short palpebral fissures, mild alar hypoplasia, a broad nasal bridge with anteverted nares, low-set and posteriorly rotated ears, a bifid uvula, prominent lower lip, ankyloglossia, hypoplastic nails and distal phalanges, particularly of the 5th digits and 5th finger clinodactyly.

During the second year of life, he had an adenoidectomy and tonsillectomy to reduce his airway obstruction and orchiopexy for his cryptorchidism. Despite these interventions and gradual improvement of his gastroesophageal reflux, he continued to have multiple problems including increasing central hypotonia and convex right thoracic scoliosis; the latter was treated with Risser serial casting after bracing failed. On examination at 2 years, he had a weight of 11.6 kg (20th centile), height of 81.3 cm (7th centile), and a head circumference of 45 cm (<1st centile). Additional

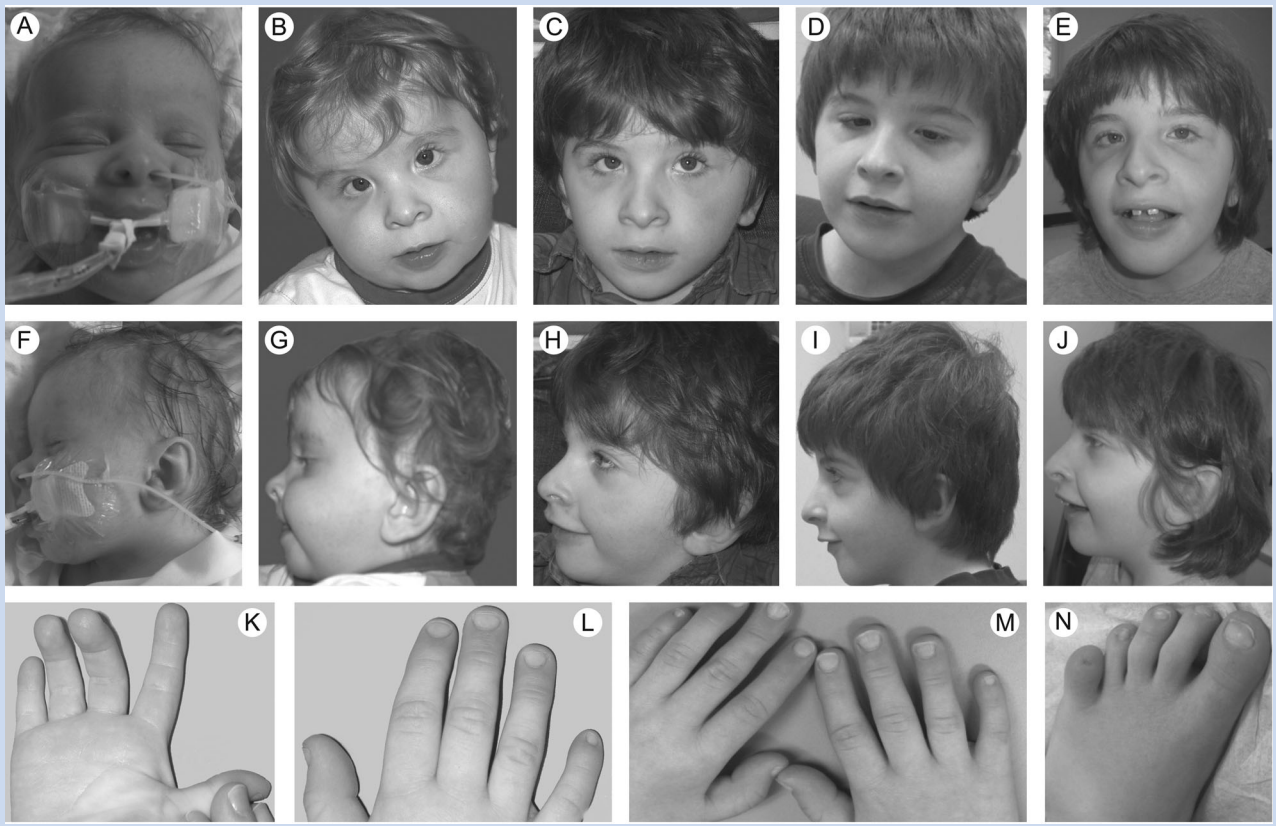

FIG. 1. Clinical photographs of the propositus from birth to age 7 years and 9 months. Frontal and profile photographs from birth (A,F), 1 year (B,G), 5 years (C,H), 6 years (D,I), and 7 years (E,J) show the evolution of CSS-associated features. Anterior and posterior views of the hands at age 4 years 2 months (K,L) and a posterior view at age 6 years 8 months (M) show the distal fingers and hypoplastic fingernails. Photograph of the propositus' left foot at age 7 years and 9 months (N) shows the hypoplastic toenails.

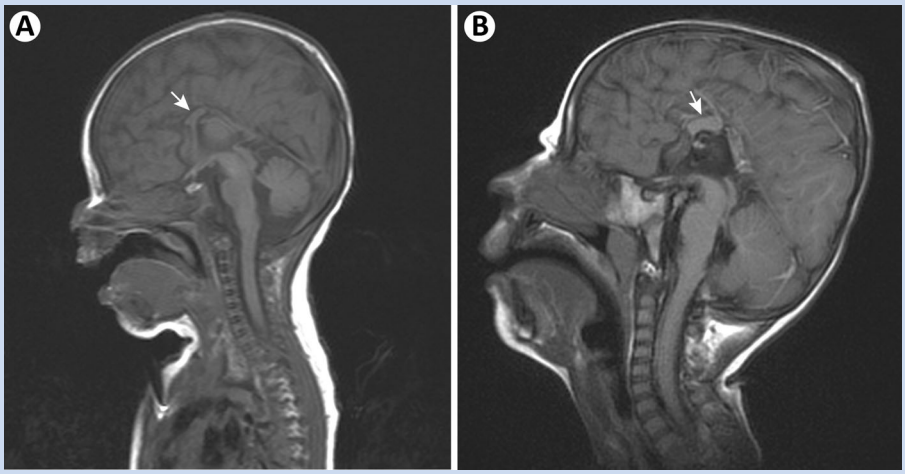

FIG. 2. T1 weighted brain MRI images of the propositus showing the partial agenesis of the corpus callosum (arrows). Images are from scans performed at birth (A) and at age 3 years (B).

dysmorphic features included a high arched palate and a mild pectus excavatum. His neurological examination was notable for the ability to sit and pull to a standing position.

Over the next 2 years, he had a z-plasty for his ankyloglossia and manifested fragmented sleeping patterns, strabismus, laryngomalacia, and staring spells. Seizures were ruled out. On examination at 4 years and 2 months, his height, weight, and head circumference were 96.43 cm (5th centile), 15 kg (19th centile), and 47 cm (<1st centile), respectively. Additional dysmorphic features included prominent eyebrows, a short forehead, a low posterior hairline, and prominent pads on all fingers. His neurological evaluation was remarkable for distal spasticity with central hypotonia, brisk deep tendon reflexes, and a wide-based unsteady gait.

Due to the worsening of his scoliosis, the propositus had spinal rods inserted at the age of 6 years. He remains closely monitored for this.

The propositus was re-evaluated at the age of 6 years and 8 months. His weight, height and head circumference were 21.7 kg (43rd centile), 106.5 cm (1st centile), and 48 cm (<1st centile), respectively. His dysmorphic features were unchanged; he had no new health problems.

His fifth and most recent evaluation at age 7 years and 9 months revealed the presence of all previously stated dysmorphic features and health issues with continued slow and steady developmental progress. His weight, height and head circumference were 24 kg (40th centile), 112.5 cm (1st centile), and 48.75 cm (1st centile), respectively.

The propositus underwent extensive testing that was not diagnostic of his underlying disorder. He had a cardiac echocardiogram that showed normal cardiac anatomy and function, a normal abdominal ultrasound and hand and wrist radiographs showing hypoplasia of the 5th distal phalanx and normal bone age. Genetic testing revealed a normal male karyotype (46, XY; 450–500 band resolution), absence of deletions or duplications of 22q.11.2 or subtelomeric regions detectable by FISH. Microarray (CGH) analysis did not detect any abnormal copy number variants (SignatureChipOS; hg18 assembly). He had normal transferrin iso-electric focusing and *SNRPN* methylation.

MOLECULAR ANALYSES

Based on his features and negative testing, the diagnosis of CSS was first entertained when the propositus was age 4 years. This diagnosis remained contentious though because of the prominent unassociated features of neonatal and infantile hypertonia, vocal cord paralysis, and upper airway obstruction (Table I and Supplementary Table III in supporting information online).

Upon report of the molecular cause of CSS [Tsurusaki et al., 2012], we chose to clarify the propositus' diagnosis through molecular testing. Using the primers (see Supplementary Table I in supporting information online), and methods described in the Supplementary Methods and Results we sequenced all coding exons of the *SWI/SNF* complex genes (*SMARCB1*, *SMARCA4*, *SMARCA2*, *SMARCE1*, *ARID1A*, *ARID1B*) excepting exon 1 of *ARID1A* and *ARID1B*. This revealed several polymorphisms (Supplementary Table II in supporting information online) and a de novo *SMARCA4* heterozygous missense mutation in exon 17 (NM_001128849.1:c.2434C>T; p.Leu812Phe) (Fig. 3). This mutation resides in motif Ia of the SNF2 conserved domain of SMARCA4 and is predicted to alter the active site (Fig. 3D) [Smith and Peterson, 2005].

DISCUSSION

We report on a 7-year-9-month-old patient with CSS and the first *SMARCA4* mutation within the SNF2 Ia motif. With the exception of p.Lys546del, which removes a conserved amino acid between the HAS and BRK domains (Table I and Fig. 3), all reported *SMARCA4* CSS-associated variants alter conserved amino acids within the SNF2 domain (Fig. 3D). Given that the SMARCA4 SNF2 domain

TABLE I. Phenotypic comparison of the propositus to other CSS patients with *SMARCA4* mutations*

	Patient							
Feature	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Propositus**
Age (years)	18	20	9	11	16	4	8	7.75
Sex	M	M	M	M	F	M	F	M
Mutation (NP_001122321.1)	p.Lys546del	p.Thr859Met	p.Arg885Cys	p.Leu921Phe	p.Met1011Thr	p.Arg1157Gly	p.Arg885His	p.Leu812Phe
SNF2 domain affected	Outside of SNF2 domain	Ia-II linker	Motif II/IIa	Motif III	III-IV linker	Motif V	Motif II/IIa	Motif Ia
Growth								
Birth weight (SD)	−1.77	−2.2	−1.2	−1.7	−1.0	−1.1	−2.6	−1.5
Birth length (SD)	NR	NR	−0.9	−1.6	−1.9	−2.3	−2.7	−0.9
Birth OFC (SD)	NR	NR	−0.9	−0.6	+0.1	−1.3	−3.9	−1.6
Weight (SD)[a]	NR	−0.2	−1.5	−1.8	−1.9	−3.0	−1.9	−0.2
Height (SD)[a]	−1.8	−2.6	−3.2	−3.1	−1.9	−3.4	−1.8	−2.6
OFC (SD)[a]	−2.3	−3.8	−3.6	−2.9	−2.3	−2.7	−3.0	−2.6
Psychomotor								
Developmental delay/intellectual disability	Mild	Severe	Severe	Severe	Severe	Severe	Moderate	Severe
Speech delay	Mild	SW	NW	NW	SC	NW	Mild	NW
Seizures	+	−	−	+	−	−	−	−
Hypotonia	+	+	+	−	+	−	+	+
Autistic features/behavioral abnormalities	NR	H, Imp	ASD (H, HST, Ob, SHB)	−	RB	NR	H	RB
Brain anomaly	NR	NR	HCC,HCV	NR	NR	HCC	−	HCC
Craniofacial								
Sparse hair	−	+	−	+	−	+	−	−
Thick eyebrows	+	+	+	+	+	+	+	+
Thick eyelashes	+	+	+	+	+	+	+	+
Ptosis	+	+	+	+	−	+	+	+
Abnormal ears	−	+	+	+	+	+	−	+
Nasal bridge	Narrow	Narrow	Normal	Flat	Flat	Flat	Flat	Narrow
Thick, anteverted alae nasi	−	−	−	−	−	−	−	+
Wide mouth	−	−	+	−	+	−	+	−
Philtrum	Short	Short	Short	NR	Short	NR	Short	NR
Upper lip vermilion	Everted	Everted	Everted	Thin	Everted	Normal	NR	Thin
Thick lower lip vermilion	−	+	+	+	+	+	+	+
Palatal abnormality	SCP	HP	CP	HP	HP	CP	HP	HP
Skeletal-limb								
Hypoplastic/absent fifth finger/toe	Fr	Fr/T	T	Fr/T	Fr/T	Fr/T	T	Fr/T
Hypoplastic/absent nail (fifth finger/toe)	Fr	Fr/T	T	Fr/T	Fr/T	Fr/T	T	Fr/T
Hypoplastic/absent nail (other fingers/toes)	NR	Fr/T	T	Fr/T	Fr/T	Fr/T	−	Fr/T
Prominent interphalangeal joins	−	+	−	−	+	−	−	−
Prominent distal phalanges	−	+	+	+	+	−	NR	−

(*Continued*)

TABLE I. (*Continued*)

Feature	Patient 1	2	3	4	5	6	7	Propositus
Scoiosis/spinal abnormalities	−	+	−	−	−	−	−	+
Joint laxity	−	+	+	−	+	−	+	−
Others								
Hirsutism	+	+	+	+	+	+	+	−
Congenital heart defects	−	−	−	VtSD,PDA	−	MA,PA,SRV, AtSD,PDA	+	−
Genitourinary defects	−	NR	Crp	−	−	Crp	−	Crp
Gastrointestinal abnormalities	NR	GO	C	DU	C	GR	GR	GR
Inguinal (I)/umbilical (U) hernia	−	I	−	I	−	Om	I/U	−
Sucking difficulty	−	+	+	+	+	+	+	+
Feeding difficulty	−	+	+	+	+	+	+	+
Hearing impairment	−	+	+	−	+	−	−	+
Visual impairment	+	+	+	+	+	−	−	+
Recurrent infections	−	+	−	+	+	+	+	−

ASD, autism spectrum disorder; AtSD, atrial septal defect; C, constipation; CP, cleft palate; Crp, cryptorchidism; DU, duodenal ulcer; F, female; Fr, finger; GO, gastric outlet obstruction; GR, gastroesophageal reflux; H, hyperactivity; HCC, hypoplastic corpus callosum; HCV, hypoplastic cerebellar vermis; HP, high palate; HST, hypersensitivity; I, inguinal; Imp, impulsiveness; M, male; MA, mitral atresia; NR, not reported; NW, no words; Ob, obsession; OFC, occipital-frontal circumference; Om, omphalocele; PA, pulmonary atresia; PDA, patent ductus arteriosus; RB, repetitive behavior; SC, simple conversation; SCP, submucosal cleft palate; SD, standard deviation; SHB, self-harming behavior; SRV, single right ventricle; SW, several words; T, toe; VtSD, ventricular septal defect.

*Excepting the propositus, all patients with *SMARCA4* mutations included in this table were reported by [Kosho et al., 2013].

[a]Standard deviation (SD) of the respective growth parameter recorded for individual at the age he or she was reported.

forms the active site for ATP hydrolysis and couples ATP hydrolysis to chromatin-remodeling activity [Smith and Peterson, 2005] and that the altered amino acids are conserved, we hypothesize that each mutation impedes SMARCA4 chromatin remodeling. A caveat to this explanation is the absence of deletion, nonsense or frameshift mutations of SMARCA4 among CSS patients; this observation could suggest that hemizygosity for SMARCA4 is lethal or causes a different disease, or that the genetic mechanism is not that of a hypomorph or amorph but rather that of a neomorph or antimorph. Arguing against these considerations, however, is the observation that loss of one dose of SWI/SNF complex members SMARCA2 or ARID1A is sufficient to cause CSS [Tsurusaki et al., 2012].

Since the SWI/SNF complex is a chromatin regulator of gene expression, there are several nonexclusive explanations for the pleiotropism of CSS and the presence of additional features in the propositus. These include differences in the consequences of the *SMARCA4* mutations on enzymatic function, differences in the sensitivity of the genetic background to SWI/SNF dysfunction, and stochastic events.

Prior biochemical studies of the *S. cerevisiae* homologue Swi2/Snf2 have found that mutagenesis of the different conserved SNF2 domains have qualitatively and/or quantitatively different enzymatic consequences [Smith and Peterson, 2005]. In *S. cerevisiae* substitution of an alanine for the proline immediately preceding the leucine mutated in motif Ia of the propositus reduced enzymatic activity, increased the K_m for ATP, decreased the V_{max} of ATP hydrolysis and decreased substrate turnover. This suggests that the p.Leu812Phe mutation observed in the propositus is a loss of function mutation. Secondly, because the *S. cerevisiae* mutation in domain Ia had different enzymatic consequences than mutations in the other domains, we speculate that the unusual phenotypic features of the propositus might be attributable to the distinctive enzymatic consequence of a mutation in SNF2 domain Ia of SMARCA4.

Alternatively, besides differences in genetic susceptibility, the pleiotropism of CSS might reflect a more general principle of SWI/SNF complex biology. Specifically, because individuals reported with *SMARCA4* mutations inconsistently manifest cardiac malformations, behavioral and cognitive problems, skeletal anomalies and abdominal wall malformations, the manifestation of disease features might be arising from stochastic movement of gene expression past a disease threshold as demonstrated in model organisms for trait penetrance [Raj et al., 2010].

The propositus also demonstrates the evolution of the features of CSS. As an infant and young child, his face lacked the coarseness, and thick lips typically associated with CSS. His facial features became more pronounced by 4 years and allowed a clinical diagnosis. Interestingly, the propositus and others reported with *SMARCA4*-associated CSS do not commonly have a thick upper lip as do individuals with other genetic causes of CSS [Schrier et al., 2012; Tsurusaki et al., 2012; Van Houdt et al., 2012; Kosho et al., 2013; Santen et al., 2013].

In summary, we associate a novel *SMARCA4* mutation with CSS and expand the phenotypic spectrum of *SMARCA4*-associated CSS. We also find that the pathognomic clinical features of *SMARCA4*-associated CSS evolve and that the few reported individuals with

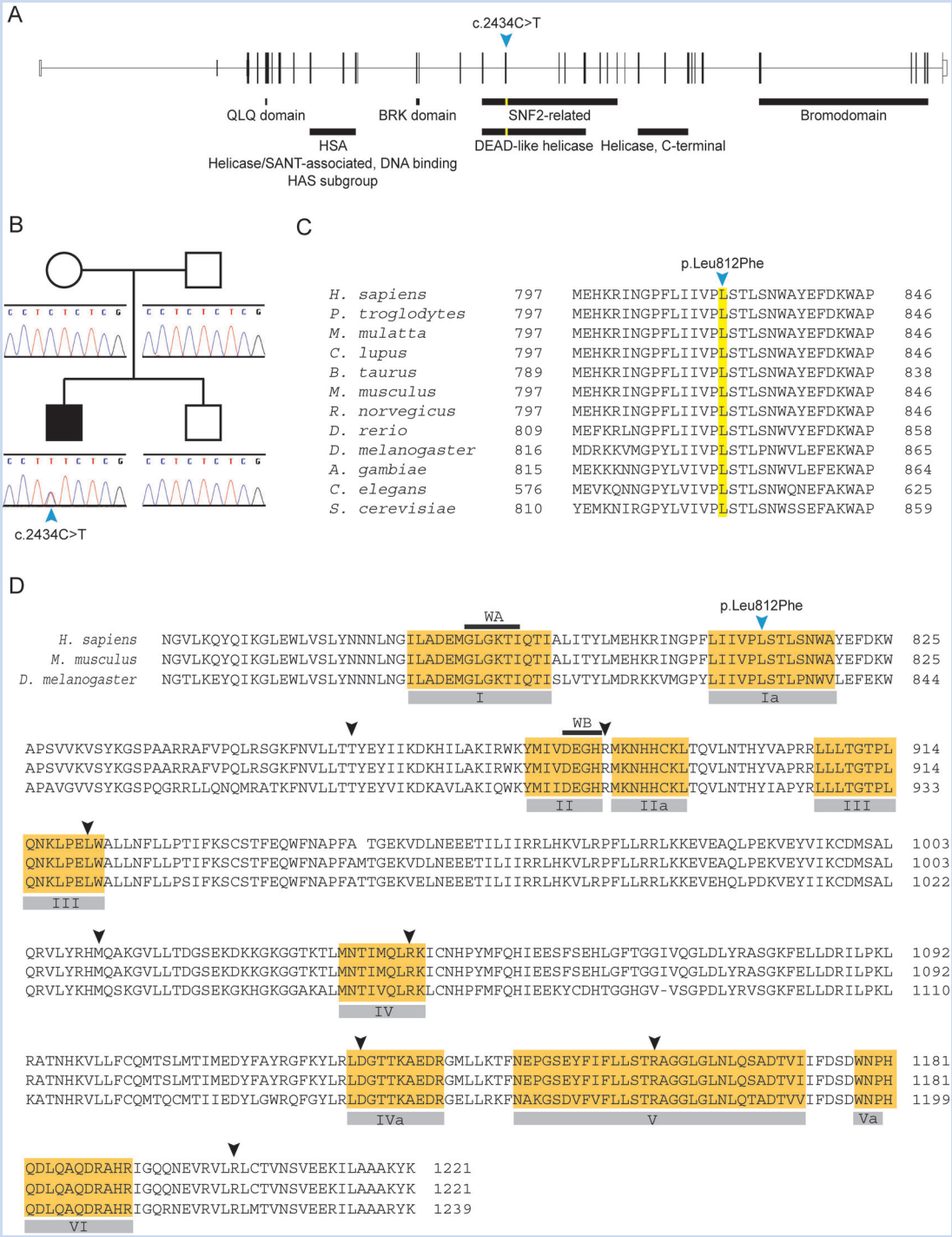

FIG. 3. The propositus carries a novel de novo heterozygous missense mutation in *SMARCA4*. A: Structure of the *SMARCA4* gene and the motifs encoded by the exons. The propositus' mutation c.2434C>T was located in exon 17, which encodes a portion of the SNF2 domain. B: The propositus was heterozygous for c.2434C>T. This mutation was not detected in the blood DNA of any other family members. C: The mutation p.Leu812Phe alters an amino acid conserved across species. D: Amino acid sequence of the SMARCA4 SNF2 domain with the location of CSS-associated mutations represented by arrowheads. The conserved motifs characteristic of SNF2 domains are highlighted in orange and labeled below the sequence. The amino acids of the Walker A (WA, phosphate binding) and Walker B (WB, magnesium binding) sites are represented by black bars over the sequence. Compared to reported CSS-associated SMARCA4 mutations (black arrows), the propositus' mutation (blue arrow) is the only one located in motif Ia.

this condition do not demonstrate a clear genotype–phenotype correlation.

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