

CHAMP1 Mutations cause Refractory Infantile Myoclonic Epilepsy

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Abstract

The chromosome alignment maintaining phosphoprotein 1 (*CHAMP1*) gene has a key role in neurodevelopment. It is involved in kinetochore-microtubule attachment and in the regulation of chromosomes alignment during mitosis. So far, 17 cases of *CHAMP1* mutations have been reported with a common clinical picture of developmental delay and intellectual disability, dysmorphic facial features, hypotonia and/or spasticity, and microcephaly. Four patients had epilepsy of whom three had focal seizures and one had generalized epilepsy. We report two new cases, which have in addition to developmental delay, refractory myoclonic epilepsy. These cases suggest that the phenotypic spectrum of *CHAMP1* mutations may be broader and includes refractory myoclonic epilepsy as well.

Keywords

- ▶ *CHAMP1* Gene
- ▶ developmental delay
- ▶ myoclonic epilepsy

Introduction

The *CHAMP1* protein was first discovered in 2011 by Itoh et al.¹ They reported a novel protein involved in kinetochore-microtubule attachment and named it chromosome alignment-maintaining phosphoprotein (CAMP), later on called *CHAMP1* (Chromosome alignment maintaining phosphoprotein 1). CAMP is a zinc-finger protein that localizes to chromosomes and the spindle and is involved in the attachment of sister kinetochores on a replicated chromosome to microtubules from opposite spindle poles (bi-orientation), thus allowing accurate chromosome segregation during mitosis.¹ Mutations affecting genes encoding proteins that

regulate chromosome alignment and/or spindle assembly are well-established causes of a variety of syndromic and nonsyndromic developmental disorders.²

The Deciphering Developmental Disorders Study³ used a genotype-driven approach to investigate 1,133 children with severe, undiagnosed developmental disorders, and their parents, using a combination of exome sequencing and array-based detection of chromosomal rearrangements. They discovered 12 novel genes associated with developmental disorders including *CHAMP1*. These newly implicated genes increased by 10% the proportion of children that could be diagnosed. They reported the first three patients with *CHAMP1* mutations causing a developmental disorder.

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Since then, three series of patients with *CHAMP1* mutations^{2,4,5} and a clinical report of another patient,⁶ which include 17 cases altogether were published. Hempel et al² firmly established mutations in *CHAMP1* as the cause of a developmental disorder and provided the first detailed clinical description of *CHAMP1*-associated disorders. The clinical features of the syndrome are still being revealed. All patients had developmental delay and intellectual disability, and most of them had dysmorphic facial features, hypotonia, and/or spasticity and microcephaly.

Four patients had epilepsy of whom three had focal seizures and one had generalized epilepsy.

We report two children with *CHAMP1* mutations who have in addition to developmental delay, refractory myoclonic epilepsy.

Case Histories

Case 1

A female infant was born after an uneventful pregnancy and delivery at 39 weeks of gestation, with a birthweight of 3,150 g. The perinatal period was uneventful. During her first year of life she was healthy and showed minimal motor delay. She began crawling at the age of 8 months, sat at 10 months, and said her first words at the age of 14 months. Since the age of 12 months her parents noticed irritability and clusters of myoclonic jerky movements involving the head that were more frequent upon awakening.

At 18 months, she was first admitted for evaluation. Neurologic examination was normal. Electroencephalograph (EEG) examination showed generalized spike-wave and polyspike-wave epileptiform discharges and bilateral temporal discharges including electro clinical events (→ Fig. 1A).

She was diagnosed with myoclonic epilepsy. The seizures semiology changed over time to blinking episodes and to events of jerky backward movement of the head and hands associated with eye rolling and a frightened look. Seizures were refractory to lamotrigine and levetiracetam. Topiramate was stopped due to worsening of seizures. Clonazepam and sulthiame were stopped due to worsening of hypotonia and behavioral side effects, respectively. The parents refused vagal nerve stimulation treatment and the ketogenic diet. At 7 years of age, seizures are partially controlled by valproic acid and clobazam, still having 3 to 10 short myoclonic seizures daily.

The girl started walking independently at 22 months and combined 2 words at 3 years. At the age of 38 months her mental developmental index (Bayley's scales of infant development test 2) was 57. At 6 years of age, she scored 62 on the Kaufman's test of educational achievement, third edition. She is currently attending a special education school.

At 6 years of age, on examination, she had mild hypotonia, head circumference (HC) was 49 cm (2%), and a short philtrum was noted (→ Fig. 1B). Parental HC are normal.

A thorough investigation was undertaken. Brain magnetic resonance imaging (MRI), metabolic screen including blood lactate, amino acids, ammonia, urine organic acids, cerebrospinal fluid (CSF) for glucose and chromosomal microarray were all normal. The result of whole exome sequencing of the patient (Department of Human Genetics in Yokohama City University) showed no pathological variants in known epilepsy related genes (mean read depth of RefSeq coding sequence is 70.8), but later on, after *CHAMP1* de novo mutations had been published, the laboratory reanalyzed its database and found a heterozygous missense mutation in the *CHAMP1* gene (NM_032436.2:c.46T > C, p.(Cys16Arg)),

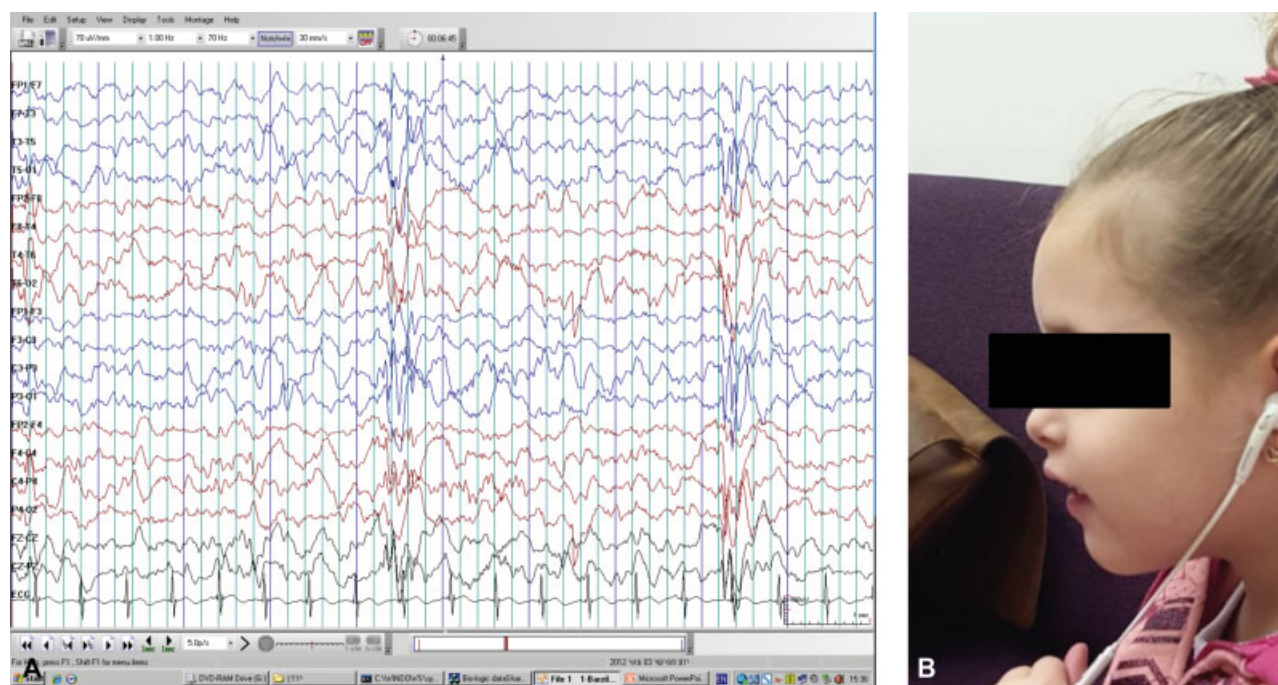


Fig. 1 (A) EEG of case 1 showing generalized epileptiform discharges of polyspike-slow wave. (B) Case 1, examination at 6 years. EEG, electroencephalograph.

which was confirmed as de novo by Sanger's sequencing using patient's and her parental DNA.

Case 2

The second child is a 3-year-old boy who is the third child of healthy unrelated parents. He was born at 38 weeks of gestation after a normal pregnancy, via vacuum-assisted vaginal delivery due to fetal distress. Birthweight was 3,250 g and the postpartum period was uneventful. Developmental delay first became evident at the age of 3 to 4 months when he did not reach for objects. He rolled over at 7 months and at 22 months he cruised around furniture and could speak 3 to 4 words. Myoclonic seizures began at 1 year of age with head dropping backward while sitting or standing, sometimes with falling. These occurred both during awakening and sleep, and recurred dozens of times daily. Physical examination at 1 year and 10 months was notable for dolichocephaly, sagittal suture ridging, a short philtrum, and borderline small HC (HC: 46 cm = 2nd

percentile; ▶**Fig. 2A**). Neurologic examination revealed axial and upper limb hypotonia with pyramidal signs in the lower limbs, including ankle hypertonia, hyperreflexia, and extensor plantar reflex. Myoclonic seizures were observed during the physical examination.

Recurrent multiple EEG examinations demonstrated frequent generalized, mainly bifrontal epileptic bursts of multi-spike, and multispikes-wave activity (▶**Fig. 2B**). Myoclonic jerks were associated with generalized spike and wave activity followed by decrementation.

Seizures were refractory to multiple medications. Valproic acid was discontinued due to thrombocytopenia. Levetiracetam and clobazam were both stopped due to no significant effect. Phenobarbital decreased the seizure frequency and severity. A ketogenic diet was started at 1 year and 9 months and resulted in a significant decline in the seizure frequency from 10 to 15 an hour to 3. Unfortunately, due to feeding difficulties the ketogenic diet was

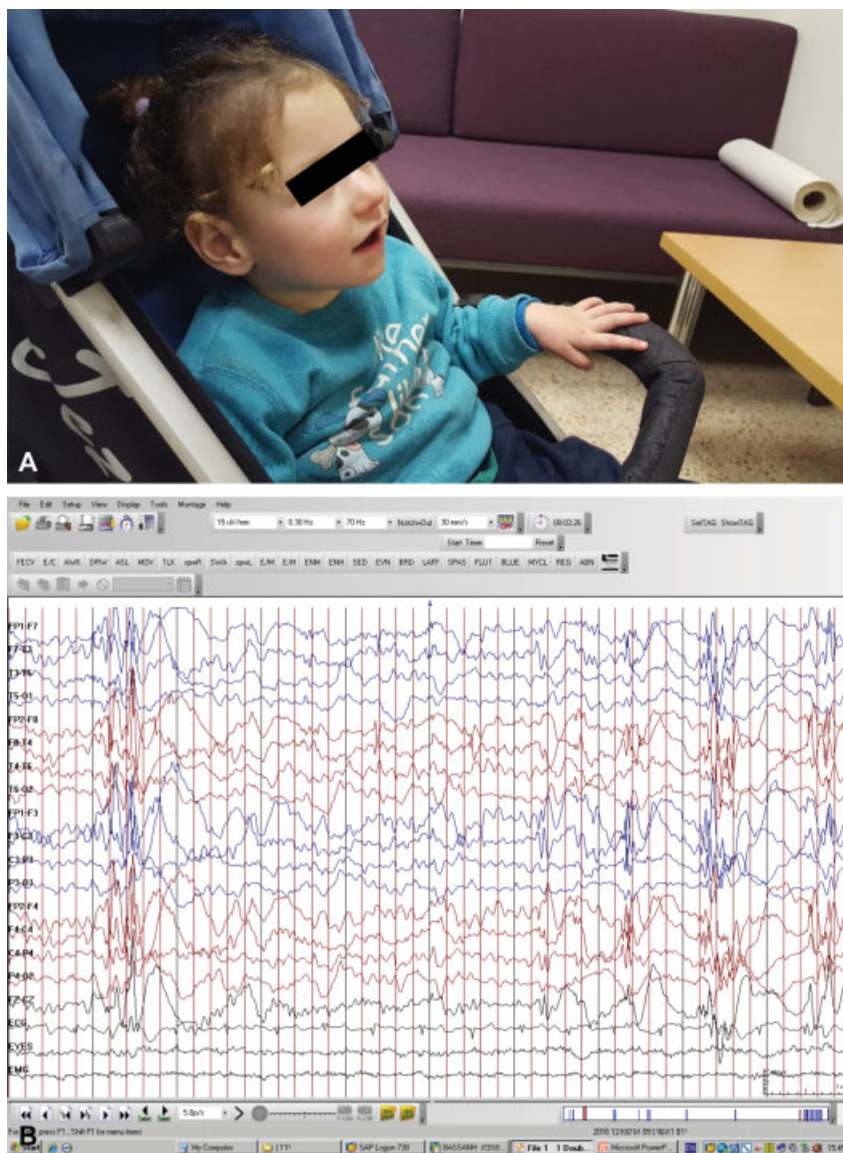


Fig. 2 (A) Case 2, age 1 year. (B) EEG of case 2 showing generalized epileptiform discharges of polyspike-slow wave. EEG, electroencephalograph.

discontinued. Medical cannabis treatment was inefficient. He has recently started felbatol with no response so far. The parents refused vagal nerve stimulation treatment.

Brain MRI at the age of 1 year showed brain atrophy. Chromosomal micro-array test revealed a microdeletion of 165 kb that includes the *CHAMP1* gene: Chr13:115,004,924–115,169,878.

This deletion includes three OMIM genes, and except for *CHAMP1*, none of them was described in association with epilepsy

Discussion

We describe two children with a similar clinical picture of global developmental delay, mild dysmorphic features, and refractory myoclonic epilepsy. Genetic evaluation revealed a missense mutation in the *CHAMP1* gene in the first child, and a 165 kb microdeletion that includes *CHAMP1* in the second.

As of today, there are only five reports of patients with *CHAMP1* mutations (►Table 1). The Deciphering Developmental Disorders Study³ discovered three cases with *CHAMP1* mutations out of 1,133 children with severe, undiagnosed developmental disorders, using a combination of exome sequencing and array-based detection of chromosomal rearrangements. The clinical picture of these three patients was reported in the study by Isidor et al.

Hempel et al² studied five patients with *CHAMP1* mutations. Similar to our cases, all manifested developmental delay, hypotonia, and mild dysmorphic features. The most consistent dysmorphic features were short philtrum, tented upper lip, and everted lower lip. Three had microcephaly. Although motor development improved over time, the speech impairment remained significant. A friendly behavior was described in all five individuals.

Three of the patients had a normal brain MRI and two had abnormalities, one had a myelination delay, and one had mild generalized atrophy of the brain, a simplified gyral pattern, and mild cerebellar cortical dysplasia.

The study of Tanaka et al⁴ included five females with *CHAMP1* mutations, all significantly intellectually disabled, three had congenital microcephaly, and one had postnatal microcephaly. The patients were either nonverbal or minimally so. Concerns were evident already in the neonatal period with congenital microcephaly, hypotonia, and feeding difficulties. In addition, spasticity was a common feature. Some individuals, but not all, had congenital anomalies including choanal atresia, intestinal malrotation, bicuspid aortic valve, and a ventricular septal defect. All individuals exhibited short stature. They all had abnormal behaviors but not always friendly behavior like the patients described by Hempel et al. There was a range of abnormal behaviors including self-injurious behavior in the oldest individual, repetitive behaviors, and inappropriate laughter. Ophthalmologic problems and hearing loss were common. Dysmorphic features were common to all the individuals and included hypertelorism, epicanthal folds, short philtrum, and upslanting or down slanting palpebral fissures. Brain

Table 1 The clinical features of patients with *CHAMP1* mutations

Study	No. of pts. with <i>CHAMP1</i> mutations	Mutations	ID/GDD	Muscular hypotonia ± spasticity	Microcephaly	Dysmorphic features	Abnormal behavior	Epilepsy	Brain MRI
Deciphering Developmental Disorders Study 2015 ³	(3)	De novo nonsense	(3/3)	NA	NA	NA	NA	NA	NA
Hempel et al ²	5	De novo: 2 frameshift, 3 nonsense	5/5	5/5 hypotonia	3/5	5/5	5/5 friendly behavior	1/5 fronto temporal	3 N, 2 AN
Tanaka et al ⁴	5	De novo 2 frameshift, 3 nonsense	5/5	4/5 Hypotonia, 3/5 spasticity	4/5; congenital 3, acquired 1	5/5	5/5	1/5 generalized	2 N, 3 AN
Isidor et al ⁵	6	De novo truncating	6/6	6/6 hypotonia	3/6	5/6	3/6	1/6	N/NS
Okamoto et al ⁶	1	De novo frameshift	1/1	0/1 hypotonia, 1/1 spasticity	0/1	1/1	1/1	1/1 partial	1 AN

Abbreviations: AN, abnormal; *CHAMP1*, chromosome alignment maintaining phosphoprotein 1; GDD, global developmental delay; ID, intellectual disability; MRI, magnetic resonance imaging; N, normal; NA, not available; NS, nonspecific.

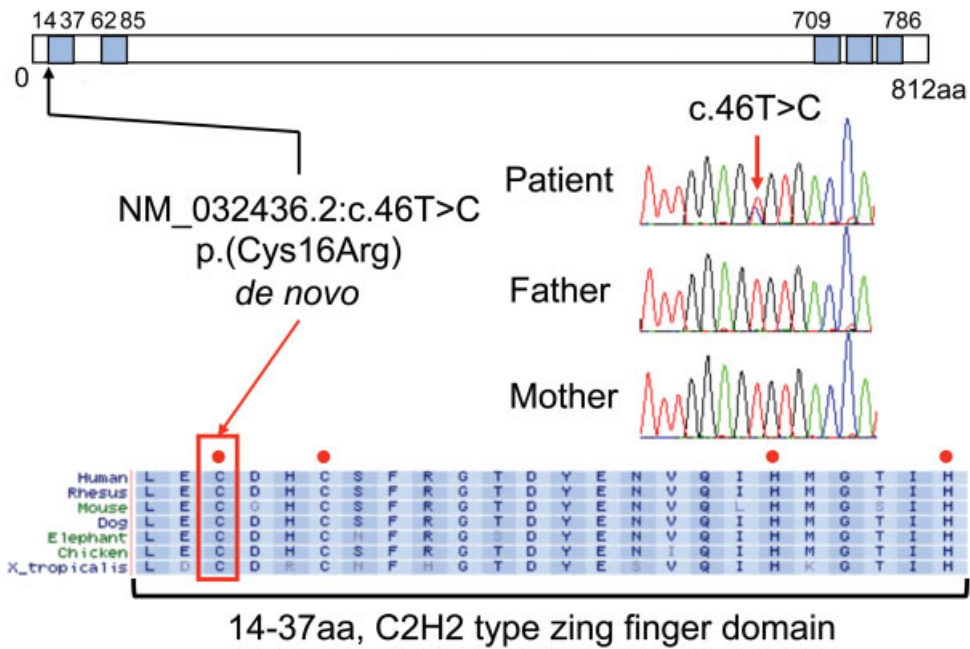


Fig. 3 Missense mutation of patient 1 in *CHAMP1* gene. CHAMP1, chromosome alignment maintaining phosphoprotein 1.

MRI in two patients suggested no specific structural abnormalities, whereas in the other patients, there was decreased brain volume and white matter in one, a hypoplastic corpus callosum in another and cerebellar atrophy with mild inferior vermian hypogenesis in a third.

Isidor et al⁵ in a multicenter study reported six patients. Their clinical observations confirm the phenotypic homogeneity of the syndrome, and their functional studies show that CHAMP1 protein variants are delocalized from chromatin and are unable to bind to two of its direct partners, POGZ (pogo transposable element-derived protein with zinc finger domain) and HP1 (heterochromatin protein 1). These data suggest a pathogenic mechanism for the *CHAMP1*-associated intellectual disability syndrome mediated by direct interacting partners of CHAMP1 protein, several of which are involved in chromo/kinetochore-related disorders.

Okamoto et al⁶ have recently reported a novel patient with a *CHAMP1* mutation who had feeding difficulties, failure to thrive, delayed motor development, severely delayed acquisition of language skills, and intellectual disability. This patient showed spasticity of lower extremities, like the second patient we presented. They isolated lymphoblast cells from this patient, observed chromosome segregation, and found that these cells exhibited an increase in centrosome number resulting in multipolar spindle formation, suggesting that CHAMP1 protein is critical for progression of cytokinesis and maintenance of centrosome number.

Altogether, epilepsy has been reported in only four patients. The study of Hempel et al² included a patient with nocturnal frontotemporal epilepsy, probably causative for sleep apnea that was successfully treated with carbamazepine. One patient in Tanaka et al's⁴ study had generalized seizures that started at the age of 3 years and were adequately treated with levetiracetam. Isidor et al⁵ and

Okamoto et al⁶ have also reported one patient with epilepsy, each.

Refractory myoclonic epilepsy has not been described as part of the clinical presentation of *CHAMP1* mutations in the former studies.

Patient 2 has a microdeletion of 165 kb that includes *CHAMP1*. One could argue that his developmental delay and facial features are due to the lack of CHAMP1 protein and that the myoclonic epilepsy may be caused by an abnormality in another gene included in the deletion, in a contiguous gene mechanism. However, the similar epilepsy characteristics of patients 1 and 2, and the fact that patient 1 has a missense mutation in *CHAMP1* supports the association between *CHAMP1* mutations/deletions and refractory myoclonic epilepsy. Patient 1 is the first patient reported with missense mutation. The variant c.46T > C (MN_0324362); p.Cys16Arg is a missense substitution in exon-3 of the *CHAMP1* gene, causing a change of cysteine to arginine. There is a large physicochemical difference between cysteine and arginine, and it is a moderately conserved nucleotide (phyloP:3.68 [-14.1;6.4]). The mutation substitutes a cysteine residue involved in zinc coordination in C2H2 type zinc finger domain, strongly suggesting that the mutation would interfere with CHAMP1 protein binding to its targets (→ Fig. 3).

The variant is absent from database of human population, the 1,000 genomes project and EXAC database (last accessed in November 2018). The coverage of the *CHAMP1* gene in these databases is more than 20X among at least 95% of the samples. Previous mutations reported by Hampel et al were also missing from the population database, indicating that these changes are very rare and unlikely to be disease unrelated changes. In silico analysis, using PolyPhen-2, SIFT, MutationTaster, and Align GVGD predicted the variant to be deleterious (→ **Supplementary Table S1**; available in online version only).

We thus suggest that the phenotype of *CHAMP1* mutations is wider and should include refractory myoclonic epilepsy.

Funding

None.

Conflict of Interest

None declared.

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