

De novo mutations in *CSNK2A1* are associated with neurodevelopmental abnormalities and dysmorphic features

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Abstract Whole exome sequencing (WES) can be used to efficiently identify de novo genetic variants associated with genetically heterogeneous conditions including intellectual disabilities. We have performed WES for 4102 (1847 female; 2255 male) intellectual disability/developmental delay cases and we report five patients with a neurodevelopmental disorder associated with developmental delay, intellectual disability, behavioral problems, hypotonia, speech problems, microcephaly, pachygyria and dysmorphic features in whom we have identified de novo missense and canonical splice site mutations in *CSNK2A1*, the gene encoding CK2 α , the catalytic subunit of protein kinase CK2, a ubiquitous serine/threonine kinase composed of two regulatory (β) and two catalytic (α and/or α')

subunits. Somatic mutations in *CSNK2A1* have been implicated in various cancers; however, this is the first study to describe a human condition associated with germline mutations in any of the CK2 subunits.

Introduction

Neurodevelopmental disorders affect 1–3 % of children and encompass a wide range of severity and associated behavior differences (Soden et al. 2014). Identifying the etiology of neurodevelopmental disorders has been challenging given the diversity of genetic and non-genetic causes. Whole exome sequencing (WES) is an effective tool to diagnose patients with phenotypically similar and etiologically diverse neurodevelopmental disorders and to discover new genetic causes. Many of these conditions arise from de novo mutations in genes with a critical role in brain development and/or function (Ku et al. 2013).

Protein kinase CK2 (formerly Casein kinase 2) is a ubiquitous serine/threonine kinase composed of two regulatory (β) and two catalytic (α and/or α') subunits and regulates its substrates via phosphorylation at acidic clusters containing the consensus sequence XS/TXXE/D (Wirkner et al. 1998). CK2 is a heterotetramer composed of $\alpha\beta\beta\alpha$, $\alpha\beta\beta\alpha'$ or $\alpha'\beta\beta\alpha'$, and all three subunits are encoded by different genes. The α subunit is encoded by *CSNK2A1* (MIM #115440) and maps to 20p13. In addition to their roles in the holoenzyme, all subunits have also been proposed to have independent roles in specific tissues. In the brain, for example, the α subunit is highly expressed, suggesting a role in brain development and/or function (Ceglia et al. 2011). Somatic mutations in *CSNK2A1* have been implicated in various cancers (Benveniste et al. 2015); however, no germline mutations in any of the genes comprising CK2

Data deposition and access: These *CSNK2A1* variants have been deposited in ClinVar.

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have previously been described in humans. We present five patients with neurodevelopmental disabilities and dysmorphic features in whom we identified five different de novo novel variants in *CSNK2A1*.

Methods

This study was approved by the Institutional Review Board of Columbia University. Informed consent was obtained from all participants included in the study. Genomic DNA was extracted from whole blood from the affected children and their parents. Exome sequencing was performed in 4102 (1847 female; 2255 male) individuals with developmental delay/intellectual disabilities using a trio design with exon targets isolated by capture using the Agilent SureSelect Human All Exon V4 (50 Mb) kit or the Clinical Research Exome (Agilent Technologies, Santa Clara, CA, USA). The sequencing methodology and variant interpretation protocol have been previously described (Tanaka et al. 2015). All *CSNK2A1* variants were confirmed by Sanger sequencing.

Results

Exome sequencing produced an average of ~8.6 Gb of sequence per sample. Mean coverage of captured regions was ~98× per sample with >97 % covered with at least 10× coverage, an average of 95 % of base call quality of Q30 or greater, and an overall average mean quality score of >Q37. Five unrelated patients were found to have five different novel, de novo heterozygous variants in *CSNK2A1* including one splice site variant (c.824 + 2T>C) and four missense variants (p.R47Q, p.Y50S, p.D175G, p.K198R) that are predicted to be deleterious by multiple prediction algorithms including SIFT, Mutation Taster, Provean, and CADD (Table 1). Variant read ratios were 47.5, 46.1, 53,

47.8 and 47.2 % for p.R47Q, p.Y50S, p.D175G, p.K198R and c.824 + 2T>C, respectively, which is approximately 50 % of the reads in each case and suggests there is no somatic mosaicism. The WES data were also analyzed for copy number variations (CNVs) and no CNVs of clinical significance were identified.

The missense variants are located in highly conserved functional domains (Fig. 1). None of these variants were observed in 1000 Genomes (Abecasis et al. 2012), in the NHLBI GO Exome Sequencing Project (Exome Variant Server, <http://evs.gs.washington.edu/EVS>), in ExAC (exac.broadinstitute.org) or in our own local database of 24,578 exomes. There are loss-of-function mutations in *CSNK2A1* in the ExAC and COSMIC (Forbes et al. 2015) databases.

All five patients with the novel, de novo variants in *CSNK2A1* are female and range in age from 2 to 13 years old (Table 2). Prenatal histories were largely unremarkable except for polyhydramnios in one patient. Laryngomalacia in one patient and umbilical hernia in another were noted at birth. Features common to the majority of the probands include developmental delay (5/5), intellectual disability (4/5), behavioral problems (4/5), hypotonia (4/5), speech problems (4/5), gastrointestinal problems (4/5), dysmorphic facial features (4/5) (Fig. 2), microcephaly (3/5), pachygyria observed on brain MRI (3/5) (Fig. 3), musculoskeletal (3/5) and immunologic (3/5) problems (Table 2). Three of the patients have variable dysmorphic features including thin hair, low set and folded ears, arched eyebrows, mild synophrys, ptosis, epicanthal folds, hypertelorism, broad nasal bridge, upturned nose, high palate, thin upper lip, protruding tongue, clinodactyly, and brachydactyly. All patients have behavioral problems such as tantrums, volatile mood, clapping, hand-flapping, and ADHD features. Two patients also have sleep problems. Four patients had gastrointestinal symptoms including dysphagia with gastroesophageal reflux disease (GERD), constipation and feeding problems requiring gastrostomy tube placement. Three patients have musculo-skeletal problems manifesting as scoliosis

Table 1 Predicted pathogenicity of novel de novo *CSNK2A1* variants

Variant	Chr20 coordinates (GRCh38)	Polyphen-2	SIFT	Mutation Taster	PROVEAN	CADD Phred
c.824 + 2T>C	488676	N/A	N/A	Disease causing (0.70825)	N/A	29.7
c.593A>G:p.K198R	492282	Possibly damaging (0.5446)	Damaging (0.001)	Disease causing (0.70825)	Deleterious (−2.91)	26.6
c.524A>G:p.D175G	492351	Benign (0.37943)	Damaging (0.027)	Disease causing (0.70825)	Deleterious (−6.83)	29.8
c.149A>C:p.Y50S	505191	Damaging (0.999)	Damaging (0.001)	Disease causing (0.999)	Deleterious (−8.34)	27.1
c.140G>A:p.R47Q	505182	Possibly damaging (0.56788)	Damaging (0.001)	Disease causing (0.70825)	Deleterious (−3.61)	34

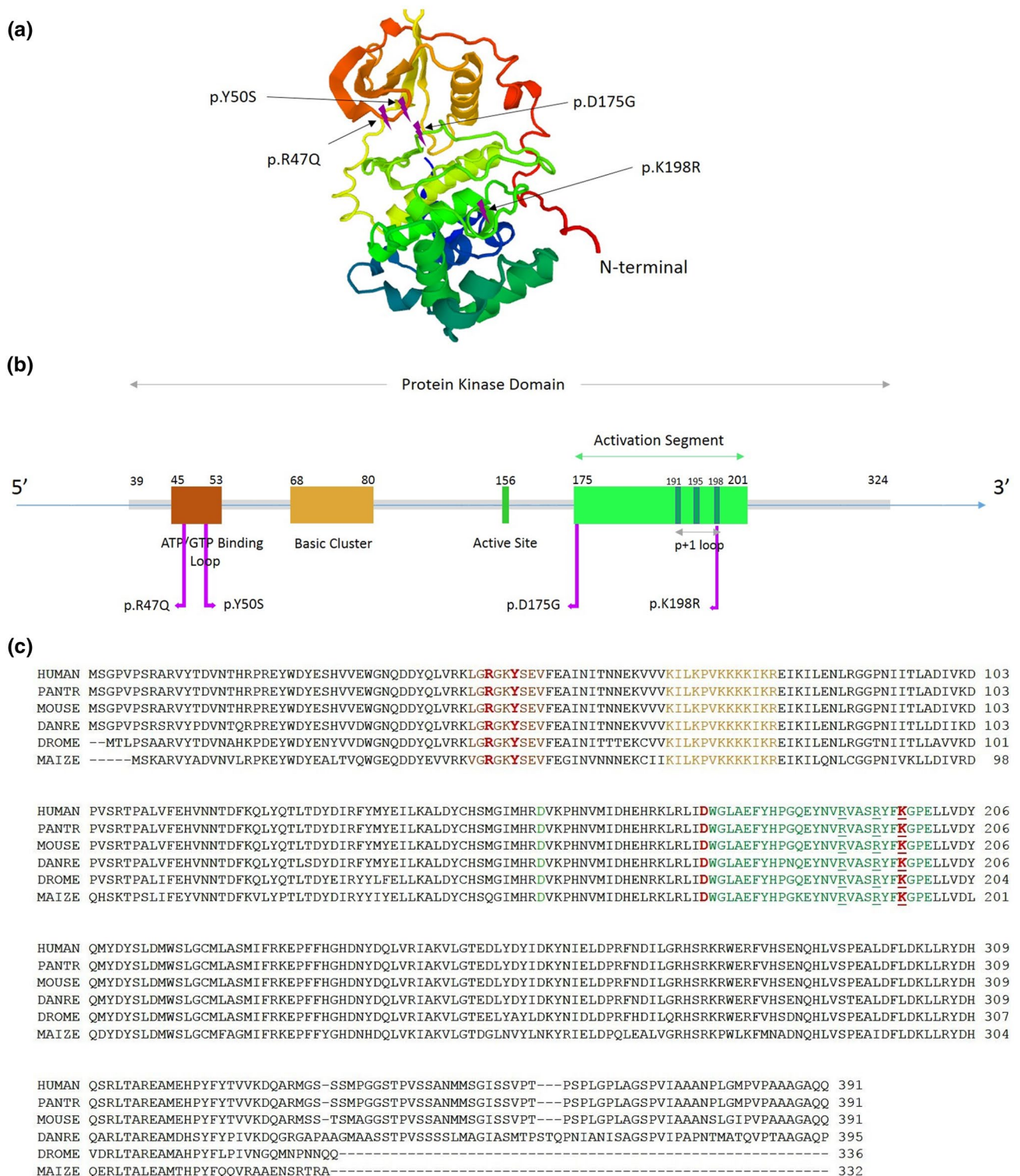


Fig. 1 **a** 3D structure of *CSNK2A1*, **b** domains, and **c** sequence alignment. **a** 3D structure of human CK2- α protein was retrieved from RCSB Protein Data Bank (PDB) (<http://www.rcsb.org>) constructed by PV Protein Viewer from PDB ID 3WOW (doi:10.2210/pdb3wow/pdb). Purple strikes represent mutation sites. **b** Domains of *CSNK2A1* and locations of de novo variants. **c** Sequence alignment

of ATP/GTP binding loop (tile red), basic cluster (orange), active site (light green), activation segment (green). Basic amino acids into the p + 1 loop were underlined. De novo amino acids are shown in bold red text. Abbreviations for species: chimpanzee (Pantr, *Pan troglodytes*), zebrafish (Danre, *Danio rerio*), fruit fly (Drome, *Drosophila melanogaster*) (color figure online)

Table 2 Detailed clinical findings of patients with novel, de novo *CSNK2A1* variants

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	6 yo	4.5 yo	4 yo	13 yo	2 yo
Gender	Female	Female	Female	Female	Female
Mutation	p.R47Q	p.K198R	p.D175G	c.824 + 2T>C	p.Y50S
DD	Yes	Yes	Yes	Yes	Yes
Intellectual disability	Yes	Yes	Yes	Yes (IQ 60)	N/A
OFC	Birth: 29 cm (<3 %) At 3 yo: 46.4 cm (<3 %) ^a	Birth: unknown At 4.5 yo: 48 cm (12 %)	Birth 32 cm (5–10 %) At 4 yo: 46 cm (<3 %)	Birth: normal At 13 yo: 55 cm (75–90 %)	Birth: unknown At 2 yo: 44.5 cm (<3 %)
Birth weight and body length	Wt: 1796 g (3–10 %) Length: 44 cm (3–10 %) ^a	Wt: 2551 g (3–10 %) Length: 44.5 cm (<3 %)	Wt: 2950 g (10–25 %) Length: 50 cm (50–75 %)	Wt: 3486 g (50–75 %) Length: 48.2 cm (25–50 %)	Wt: 3345 g (25–50 %)
Age at sitting	15 mos	1 yo	12 mos	10 mos	8 mos
Age at walking	28 mos	2 yo	Not acquired	16 mos	20 mos
Age at talking	>2 yo, still 200 words and short sentences	At 22 mos had 2 words, still impaired speech ability	Not speaking yet	2 yo, no speech problem	12 mos, 2 words
Neurologic and behavioral problems	Hypotonia, tantrums, ADHD features, ataxia	Past hypotonia Volatile Tantrums	Clapping, hand-flapping, atonic seizures, ataxia, sleep problems	Hypotonia, ADHD, sleep problems	Hypotonia, seizures or severe breath holding spell (EEG normal)
Brain MRI	Pachygyria, microcephaly	Relative underdevelopment of the left operculum and some secondary enlargement of the Sylvian fissure	Simple gyral cortication, no significant structural defects	Normal	Normal
Dysmorphic	Hypertelorism, low set and folded ears, high palate, micrognathia, ptosis, high arched eyebrows, 5th finger clinodactyly, brachydactyly, unilateral single palmar crease	Round face, epicanthal folds, slightly low set ears, cupped ears that protrude, high palate, thin upper lip, generous tongue that protrudes, thin hair, mild synophrys, arched eyebrows	Broad nasal bridge, short upturned nose, epicanthal folds	None	Extra fold in helix, Inverted epicanthal folds, broad great toes
Musculo-skeletal	None	Wears leg braces for gait abnormality	None	Scoliosis (19 degrees)	Loose joints
GI	None	FTT, G-tube, severe GERD. Silent aspiration, pharyngeal dysphagia issues	Constipation	FTT, G-tube, constipation	Constipation/diarrhea, delayed and disorganized oral preparatory skills, delayed swallow initiation
Immunologic	None	Hypogammaglobulinemia requiring IVIG	None	Mild Ig A deficiency	Frequent upper respiratory infections, low IgG
Other	Umbilical hernia at birth Palmar erythema, cutis marmorata	Polyhydramnios, laryngomalacia at birth, dry skin, labial adhesions, intermittent esotropia	Heat intolerance, mild hearing loss	Easy fatigability, inguinal hernia, carnitine deficiency	Short stature Mild iris coloboma vs. anisocoria; blue sclera Hyperpigmented plaques on posterior scalp

yo years old, *DD* developmental delay, *IQ* intelligence quotient, *OFC* occipitofrontal circumference, *mos* months old, *ADHD* attention deficit/hyperactivity disorder, *GI* gastrointestinal issues, *FTT* failure to thrive, *GERD* gastroesophageal reflux disease, *IgA* immunoglobulin A, *IgG* immunoglobulin G, *IVIG* intravenous immunoglobulin

^a The patient was born at 35 weeks of gestational age

Fig. 2 Facial characteristics of Patient 3 at 3 months (*left*) and 4 years (*right*) of age. Facial features are notable for broad nasal bridge, short upturned nose, and epicanthal folds

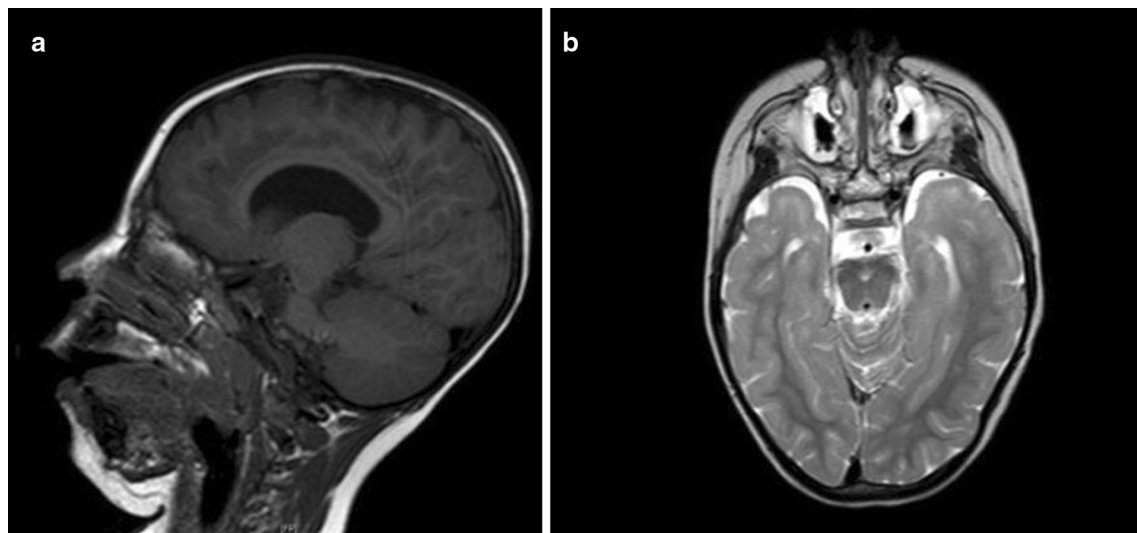


Fig. 3 Brain MRI of patient 1 at 32 months of age. **a** Sagittal and **b** axial images showing pachygyria and microcephaly

and joint laxity. Three patients have immunologic findings of hypogammaglobulinemia and mild IgA or IgG deficiency. Two patients have ataxia. Only one patient has daily atonic seizures with abnormal EEG showing generalized symptomatic epilepsy. Uncommon findings include palmar erythema, cutis marmorata, dry skin, labial adhesions, intermittent esotropia, heat intolerance, easy fatigability, inguinal hernia and carnitine deficiency and may or may not be related to the *CSNK2A1* mutations (Table 2).

Discussion

Patients from five independent families with overlapping neurodevelopmental disorders and dysmorphic features were found to have likely damaging de novo splice site or

missense variants in highly conserved regions of *CSNK2A1*. To our knowledge, this is the first report implicating germline variants in *CSNK2A1* in a human genetic condition.

Protein kinase CK2 is ubiquitously expressed and is involved in many biological processes including cell proliferation, cell survival, transcriptional regulation, and embryonic development (St-Denis and Litchfield 2009). Overexpression of CK2 and somatic mutations in either subunit have been found to be related with various cancers by regulating downstream cancer-associated genes such as JAK/STAT, NF- κ B, PI3K/AKT (Zheng et al. 2013).

The α and α' subunits (encoded by *CSNK2A1* and *CSNK2A2*, respectively), are the catalytic domains of CK2. Although there seems to be no difference in the catalytic activities of α and α' , CK2 α is expressed nearly ubiquitously at high levels, especially in the brain, starting

in early embryonic development (Ceglia et al. 2011). In studies with conditional knock-outs of CK2 α , mice with homozygous deficiencies of CK2 α (CK2 $\alpha^{-/-}$) were embryonic lethal with severe embryonic abnormalities, especially in the heart and neural tube (Dominguez et al. 2011; Landesman-Bollag et al. 2011; Lou et al. 2008; Seldin et al. 2008). Among the heterozygotes, 13 % of the embryos were noted to have failure of neural tube closure (Seldin et al. 2008) and ≤ 2 branchial arches (Lou et al. 2008).

The four novel, de novo missense variants we identified, p.R47Q, p.Y50S, p.D175G, and p.K198R, all reside in the glycine-rich ATP binding loop or activation site (Fig. 1). These regions are highly conserved across species (Fig. 1). Moreover, these residues are involved in the regulation and activation of CK2 α and CK2.

p.R47Q and p.Y50S are located in a highly mobile G⁴⁶RGKYS⁵¹ ATP binding loop in CK2 α . This loop shifts between stretched and collapsed conformations according to the activation state of CK2 α and has an important role in the three conformations of the fully active, partially active, and inactive states of CK2 (Niefind and Issinger 2010).

The activation site of CK2 α extends from amino acids Asp175 to Glu201 and contains many basic amino acid residues important in binding the acidic residues in the vicinity of Ser/Thr residues that are substrates of phosphorylation. The highly conserved D¹⁷⁵WG¹⁷⁷ and G¹⁹⁹PE²⁰¹ residues are responsible for the formation of CK2 α activation loop (Baier et al. 2015). Asp175 also has a canonical Mg²⁺/Mn²⁺ binding role during utilization of ATP/GTP as a phosphate donor (Lolli et al. 2012; Niefind and Issinger 2010). Substitution of this aspartic acid with a glycine affects the charge and could disrupt Mg²⁺/Mn²⁺ binding.

The basic amino acids in the “p + 1 loop” of the activation site (R191, R195, and K198) are responsible for the recognition of acidic residues at positions −1, +1, +3, +5 relative to Ser/Thr phosphorylation sites in the substrate, and experimentally, substitution of these residues with alanine resulted in decreased phosphorylation capacity of CK2 α (Sarno et al. 1996, 1997). Although the p.K198R variant does not alter charge of the amino acid, it may produce conformational differences that could disrupt the activation site. Mutations in CK2 α may alter phosphorylation of important substrates of the Wnt and Notch signaling pathways which are important in neurodevelopmental processes.

Crystallography studies have revealed new holoenzyme complexes of CK2 including trimer of tetramers and filaments of tetramers (Lolli et al. 2012, 2014; Niefind et al. 2001). In addition to the possible aforementioned effects of Asp175 and Lys198 on the individual CK2 α activity, these amino acid substitutions could also have roles in the higher-order structures of CK2 tetramers.

In addition to the four de novo missense variants, we observed one de novo variants in the canonical splice donor

site of intron 10, c.824 + 2T>C, that is predicted to disrupt proper splicing. The splice site variant suggests that loss of function could be the mechanism of action for the CSNK2A1 variants we report, but there are predicted loss-of-function alleles in ExAC suggesting other possible molecular mechanisms. Functional studies and a larger allelic series will be needed to elucidate the genetic mechanism of the mutations.

Because all of our patients are female and they show some degree of phenotypic variability we searched for additional variants on the X chromosome and other loci throughout the genome, and did not identify any other variants contributing to the phenotype. Thus, we believe the phenotypic variability in females is most likely due to random X inactivation.

In conclusion, we describe the first human condition associated with germline mutations in any of the CK2 subunits, with a clinical phenotype of neurodevelopmental disabilities and dysmorphic features. We hypothesize that the mutations alter CK2 function and phosphorylation of CK2 targets, leading to deleterious effects on brain development and function.

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Compliance with ethical standards

Conflict of interest Megan Cho, Lindsay Henderson, Kyle Retterer, Amy Dameron, Rebecca Willaert, Berivan Baskin, and Jane Juusola are employees of GeneDx. Wendy Chung is a consultant to BioReference Laboratories.

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