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Neurodevelopmental phenotypes in individuals with pathogenic variants in *CHAMP1*

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Abstract De novo pathogenic variants in *CHAMP1* (chromosome alignment maintaining phosphoprotein 1), which encodes kinetochore-microtubule associated protein on 13q34, cause a rare neurodevelopmental disorder. We enrolled 14 individuals with pathogenic variants in *CHAMP1* that were documented by exome sequencing or gene panel sequencing. Medical history interviews, seizure surveys, Vineland Adapted Behavior Scales Second Edition, and other behavioral surveys were completed by primary caregivers of available participants in Simons Searchlight. Clinicians extracted clinical data from the medical record for two participants. We report on clinical features of 14 individuals (ages 2–26) with de novo predicted loss-of-function variants in *CHAMP1* and compare them with previously reported cases (total $n = 32$). At least two individuals have the same de novo variant: p.(Ser181Cysfs*5), p.(Trp348*), p.(Arg398*), p.(Arg497*), or p.(Tyr709*). Common phenotypes include intellectual disability/developmental delay, language impairment, congenital and acquired microcephaly, behavioral problems including autism spectrum disorder, seizures, hypotonia, gastrointestinal issues of reflux and constipation, and ophthalmologic issues. Other rarely observed phenotypes include leukemia, failure to thrive, and high pain tolerance. Pathogenic variants in *CHAMP1* are associated with a variable clinical phenotype of developmental delay/intellectual disability and seizures.

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Ontology terms: intellectual disability; severe microcephaly; severe global developmental delay

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INTRODUCTION

Neurodevelopmental disorders (NDDs) such as intellectual disability (ID) and autism spectrum disorder (ASD) are both genetically and phenotypically heterogeneous. Because of the pleiotropic nature and genetic heterogeneity of these conditions, exome sequencing (ES) is an initial diagnostic approach for individuals with NDDs (Srivastava et al. 2019).

CHAMP1 (MIM: 616327), located on 13q34, encodes an 812-amino acid zinc finger phosphoprotein. *CHAMP1* protein functions to maintain proper kinetochore–microtubule attachment and chromosome alignment on the metaphase plate (Itoh et al. 2011). The first three patients with *CHAMP1* variants associated with a developmental disorder were identified in the Deciphering Developmental Disorders Study of 1133 children with severe developmental disorders (Fitzgerald et al. 2015). Subsequently, six additional manuscripts identified 20 additional individuals. These publications included data on individuals with 12 nonsense variants (60%), six frameshift variants (30%), one missense variant (5%), and one microdeletion including *CHAMP1* (5%) (Hempel et al. 2015; Isidor et al. 2016; Tanaka et al. 2016; Okamoto et al. 2017; Ben-Haim et al. 2020; Wang et al. 2020).

Common clinical manifestations of individuals with the *CHAMP1* disorder include intellectual disability, speech and language impairment, motor developmental delay, microcephaly, seizures, ophthalmologic issues, hypotonia, and dysmorphic facial features (Hempel et al. 2015; Isidor et al. 2016; Tanaka et al. 2016; Okamoto et al. 2017; Ben-Haim et al. 2020; Wang et al. 2020). In this study, we refine the phenotype associated with de novo pathogenic/likely pathogenic variants in *CHAMP1* in 12 previously unreported individuals enrolled in Simons VIP/Searchlight by providing data on clinical features and standardized neurobehavioral measures. We also include a single case with leukemia. Characterization of additional patients is necessary to determine whether cancer is more common in individuals with *CHAMP1* variants.

RESULTS

Molecular Findings

We analyzed 12 new individuals and two previously reported individuals (Isidor et al. 2016; Tanaka et al. 2016) with pathogenic or likely pathogenic variants in *CHAMP1* identified on clinical testing. Among these 14 individuals, there are 11 nonsense and three frameshift variants, all of which were de novo and predicted to result in nonsense-mediated decay (Table 1). The c.1489C > T; p.(Arg497*) variant is recurrent and was independently identified in four unrelated individuals in our cohort and one previously reported individual (Isidor et al. 2016). The c.542_543delCT; p.(Ser181Cysfs*5) variant is also recurrent and has been independently reported in two unrelated individuals, one in our cohort and one previously reported (Tanaka et al. 2016). The other recurrent variants were p.(Trp348*), p.(Arg398*), and p.(Tyr709*). All other variants are unique to a single individual.

Clinical Findings

Of the 14 individuals, eight are females and six are males. The average age at assessment was 9.3 yr, with a range from 2.2 yr to 26.3 yr. Three individuals had prenatal/perinatal complications including small gestational age observed during ultrasound (14.3%) or a broken clavicle (7.1%). Seven individuals had complications prior to newborn hospital discharge including respiratory distress (35.7%), neonatal jaundice (35.7%), and abnormal hearing (21.4%). Twelve individuals had neonatal symptoms of feeding difficulty (35.7%), hypotonia (35.7%), lethargy (28.6%), irritability (21.4%), and difficulty sucking (21.4%).

All individuals demonstrated delayed developmental milestones (Table 1; Supplemental Table 1). Developmental milestones include sitting at an average age of 15.9 mo, walking at an average age of 33.9 months ($n = 1$ achieved past the age of 7; $n = 1$ did not acquire), first words spoken at an average age of 35 mo ($n = 1$ achieved past the age of 7; $n = 2$ did not acquire), and self-feeding achieved at an average age of 60 mo ($n = 3$ achieved past the

Table 1. Clinical manifestations of patients with de novo variants in CHAMP1

ID	I-1	I-2	I-3	I-4	I-5	I-6	I-7	I-8	I-9	I-10	I-11	I-12	I-13	I-14	Frequency/ average in the cohort
Previously reported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Tanaka et al. 2016	Unreported	Unreported	
Sex	Male	Male	Female	Male	Female	Male	Male	Female	Female	Female	Female	Female	Male	Female	8 female; 6 male (57.1%; 42.9%)
Age (yr)	4.2	9.8	8.5	11.5	2.2	3.3	10.3	13.4	26.3	14.8	3.4	15.3	2.2	5.0	Avg: 9.3 (n = 14)
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	
HGV5 DNA reference	c.542_543delCT	c.661dup	c.959dup	c.1002G>A	c.1489C>T	c.1489C>T	c.1489C>T	c.1489C>T	c.1544G>A	c.1657G>T	c.1850dupA	c.1969C>T	c.2127T>G	c.2127T>G	
HGV5 protein reference	p.(Ser181Cysfs*5)	p.(Thr221Asnfs*3)	p.(Arg321*)	p.(Trp334*)	p.(Arg497*)	p.(Arg497*)	p.(Arg497*)	p.(Arg497*)	p.(Trp515*)	p.(Glu553*)	p.(Lys618Glufs*13)	p.(Gln657*)	p.(Tyr709*)	p.(Tyr709*)	
ClinVar ID	217909	827777	NA	210049	210050	210050	210050	210050	217907	984804	280855	217916	523879	523879	
ACMG/AMP classification	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	
ID/DD	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100% (n = 14)
Hypotonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100% (n = 14)
Microcephaly	-	+	+	-	-	+	-	-	+	+	+	+	-	+	57.1% (n = 14)
Failure to thrive	-	-	-	-	-	-	-	-	-	+	-	-	-	-	7.1% (n = 14)
Autism spectrum disorder	-	-	+	-	-	-	+	+	+	-	+	-	-	-	35.7% (n = 14)
Seizures	+	-	-	-	-	+	+	-	+	-	-	+	-	-	35.7% (n = 14)
Skeletal abnormalities	-	-	-	+	-	-	+	-	+	-	-	-	+	+	28.6% (n = 14)
GERD	+	+	-	+	-	+	-	+	-	+	+	-	+	-	57.1% (n = 14)
Constipation	+	+	-	-	-	+	+	+	+	+	+	-	-	+	64.3% (n = 14)
Otitis media	+	+	-	+	+	+	+	-	+	+	+	+	+	-	78.6% (n = 14)
Hearing deficit	-	-	-	-	-	-	-	-	+	-	-	-	-	-	7.1% (n = 14)
Ophthalmologic issues	+	+	-	+	+	+	+	+	+	+	+	+	+	+	92.9% (n = 14)
Strabismus	-	-	-	+	+	+	-	-	+	+	+	+	-	+	57.1% (n = 14)
Hyperopia	+	-	-	+	+	+	+	+	-	+	-	+	+	-	57.1% (n = 14)
Nystagmus	-	-	-	-	+	+	-	-	+	+	-	-	-	-	21.4% (n = 14)
Feeding difficulties	+	-	-	-	+	+	-	-	-	+	+	+	-	+	42.9% (n = 14)
Urinary incontinence	-	+	-	-	-	-	+	-	+	+	+	-	-	-	35.7% (n = 14)
Fecal incontinence	-	+	-	-	-	-	-	-	+	+	+	-	-	-	28.6% (n = 14)
Age at sitting (mo)	NR	NR	18 mo	21 mo	9 mo	12 mo	NR	NR	18 mo	24 mo	11 mo	24 mo	NR	6 mo	Avg: 15.9 mo (n = 9)
Age at first words (mo)	NR	NR	48 yo	66 mo	20 mo	14 mo	NR	NR	>7 yr	36 mo	Not achieved	Not achieved	NR	26 mo	Avg: 35 mo (n = 6)

(Continued on next page.)

Table 1. (Continued)

ID	I-1	I-2	I-3	I-4	I-5	I-6	I-7	I-8	I-9	I-10	I-11	I-12	I-13	I-14	Frequency/ average in the cohort
Age at walking (mo)	NR	NR	30 mo	36 mo	23 mo	Not achieved	NR	NR	48 mo	48 mo	33 mo	>7 yr	NR	19 mo	Avg: 33.9 mo (n = 7)
Age of self-feeding (mo)	NR	NR	Not achieved	>7 yr	Not achieved	Not achieved	NR	NR	>7 yr	>7 yr	Not achieved	72 mo	NR	48 mo	Avg: 60 mo (n = 2)
Vineland composite score	61	52	NR	46	73	60	63	45	20	NR	52	29	83	NR	Avg: 53.1 (n = 11)
Communication standard score	69	57	NR	50	79	67	64	45	21	NR	49	30	89	NR	Avg: 56.4 (n = 11)
Daily living skills standard score	64	52	NR	47	71	60	69	50	21	NR	53	25	87	NR	Avg: 54.5 (n = 11)
Socialization standard score	69	47	NR	42	78	68	59	43	20	NR	61	42	89	NR	Avg: 56.2 (n = 11)
Motor skills standard score	59	NR	NR	NR	79	54	NR	NR	NR	NR	54	NR	77	NR	Avg: 64.6 (n = 5)

The reference transcript is NIM_032436.4.
 ACM3/AMP criteria and ClinVar IDs have been added into rows 8 and 9.
 (HGVS) Human Genome Variation Society, (DD) developmental delay, (ID) intellectual disability, (GERD) gastroesophageal reflux disease.

age of 7; $n = 3$ did not acquire). Urinary incontinence (35.7%) and fecal incontinence (28.6%) were observed ranging in ages from 3.4 to 26.3 yr old.

All of the individuals had neurological manifestations including intellectual disability or developmental delay (100%), hypotonia (100%), congenital microcephaly (21.4%), acquired microcephaly (21.4%), clumsiness (21.4%), and movement abnormalities (14.3%). There was no history of developmental regression.

Other neurobehavioral phenotypes included autism spectrum disorder (35.7%), nonverbal learning disorder (7.1%), language dyspraxia (7.1%), and anxiety (7.1%).

There have been a number of dysmorphic features seen in our cohort. Hypertelorism, short philtrum, and broad nasal bridge were the common findings (Fig. 1). One patient (I-3) has hypertelorism, anteverted nose, prognathism, syndactyly with doughy skin, and joint laxity (Fig. 1B).

We have brain magnetic resonance imaging (MRI) images for some of our patients. Dysplastic corpus callosum, cerebellar asymmetry, and simplified sulcation were seen in one patient. Another patient had slightly delayed myelination at age 6 (Supplemental Table 1).

We assessed adaptive development in 11 individuals using the Vineland Adaptive Behavior Scales (VABS) assessment of adaptive behaviors (composite score [53.1 ± 18.1]). Subscales showed below average scores for all subscales approximately equivalently: communication (56.4 ± 20.2), daily living skills (53.5 ± 18.8), socialization (57.1 ± 20.0), and motor skills scores (64.6 ± 12.4) (Fig. 2). Nine individuals had low standardized VABS composite scores between 20 and 70 (< -2 SD) and two had moderately low scores between 70 and 80 (< -1 SD) (Sparrow et al. 2005).

For the six individuals who were in the appropriate age range for a VABS motor skills assessment, the average score was 64.6 (SD = 12.4; range = 54–79).

Most of the individuals had typical childhood infections (83.3%, $n = 12$), and no individuals were diagnosed with an immunodeficiency disorder. Most individuals had otitis media

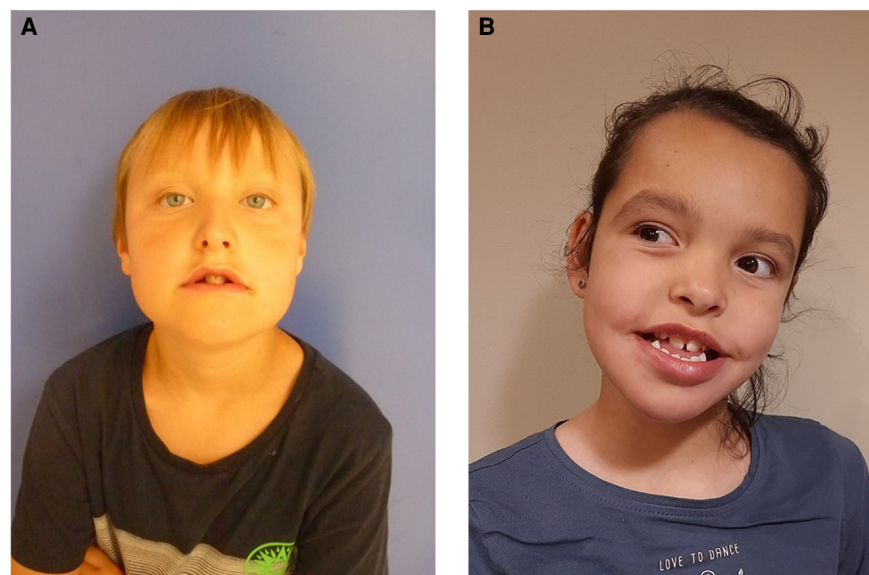


Figure 1. Photographs of patients: (A) I-2 and (B) I-3. Short philtrum, broad nasal bridge, and hypertelorism can be observed in both patients.

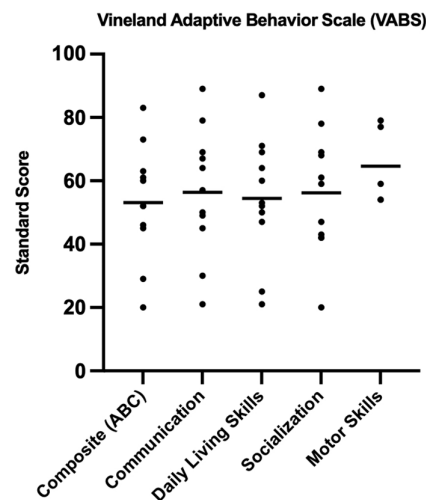


Figure 2. Vineland Adaptive Behavior Scale Scores (edition two) for 11 individuals with averages.

(75%), some requiring tympanostomy tubes. Pneumonia (41.7%) and urinary tract infections (8.3%) were also reported.

Gastrointestinal problems were also commonly reported, including gastroesophageal reflux disease (GERD) (57.1%) and constipation (64.3%). Four individuals reported taking laxatives for constipation. One individual requires a gastrostomy tube, and intestinal malrotation was observed once. Weight gain was difficult for one child. Delayed gastric emptying was observed once.

Endocrine problems included short stature (16.7%), obesity (8.3%), and irregular menses (8.3%).

The ophthalmologic issues were another major group of problems (93%) including alternating esotropia, poor visual attention, delayed visual maturation, intermittent exotropia, bilateral refractive amblyopia, strabismus, and hyperopia.

Five of 14 individuals reported a history of seizures (35.7%). Two individuals reported complex partial seizures (14.3%), two reported febrile seizures (14.3%), two reported petit mal seizures (14.3%), and two reported grand mal seizures (14.3%). One individual had several abnormal electroencephalogram (EEG) results on right occipital region without a clinical seizure. Four individuals had more than one type of seizure. All of these individuals currently have their seizures medically treated and seizures are medically controlled. The two most effective antiepileptics reported were divalproex sodium and levetiracetam.

Other infrequent problems included scoliosis (28.6%), apneic episodes (7.1%), undescended testicles (7.1%), dystonia (7.1%), oral sensory hypersensitivity (7.1%), and deafness (7.1%; both conductive and sensorineural hearing loss treated with a hearing aid).

Other notable features included high pain tolerance (41.7%), sleep issues (35.7%), and dental issues (21.4%).

There is one individual in our cohort diagnosed with leukemia (I-7). He is currently 12 yr old and was diagnosed with acute myeloid leukemia with myelodysplasia related changes at 8 yr old. He has a *de novo* CHAMP1 c.1489C > T; p.(Arg497*) variant. At diagnosis, his bone marrow cytogenetics showed 46,XY,t(3;21)(q26;q22),del(7)(q11.2q32)[28]/46,XY[5]. ish t(3;21)(D3S3364+,EV1+,RUNX1+;RUNX1+,D3S3523+). He was treated using the COG AAML1031 protocol. He had new onset grand mal seizures during chemotherapy and was treated with levetiracetam and has continued on this medication.

At the age of 8.5 yr he had an allogeneic stem cell transplantation. He relapsed 27 mo after the first transplant with additional cytogenetic changes with a new clone, with no central nervous system (CNS) involvement. He was treated according to the acute myeloid leukemia (AML) relapse therapy protocol including FLAG (fludarabine, cytarabine, granulocyte colony-stimulating factor) therapy and a gemtuzumab/cytarabine combination. He had poor bone marrow recovery at the end of the gemtuzumab/cytarabine cycle, and his bone marrow showed >20% leukemic blasts and hypocellularity consistent with refractory AML. The bone marrow cytogenetics at relapse demonstrated 46,XY,t(3;21)(q26;q22),del(7)(q11.2q32),der(20)t(1;20)(q25;p11.2)[17]/46,XX[2].ish der(20)t(1;20)(wcp1+;wcp20+)x2[6].

He received a haploidentical hematopoietic stem cell transplantation (HSCT) in aplasia induced by clofarabine. He received a bone marrow transplant from his father at 11 yr old. At this time, his bone marrow aspiration was consistent with remission and full chimerism, but he had a de novo del(20)(q11.2q13.1) of unknown significance not present in his father. Soon after transplant he developed thrombocytopenia, and his bone marrow aspirate showed remission and full chimerisms from the donor with persistence of the del(20)q (46,XY,del(20)(q11.2q13.1)[12]/46,XY[13].nuc ish(D7Z1,D7S486)x2[200]). No other abnormalities were observed. His complete blood count is normal with no evidence of leukemia or myelodysplastic syndromes (MDS). He developed graft versus host disease of the oral mucosa and skin and was treated with oral budesonide and sirolimus systemically. He is discontinued from immunosuppression and currently asymptomatic without any signs of graft versus host disease.

DISCUSSION

CHAMP1 is a zinc finger protein with five C2H2-type zinc finger motifs (Itoh et al. 2011). Twenty-four de novo pathogenic/likely pathogenic variants in *CHAMP1* have been described: one missense, one microdeletion, eight frameshift, and 14 nonsense. The first reported missense variant (Ben-Haim et al. 2020) has multiple lines of computational evidence supporting a deleterious effect (PP3), is absent in controls (PM2), has confirmed de novo inheritance via parental DNA analysis (PS2), and is likely pathogenic by the American College of Medical Genetics and Genomics/American Molecular Pathology criteria (Richards et al. 2015). All other reported variants are null, pathogenic, or likely pathogenic variants and are predicted to cause loss of function leading to haploinsufficiency. To date there are no obvious genotype–phenotype correlations. Previous studies reported a recurrent *CHAMP1* variant in two individuals c.1192C>T; p.(Arg398*) (Hempel et al. 2015). Two other previously reported individuals have different DNA variants, c.1044delG (Tanaka et al. 2016) and c.1043G>A (Isidor et al. 2016), leading to the same protein variant, p.(Trp348*). There are two individuals with a de novo c.542_543delCT, p.(Ser181Cysfs*5) variant: one in our cohort and one previously reported (Tanaka et al. 2016). We also reported two unrelated individuals who carry the same de novo variant: c.2127T>G; p.(Y709*). Additionally, there are five individuals with a de novo c.1489C>T; p.(Arg497*) variant: four in our cohort and one previously reported (Isidor et al. 2016). This is likely due to a C>T transition at a CpG dinucleotide that occurs in ~25% of de novo germline mutations (Hodgkinson et al. 2009; Alexandrov et al. 2013; Acuna-Hidalgo et al. 2016). Our findings identify a few mutational hotspots in *CHAMP1*.

In this study, we report 14 individuals with de novo pathogenic *CHAMP1* variants. Of these 14 individuals, 12 have not previously been described. The clinical manifestations of those in our cohort are similar to those previously described (Hempel et al. 2015; Isidor et al. 2016; Tanaka et al. 2016; Okamoto et al. 2017; Ben-Haim et al. 2020). All individuals have developmental delay or intellectual disability, hypotonia, and ophthalmologic issues

(i.e., hyperopia, strabismus, and nystagmus). Most of the individuals have gastrointestinal problems, primarily GERD and constipation. Other notable features include congenital and acquired microcephaly, feeding difficulties, ASD, and high pain tolerance. The positive correlation between *CHAMP1* and the development of a neurodevelopmental phenotype was also mentioned in a study that collected 60 patients who have 13q33-q34 microdeletions (Sagi-Dain et al. 2019).

Two individuals with a *CHAMP1* variant were reported to have ASD (Hempel et al. 2015; Isidor et al. 2016) compared to the five in our cohort of 14. Short stature and difficulty gaining weight have been more variable across the small clinical series and present in ~20%–40% of individuals (Hempel et al. 2015; Isidor et al. 2016; Okamoto et al. 2017; Ben-Haim et al. 2020).

Seizures have recently been recognized to be associated with *CHAMP1* variants (Ben-Haim et al. 2020) and are associated with a variety of seizure types including nocturnal frontotemporal epilepsy ($n = 1$; Hempel et al. 2015), febrile seizures ($n = 1$; Tanaka et al. 2016), generalized seizures ($n = 1$; Tanaka et al. 2016), complex partial seizures ($n = 1$; Okamoto et al. 2017), and refractory myoclonic epilepsy ($n = 2$; Ben-Haim et al. 2020).

Problems with sleep may require further characterization. In addition to the five individuals (35.7%) with sleeping difficulties on our cohort, Hempel et al. (2015) reported three cases with sleeping difficulties (60%), one with sleep disturbance without successful treatment of melatonin, one with obstructive sleep apnea, and one with sleep apnea associated with nocturnal frontotemporal epilepsy. Four of the five individuals reported in Tanaka et al. (2016) had problems falling asleep and staying asleep. Based on the VABS behavior assessment, most individuals demonstrated challenges across communication, daily living, socialization, and motor skills. There was a significant negative correlation between the age of the individual at the time of the assessment and the VABS standardized adaptive behavior composite, communication, daily living skills, and socialization scores. We have not observed developmental regression over time. Rather, with age, individuals with the *CHAMP1* pathogenic variants further diverged from their peers. Of the three subscales, the daily living skills score was the lowest and socialization was the highest. Many individuals had ASD and/or attention-deficit/hyperactivity.

CHAMP1 defects affect kinetochore–microtubule attachment, resulting in abnormal chromosome alignment along the metaphase plate, impairing chromosomal segregation and multipolar spindle formation leading to apoptosis or cytokinesis failure of neuronal progenitor cells (NPCs) during embryogenesis (Itoh et al. 2011; Okamoto et al. 2017). The disrupted protein interactions between *CHAMP1* and other microtubule and/or kinetochore protein networks, specifically *BUBR1* and *MAD2L2*, may also play a role in the pathogenesis of cancer (Fig. 3). *BUB1B* encodes *BUBR1*, a mitotic spindle checkpoint protein important for triggering apoptosis in polyploid cells and inhibiting tumor growth (Tang et al. 2001; Shin et al. 2003). Biallelic *BUB1B* variants are associated with the cancer susceptibility disorder called mosaic variegated aneuploidy (MVA). MVA manifests as childhood cancers (i.e., Wilms tumor, rhabdomyosarcoma, and leukemia) in ~40% of individuals (Ganmore et al. 2009; Suijkerbuijk et al. 2010).

Genes associated with microtubule networks have been reported to cause neurodevelopmental disorders including lissencephaly, polymicrogyria, autism spectrum disorders, and intellectual disabilities (Lasser et al. 2018). Additionally, kinetochore-associated gene variants that interact with *CHAMP1* result in phenotypically similar neurodevelopmental conditions. These genes include *CENP-E*, *CENP-F*, *BUBR1*, *CEP57*, *NDE1*, and *KNL1* (Fig. 3). Genetic variants in these corresponding genes result in genetic conditions with similar phenotypic manifestations such as microcephaly primary type 13 (OMIM #616051), Strømme syndrome (OMIM #243605), mosaic variegated aneuploidy syndrome 1 (OMIM #602860), mosaic variegated aneuploidy syndrome 2 (OMIM #614114), microhydranencephaly (OMIM #605013), and microcephaly primary type 4 (OMIM #604321). These conditions

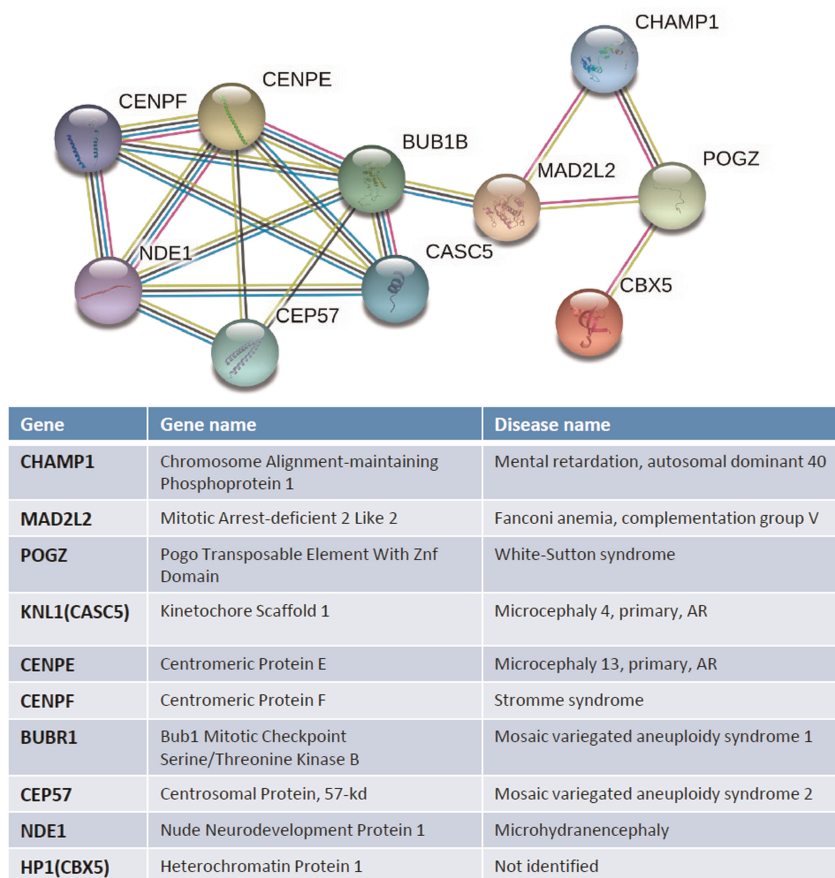


Figure 3. Protein interactors of *CHAMP1* with associated conditions with the protein–protein interaction annotation produced by <https://string-db.org/>.

involve similar clinical features including microcephaly, intellectual disability, developmental delay, short stature, dysmorphic features, hypotonia, and ophthalmological issues (Kavaslar et al. 2000; Snape et al. 2011; Mirzaa et al. 2014; Filges et al. 2016; Saadi et al. 2016; Zaqout et al. 2017). Functional studies also demonstrate that *CHAMP1* protein variants cannot bind to two of *CHAMP1*'s partners: *POGZ* (pogo transposable element-derived protein with zinc finger domain) and *HP1* (heterochromatin protein 1) (Isidor et al. 2016). De novo variants in *POGZ* are associated with developmental delay/intellectual disability, microcephaly, delayed onset of walking and talking, hypotonia, dysmorphic facial features, autism spectrum disorder, and failure to thrive (Ye et al. 2015), demonstrating similar clinical manifestations to those with *CHAMP1* variants (Fig. 3).

We report one individual (I-7) with AML, the first report of cancer found in a patient who has a germline *CHAMP1* variant. Our patient initially had a t(3;21)(q26.2;q22) translocation, which is associated with AML. Our patient relapsed after 27 mo following his second bone marrow transplant. At this time, the only cytogenetic difference was a novel interstitial deletion of Chromosome 20q. This novel del(20q) may have been induced by his cancer treatment, resulting in a relapse of acute myeloid leukemia as seen in a similar report (Kanagal-Shamanna et al. 2013). However, previous studies also demonstrate late relapses are common in patients who receive transplantation for MDS (Yeung et al. 2015). New

cytogenetic alterations that appear during a late relapse are usually due to the emergence of clones (Yeung et al. 2015) such as his del(20q). Typically, MDS with del(20q) has a good prognosis, but additional cytogenetic and molecular abnormalities may confer a worse prognosis (Bacher et al. 2014). In *CHAMP1* haploinsufficiency, proper kinetochore–microtubule attachment and chromosome alignment are deranged, resulting in higher mitotic indices and chromosome instability (Itoh et al. 2011). This genetic instability may contribute to the manifestation of cancer. As we saw leukemia in only one patient, we need to consider that this may be a somatic change not associated with the germline *CHAMP1* variant.

CHAMP1 also interacts with *MAD2L2* (mitotic arrest deficient-like 2), a component of the mitotic spindle assembly checkpoint required for genomic integrity and associated with Fanconi anemia (Itoh et al. 2011; Gay 2018). Aberrant regulation of *MAD2L2* has been demonstrated in many tumors including colon, breast, and ovarian (Niimi et al. 2014; Okina et al. 2015; Feng et al. 2016; Li et al. 2018). We believe that the dysfunctional connectivity between *CHAMP1* and the complex microtubule/kinetochore protein networks contribute to the genomic instability required to predispose one to cancer.

In summary, pathogenic *CHAMP1* variants cause a rare neurodevelopmental disorder associated with intellectual disability, speech and language impairment, microcephaly, seizures, hypotonia, ophthalmologic issues, constipation/gastroesophageal reflux, and behavioral problems including autism and sleep disturbances. We reported one case with childhood leukemia. We should continue to monitor for future reports of leukemia and other cancer phenotypes in individuals with *CHAMP1* variants.

METHODS

This study was approved by the Columbia University Irving Medical Center Human Research Protection Institutional Review Board (Protocol Approved IRB# AAAF3927). Written consent was obtained from all families. Twelve of the individuals joined the Simons VIP/Simons Searchlight study (<https://www.simonssearchlight.org/>). Participants underwent clinical whole-exome sequencing or gene panel sequencing for intellectual disability, developmental delay, autism spectrum disorder characteristics, and/or behavioral problems. Clinical exome sequencing coverage depth was 80× on average genome-wide. Genetic test reports were reviewed for eligibility based upon likely pathogenic/pathogenic variants in *CHAMP1* using American College of Medical Genetics and Genomics/American Molecular Pathology criteria (Richards et al. 2015). Fourteen individuals were enrolled who have pathogenic or likely pathogenic variants in *CHAMP1*. Two individuals had been previously reported in the literature (individual 4 from Isidor et al. 2016; individual 12 from Tanaka et al. 2016) and 12 are new to the literature. Standardized medical histories were taken by genetic counselors by telephone interview. VABS was performed by telephone interview with a trained research assistant. The Rare Epilepsy Network seizure survey was performed online (https://www.epilepsy.com/clinical_trials/rare-epilepsy-network).

ADDITIONAL INFORMATION

Data Deposition and Access

Whole-exome sequencing data are not publicly available because patient consents could not be obtained. The *CHAMP1* variants found in this study have been deposited in ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>) under accession numbers VCV000217909.3, VCV000827777.2, SCV001571201, VCV000210049.2, VCV000210050.4, VCV000217907.3,

VCV000984804.1, VCV000280855.3, VCV000217916.2, VCV000523879.4, and VCV000523879.4.

Ethics Statement

This study was approved by the Institutional Review Board of Columbia University under the protocol number AAAF3927. Written consent was obtained from all families.

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Author Contributions

M.L.G. and H.K. collected and analyzed the data and drafted and critically reviewed the manuscript. M.R-V., I.V., A.L., S.R., G.B., C.M., A.M., and B.I. provided clinical data and critically reviewed the manuscript. W.K.C. conceived of the study, provided clinical data, and drafted and critically reviewed the manuscript.

Competing Interest Statement

The authors have declared no competing interest.

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