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ORIGINAL ARTICLE

Okur-Chung neurodevelopmental syndrome: Eight additional cases with implications on phenotype and genotype expansion

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Okur-Chung syndrome is a neurodevelopmental condition attributed to germline *CSNK2A1* pathogenic missense variants. We present 8 unreported subjects with the above syndrome, who have recognizable dysmorphism, varying degrees of developmental delay and multisystem involvement. Together with 6 previously reported cases, we present a case series of 7 female and 7 male subjects, highlighting the recognizable facial features of the syndrome (microcephaly, hypertelorism, epicanthic fold, ptosis, arched eyebrows, low set ears, ear fold abnormality, broad nasal bridge and round face) as well as frequently occurring clinical features including neurodevelopmental delay (93%), gastrointestinal (57%), musculoskeletal (57%) and immunological (43%) abnormalities. The variants reported in this study are evolutionary conserved and absent in the normal population. We observed that the *CSNK2A1* gene is relatively intolerant to missense genetic changes, and most variants are within the protein kinase domain. All except 1 variant reported in this cohort are spatially located on the binding pocket of the holoenzyme. We further provide key recommendations on the management of Okur-Chung syndrome. To conclude, this is the second case series on Okur-Chung syndrome, and an in-depth review of the phenotypic features and genomic findings of the condition with suggestions on clinical management.

Annie Ting Gee Chiu and Steven Lim Cho Pei contributed equally to this study.

KEYWORDS

CSNK2A1, developmental delay, Okur-Chung syndrome, whole exome sequencing

1 | INTRODUCTION

Whole exome sequencing (WES) is emerging as a powerful diagnostic tool for identification of Mendelian conditions.[1-4] The technology has helped to shorten the diagnostic odyssey in children with neurodevelopmental disorders,[1,5] expanded the phenotypic spectrum of many known genes and led to discovery of new genes and conditions.[5,6] Okur-Chung neurodevelopmental syndrome (OMIM617062) is a condition with recognizable facial features and multisystemic involvement first reported by Okur et al in a case series of 5 female subjects with de novo, germline variants of *CSNK2A1*[7] (OMIM115440; NM_177559.2; NP_808227.1), followed by another case report from Trinh et al.[8] It was confirmed to be associated with developmental disorders in the Deciphering Developmental Disorders (DDD) study.[9]

CSNK2A1 encodes the α subunit of protein kinase CK2 (formerly known as casein kinase 2), a ubiquitous heterodimeric serine/threonine kinase consisting of 2 catalytic subunits (α and α′) and 2 regulatory subunits (β). Disruption of *CSNK2A1* in mouse embryos induces neural tube defects, cardiac malformation, hydrops fetalis, and are embryonic lethal.[10]

Okur et al suggested that X-chromosome and X-inactivation are possibly involved in pathogenesis of *CSNK2A1* variants, because only females were identified.[7] We report an addition of 6 boys and 2 girls with de novo germline variants in *CSNK2A1*. All individuals presented with neurodevelopmental and multisystemic abnormalities. With the identification of 6 male subjects, we show that *CSNK2A1* variants are not restricted to females. Furthermore, by comparing features observed in this cohort to 6 individuals previously reported, we further delineate the clinical spectrum of *CSNK2A1* variants and provide key recommendations on management of subjects with the Okur-Chung syndrome.

2 | METHODS

Subject 1 was recruited from Duchess of Kent Children's Hospital, Hong Kong, China; Subjects 2, 3 and 4 from Radboud University Medical Centre (Radboudumc), Nijmegen, the Netherlands; and Subjects 5 and 6 from Hôpital d'Enfants, Centre Hospitalier Universitaire de Dijon, Dijon, France. Subject 6 was also cared for by the Department of Genetics, Lyon University Hospitals, Lyon, France. The respective clinical geneticists became connected with the help of Genematcher (Matchmaker Exchange Project),[11] which facilitated further discussion and exchange of clinical and genomic information. Subject 7 was recruited from the Department of Medical Genetics, in the University Hospital Centre of Nantes (France) and included in the HUGODIMS Consortium project[12]; and Subject 8 from Arnaud de Villeneuve Hospital, University Hospital Centre of Montpellier, Faculty of Medicine in Montpellier-Nîmes, University of Montpellier, Montpellier, France.

WES was performed at Radboudumc in diagnostic setting for Subjects 1 to 4, as described before.[2] In brief, genomic DNA was obtained from peripheral blood of the proband-parent trios with QIAamp DNA Mini Kit (Qiagen, Germany). WES was performed using Illumina HiSeq2000 and reads were mapped using BWA 0.7.7. The sequencing depth was approximately 70- to 100-fold and variant calling and annotation were performed as described previously.[2,13] All candidate variants were confirmed by Sanger's sequencing. Diagnostic WES was approved by the medical ethics committee of the Radboud University Medical Center (Commissie Mensgebonden Onderzoek), Nijmegen, the Netherlands (registration number 2011-188). WES was performed at Laboratoire de Génétique Moléculaire, Plateau Technique de Biologie, Centre Hospitalier Universitaire de Dijon, France, for Subjects 5, 6 and 8, and at INSERM/CNRS, University of Nantes, l'Institut du thorax, France, for Subject 7 as described before.[1,12] Written informed consent for publication of photographs has been obtained from parents of Subjects 1, 2, 6, 7 and 8.

3D modeling and protein stability change prediction of the CSNK2A1 peptide monomer was simulated to elicit the spatial relationship of the variants reported in this cohort using STRUM, a method for structure-based prediction of protein stability changes upon single-point mutation built on I-TASSER predicted models.[14] Delta-delta G energy changes were used to predict the protein stability due to particular amino acid changes.[14]

3 | RESULTS

3.1 | Identification of subjects with de novo variants in *CSNK2A1*

We identified 8 subjects with de novo variants in *CSNK2A1* ((NM_177559.2):c.593A>G p.(Lys198Arg) in Subject 1; c.692C>G p.(Pro231Arg) in subject 2; c.79G>A p.(Glu27Lys) in subject 3; c.1A>G p.(Met1Val) in subject 4, c.218T>A p.(Val73Glu) in Subject 5, c.140G>A p.(Arg47Gln) in Subject 6, c.935G>A p.(Arg312Gln) in Subject 7 and c.151A>C p.(Ser51Arg) in Subject 8 (Figure 1). None of the variants have been reported in gnomAD (genome aggregation database) healthy controls.[15] The clinical features of the subjects in this cohort together with subjects in other cohort were summarized in Table 1.

3.2 | Clinical case reports of 8 subjects

Subject 1 was a 5-year-old boy who presented with mild developmental language delay, hyperlaxity of the joints and dysmorphic facial

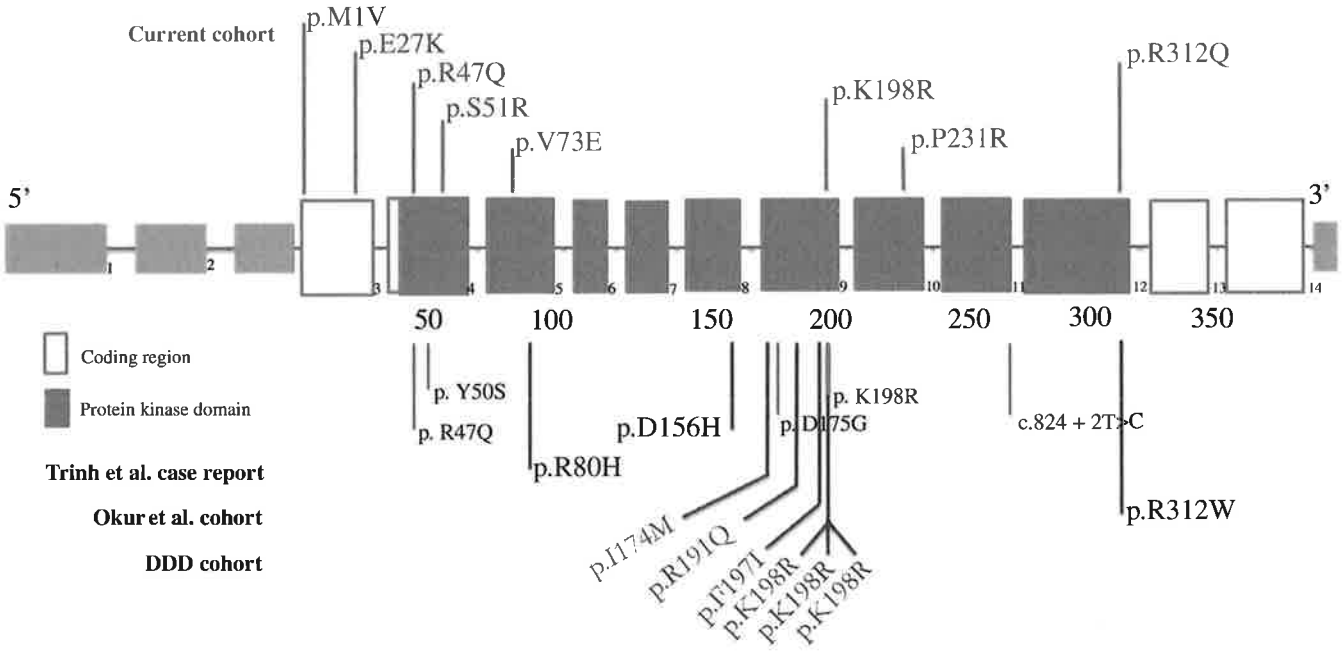

FIGURE 1 Mutation spectrum of variants reported in this cohort (above) and known variants from Okur et al, DDD cohort and Trinh et al (below). Protein kinase domain is depicted by a filled exon. [Color figure can be viewed at wileyonlinelibrary.com]

features including low set hairline with widow's peak, thick eyebrows, unilateral partial ptosis, thick lips, wide opened mouth and relatively thick fingers (Figure 2A-E). There was a history of dilated renal pelvis which resolved on repeat ultrasound by 5 years of age. He was reported to have 2 rows of teeth during the shedding of deciduous teeth. His growth parameters were normal. Previous array comparative genomic hybridization (aCGH) result was normal. A de novo heterozygous variant at *CSNK2A1*: Chr20(GRCh37):g.472926T>C; NM_177559.2:c.593A>G p.(Lys198Arg) was identified. Despite his initial developmental language delay, he had normal cognitive abilities and was assessed to be above average in "performance" and "practical reasoning" domain of the Griffiths Mental Developmental Scale at 6.5 years. He was placed in a mainstream primary school where he performed satisfactorily when he was last reviewed at 8 years of age.

Subject 2 was a 4-year-old boy who presented with microcephaly, unilateral partial ptosis and dysmorphic facial features including straight horizontal eyebrows and broad nasal bridge (Figure 2G). His development was delayed, with developmental age of 2 years at chronological age of 4 years. He spoke his first word at 3.5 years and started walking at 22 months. He also had hypotonia, stereotypic movements, tactile hypersensitivity, abnormal oromotor skills and autistic traits, with sleeping and eating problems. Physical examination showed short stature (−2.5SD), normal weight (−0.5SD) and low-normal head circumference (−1.5SD). Previous investigations including single nucleotide polymorphism array, *RAI1* analysis and *FMR1* testing were normal. A de novo heterozygous variant at *CSNK2A1*: Chr20(GRCh37): g.470455G>C; NM_177559.2:c.692C>G p.(Pro231Arg) was identified.

Subject 3 was a 14-year-old boy who presented with intellectual disability, autism spectrum disorder (ASD), hypotonia and dyspraxia. Formal psychological assessment revealed that his verbal intelligence quotient (IQ) was better than his performance IQ. He had history of recurrent ear infections, iron deficiency anemia, right inguinal hernia and idiopathic increased intracranial pressure requiring ventriculoperitoneal drainage at 9 years of age. Sleeping problem and eating difficulties were also reported. Physical examination showed pes cavus, shortened Achilles tendon, normal height (+1SD), weight (+1SD) and head circumference (+1.25SD). His magnetic resonance imaging (MRI) brain was normal post-ventriculoperitoneal shunting. Previous genetic testing, including *FMR1* analysis, karyotyping and aCGH result were normal. He was found to have a de novo heterozygous variant at *CSNK2A1*: Chr20 (GRCh37):g.489117C>T; NM_177559.2:c.79G>A p.(Glu27Lys).

Subject 4 was a 2.5-year-old girl who presented with developmental delay, stereotypic movements of hands and feet and dysmorphic facial features including plagiocephaly, flat face, almond-shaped eyes, deep nasal bridge, retrognathia and low set ears. Her developmental age was 1.5 years at chronological age of 2.5 years—she was not able to sit or stand unsupported, and spoke only single words. MRI brain was normal. She also had a history of hip dysplasia. Physical examination showed low normal height (−1.5SD), low normal weight (−2SD) and normal head circumference (−1SD). She was found to have a de novo heterozygous variant involving the start codon at *CSNK2A1*: Chr20(GRCh37):g.489195T>C; NM_177559.2:c.1A>G p.(Met1Val). This is predicted to lead to a loss of amino acid from Position 1 to 137, the position of the next in-frame start-codon.

Subject 5 was an 8-year-old boy who presented with global developmental delay and language delay. Apart from a second cousin who had a known pathogenic variant in the *DCX*, there was no family history of neurodevelopmental or psychiatric disorder. He had severe intellectual disability and was just starting to read at current age of 14 years. There was history of severe feeding difficulties during infancy with gastroesophageal reflux disease requiring fundoplication and sleep disorder until 5 years with frequent nocturnal awakening. Physical examination showed microcephaly (ie, −3SD) and short stature (−1SD for age). MRI brain was normal. Previous investigations including karyotype, testing for *ARX*, Fragile X and 22q11 microdeletion were all normal. aCGH found a Xp22.31 duplication, which was a

TABLE 1 Clinical features in 14 subjects with *CSNK2A1* variants. Patients from DDD and Trinh et al have also been included in the analysis

General information	Current cohort (n = 8)	Okur et al cohort subjects (n = 5)	Trinh et al cohort subject (n = 1)	Total frequency (n = 14)
Age at examination (y)	2-14	2-13	7	2-14
Gender (M:F)	6:2	0:5	1:0	1:1
Polyhydramnios	0/8	1/5	NR	1/14 (7%)
Failure to thrive/short stature	5/8	3/5	NR	8/14 (57%)
Dysmorphic features				
Microcephaly	4/8	3/5	1/1	8/14 (57%)
High/prominent forehead	2/8	0/5	1/1	3/14 (21%)
Round face	3/8	1/5	NR	4/14 (29%)
Hypertelorism	2/8	1/5	NR	3/14 (21%)
Arched eyebrows	2/8	2/5	NR	4/14 (29%)
Partial ptosis	2/8	1/5	NR	3/14 (21%)
Epicanthic folds	1/8	3/5	NR	4/14 (29%)
Almond-shaped eyes	3/8	0/5	NR	3/14 (21%)
Low set ears	2/8	2/5	NR	4/14 (29%)
Ear fold abnormality	2/8	3/5	1/1	6/14 (43%)
Broad nasal bridge	4/8	1/5	1/1	6/14 (43%)
High palate	1/8	2/5	NR	3/14 (21%)
Thin upper lip	2/8	1/5	NR	3/14 (21%)
Retrognathia/micrognathia	3/8	1/5	NR	4/14 (29%)
Prominent tongue	1/8	1/5	NR	2/14 (14%)
Brachydactyly broad digits	2/8	2/5	NR	4/14 (29%)
Clinodactyly/camptodactyly	2/8	1/5	NR	3/14 (21%)
Single palmer crease	2/8	1/5	NR	3/14 (21%)
Isolated occurrences of plagiocephaly, flat face, intermittent esotropia, iris coloboma/anisocoria, anteverted nares, small mouth, 2 rows of teeth, large upper incisors, shawl scrotum, ungueal hypoplasia				
Neurodevelopmental	8/8	5/5	1/1	14/14 (100%)
Global developmental delay/intellectual disability	7/8	5/5	1/1	13/14 (93%)
Mild	3/8	1/5	-	4/14 (29%)
Moderate	1/8	-	-	1/14 (7%)
Severe	1/8	-	-	1/14 (7%)
Unclassified	2/8	4/5	1/1	7/14 (50%)
Specific language impairment	2/8	0/5	NR	2/14 (14%)
ADHD/suspected ADHD	1/8	2/5	1/1	4/14 (29%)
ASD/suspected ASD	2/8	0/5	1/1	3/14 (21%)
Stereotypic movements	2/8	0/5	NR	2/14 (14%)
Tactile hypersensitivity	1/8	0/5	NR	1/14 (7%)
Neurological disorder and brain imaging	5/8	5/5	1/1	11/14 (79%)
Hypotonia	5/8	4/5	NR	9/14 (64%)
Ataxia/dyspraxia	1/8	1/5	NR	2/14 (14%)
Epilepsy/history of suspected seizures	2/8	2/5	NR	4/14 (29%)
Pachygyria	0/8	1/5	NR	1/14 (7%)
Other MRI brain abnormalities	1/8	2/5	1/1	4/14 (29%)
Increased intracranial pressure requiring shunting	1/8	0/5	NR	1/14 (7%)
Skeletal abnormalities	5/8	3/5	NR	8/14 (57%)
Pes planus	1/8	0/5	NR	1/14 (7%)
Loose joints	2/8	1/5	NR	3/14 (21%)
Scoliosis	1/8	1/5	NR	2/14 (14%)
Butterfly vertebra	1/8	0/5	NR	1/14 (7%)
Hip dysplasia requiring brace	2/8	0/5	NR	2/14 (14%)
Abnormal gait requiring brace	0/8	1/5	NR	1/14 (7%)
Shortened Achilles tendon	2/8	0/5	NR	2/14 (14%)

(*Continues*)

TABLE 1 (Continued)

General information	Current cohort (n = 8)	Okur et al cohort subjects (n = 5)	Trinh et al cohort subject (n = 1)	Total frequency (n = 14)
Skin abnormalities	1/8	3/5	NR	4/14 (29%)
Palmer erythema and cutis marmorata	0/8	1/5	NR	1/14 (7%)
Dry skin	1/8	1/5	NR	2/14 (14%)
Hyperpigmented plaques on scalp	0/8	1/5	NR	1/14 (7%)
Hernia	1/8	2/5	NR	3/14 (21%)
Umbilical hernia	0/8	1/5	NR	1/14 (7%)
Inguinal hernia	1/8	1/5	NR	2/14 (14%)
Gastrointestinal/oromotor skills	4/8	4/5	NR	8/14 (57%)
Gastroesophageal reflux (with aspiration)	1/8	1/5	NR	2/14 (14%)
Constipation	1/8	3/5	NR	4/14 (29%)
Oromotor delay	2/8	2/5	NR	4/14 (29%)
Requiring gastrostomy tube	0/8	2/5	NR	2/14 (14%)
Unrestrained eating	1/8	0/5	NR	1/14 (7%)
Selective eater	3/8	0/5	NR	3/14 (21%)
Immunological	3/8	3/5	NR	6/14 (43%)
Hypogammaglobulinaemia	0/8	1/5	NR	1/14 (7%)
Frequent upper respiratory infection (URI)/ear infection	3/8	1/5	NR	4/14 (29%)
Mild IgA deficiency	0/8	1/5	NR	1/14 (7%)
Low IgG	0/8	1/5	NR	1/14 (7%)
Other features				
Sleep problem	5/8	2/5	1/1	8/14 (57%)
Excessive temper tantrums	1/8	2/5	NR	3/14 (21%)
Isolated occurrences of dystrophic pulmonary valve, advanced bone age, long and thin fingers, widely spaced nipples, gingival hypertrophy, labial adhesion, heat intolerance, mild hearing loss, easy fatigability, carnitine deficiency and anemia due to iron deficiency, cholesteatoma, conjunctival gray spots, astigmatism, partial growth hormone deficiency				

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; URI, upper respiratory infection; NR, not reported.

polymorphism inherited from his asymptomatic mother. A de novo heterozygous variant at *CSNK2A1*: Chr20(GRCh37):g.480574A>T; NM_177559.2:c.218T>A p.(Val73Glu) was identified.

Subject 6 was a 2-year-old girl who presented with multiple congenital anomaly and global developmental delay. She was born of a consanguineous Tunisian couple with family history of encephalopathy in the maternal cousin of her mother, as well as intellectual disability in her paternal cousin. She started walking at 6 years, and still had no recognizable speech at 8 years. Her congenital anomalies included hypotonia, dystrophic pulmonary valve, butterfly vertebrae, high forehead, hypertelorism, anteverted nares, retrognathia, left camptodactyly and microcephaly (Figure 2G). She had a history of febrile seizures, which resolved after 5 years of age. She also had a history of feeding difficulties, advanced bone age, cholesteatoma requiring surgical removal at 7 years, and sleep apnea requiring nocturnal non-invasive ventilation. Currently, 8-year-old, physical examination showed frontal bossing, conjunctival gray spots, small mouth, single palmer crease, long and thin fingers, generalized joint laxity, widely spaced nipples, kyphosis, gingival hypertrophy, normal weight (+0.68SD), short stature (−2SD) and microcephaly (−2.5SD). MRI brain showed vermis hypoplasia and thin non-dysplastic corpus callosum. Previous investigations included normal karyotype, aCGH and *Jag-1* analysis. A de novo heterozygous missense variant at *CSNK2A1*: Chr20(GRCh37):g.485835C>T; NM_177559.2:c.140G>A p.(Arg47Gln) was identified.

Subject 7 was a 14-year-old boy who presented with mild developmental language delay, and dysmorphic features including bilateral epicanthus, small mouth and a thin upper lip and large central upper incisors (Figure 2H). He spoke his first word at 4.5 years and started walking at 20 months. He showed learning difficulties that required special education. Physical examination showed short stature (−2.5SD), low weight (−2.5SD) and normal head circumference (−1SD). Previous aCGH result was normal. A de novo heterozygous variant at *CSNK2A1*: Chr20(GRCh37):g.468109C>T; NM_177559.2:c.935G>A p.(Arg312Gln) was identified.

Subject 8 was a 4-year-old boy who presented with failure to thrive, developmental delay and dysmorphic features including prominent forehead, arched eyebrows, downslanting palpebral fissures, almond-shaped eyes, low set ears, retronagthia, high-arched palate, bilateral single palmer crease, bilateral fifth finger clinodactyly and bilateral hypoplasia of fifth toe nails (Figure 2I). There was history of frequent bronchiolitis and partial growth hormone deficiency. He also had hypotonia, bruxism and a history of myoclonic seizures requiring treatment with sodium valproate. Development-wise, he first walked at 30 months and could speak only single words. There was a history of sleep problem in infancy and he was a picky eater. He also had hyperkinesia, excessive temper tantrums and low attention span. There was history of bilateral hip dislocation requiring brace and short Achilles tendon. Physical examination showed short stature (−2.5SD), low body weight (−3SD), normal head circumference

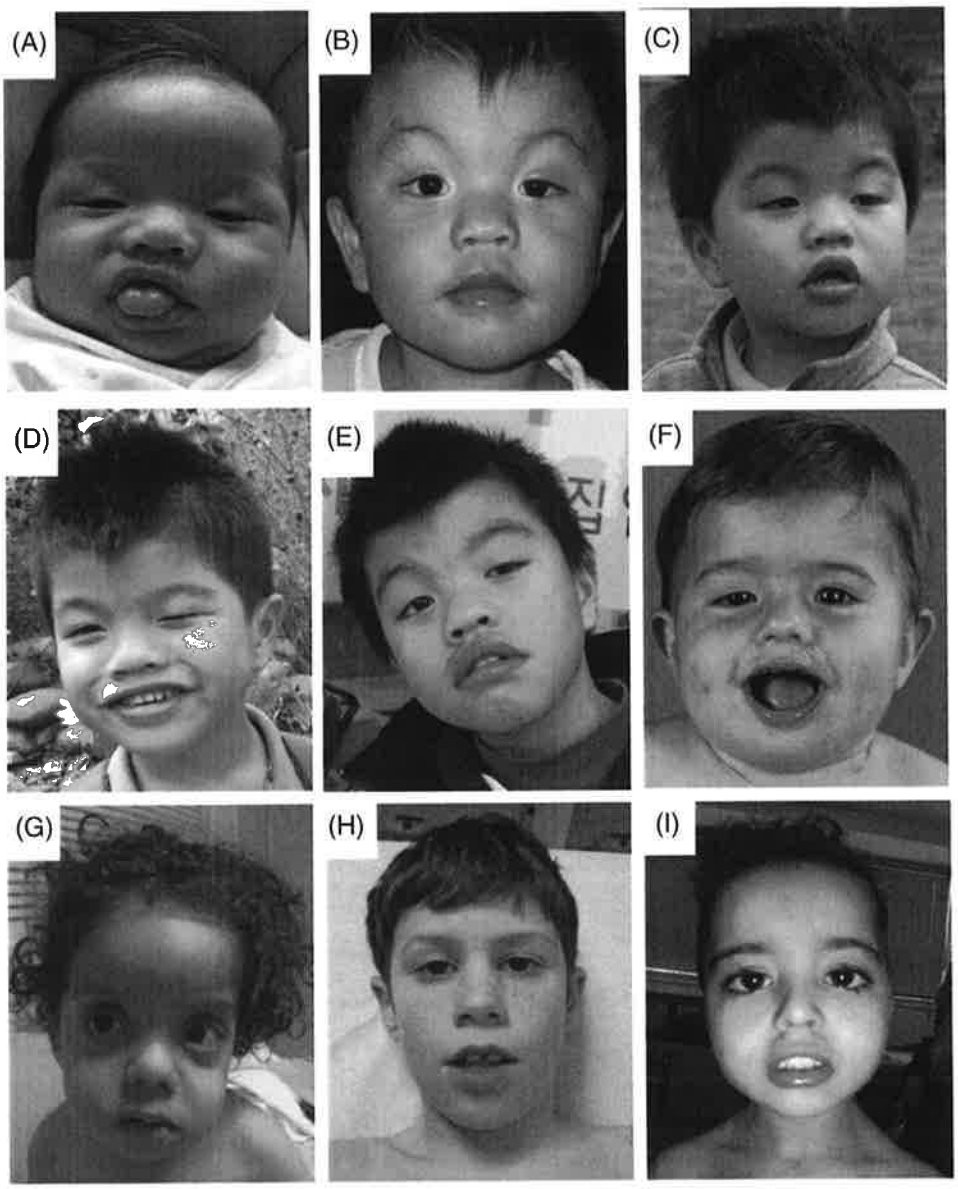

FIGURE 2 Clinical photographs of subjects reported in this cohort. Clinical photogrpahs of Subject 1 at 2 months (A), 2 years (B), 3.5 years (C), 5.5 years (D) and 7 years (E). Note the left partial ptosis, low and widow's peak, thick eyebrows, thick lips and prominent tongue. (F) Clinical photograph of Subject 2 at 14 months. Note the facial features with unilateral partial ptosis, straight horizontal eyebrows and broad nasal bridge. (G) Clinical photograph of Subject 6 at 20 months. Note the high forehead with frontal bossing, hypertelorism, anteverted nares, retrognathia, small mouth and gingival hypertrophy. (H) Clinical photograph of Subject 7 at 14 years. Note the bilateral epicanthus, small mouth, thin upper lip and large central upper incisors. (I) Clinical photograph of Subject 8 at 4 years. Note the prominent forehead, arched eyebrows, downslanting palpebral fissures, almond-shaped eyes, low set ears and retronagthia. [Color figure can be viewed at wileyonlinelibrary.com]

(−1SD) and kyphosis. He was found to have a de novo *CSNK2A1*: Chr20 (GRCh37):g.485824T>G; NM_177559.2:c.151A>C p.(Ser51Arg).

3.3 | Clinical features related to *CSNK2A1* variants, including 6 previously published subjects

Summarizing clinical features observed in all 14 subjects reported with de novo *CSNK2A1* variants (6 previously published[7,8] and 8 reported in this study), prenatal and perinatal history was unremarkable except for an isolated report of polyhydramnios.

3.3.1 | Neurodevelopmental abnormalities

Intellectual disability was the most consistent feature, occurring in 13/14 subjects (93%). Subject 1, however, entered mainstream school and was assessed to be above average in the "performance" and "practical reasoning." Behavioral problems included ASD (3/14, 21%), attention deficit hyperactivity disorder (ADHD) (4/14, 29%), sleep disorder (8/14, 57%), and excessive temper tantrums in 3/14 subjects (14%). Hypotonia has been observed frequently (9/14, 64%) and reports of previously performed MRI scans of the brain mentioned a variety of brain abnormalities (present in 6/14, 43% of the affected individuals) such as pachygyria, secondarily enlarged sylvian fissure, thin corpus callosum, vermis hypoplasia, simplified gyral cortication and cystic pineal lesion. One of the subjects (7%) had idiopathic hydrocephalus requiring neurosurgical intervention. Ataxia was present in 2 subjects (14%) and dyspraxia in another affected individual (7%).

3.3.2 | Multisystemic involvement

Multiple organ systems were affected. Failure to thrive and/or short stature was frequently reported (8/14 subjects, 57%). About 29% (4/14) of the children had skin abnormalities such as cutis marmorata, palmer erythema, dry skin and hyperpigmented lesions on scalp. Gastrointestinal involvement has been described in 57% (8/14) subjects, with various appearance of constipation, oromotor delay, and gastroesophageal reflux requiring gastrostomy in 2 subjects (2/14, 14%).

TABLE 2 Details on the bioinformatics prediction of the *CSNK2A1* variants and the in silico prediction of pathogenicity of all 8 subjects reported in this cohort (NR, not reported)

Subject	Transcript change	Amino acid change	Allelic frequency in gnomAD	GERP score	CADD score	DANN score	MutationTaster	PROVEAN	SIFT
1	c.593A>G	p.(Lys198Arg)	NR	4.84	26.9	0.9989	Disease causing	Damaging (−2.97, −2.91)	Damaging (0.0001)
2	c.692C>G	p.(Pro231Arg)	NR	4.97	28.6	0.9986	Disease causing	Damaging (−8.65, −8.94)	Damaging (0)
3	c.79G>A	p.(Glu27Lys)	NR	5.14	33	0.9990	Disease causing	Damaging (−3.39, −3.41)	Damaging (0.004)
4	c.1A>G	p.(Met1Val)	NR	4.52	24.1	0.9869	Disease causing	Neutral (−1.15, −1.14)	Damaging (0.004, 0.003)
5	c.218T>A	p.(Val73Glu)	NR	5.20	27.5	0.9901	Disease causing	Damaging (−5.67)	Damaging (0)
6	c.140G>A	p.(Arg47Gln)	NR	5.14	34	0.9996	Disease causing	Damaging (−3.59, −3.61)	Damaging (0.0001)
7	c.935G>A	p.(Arg312Gln)	NR	5.24	35	0.9996	Disease causing	Damaging (−3.57, −3.74)	Damaging (0.0001)
8	c.151A>C	p.(Ser51Arg)	NR	4.56	28	0.9982	Disease causing	Damaging (−4.67, −4.64)	Damaging (0)

The immunological system was involved in 43% subjects (6/14): abnormal immunoglobulin pattern was present in 21% (3/14) of the subjects and frequent infections in 21% (3/14), with 1 overlapped case in between. Other problems included umbilical hernia (1/14, 7%) and inguinal hernia (2/14, 14%). Features observed in only a single subject included pulmonary valve dysplasia, long and thin fingers, labial adhesion, intermittent esotropia, mild hearing loss, heat intolerance, easy fatigability, anemia, 2 rows of teeth, iris coloboma/anisocoria, gingival hypertrophy, conjunctival gray spots and carnitine deficiency. Despite reports of somatic variants involving *CSNK2A1* in cancer, none of the above children has been reported to have malignancy.

3.3.3 | Facial dysmorphism

Clinical photographs of 1 individual was provided by Okur et al in their publication. We provide additional clinical photographs of 5 subjects from this cohort to further illustrate the recognizable facial features of this syndrome (Figure 2). Frequently occurring facial features include microcephaly (8/14, 57%), round face (4/14, 29%), hypertelorism (3/14, 21%), partial ptosis (3/14, 21%), arched eyebrows (4/14, 29%), epicanthic folds (4/14, 29%), broad nasal bridge (6/14, 43%), low set ears (4/14, 29%) and ear fold abnormality (6/14, 43%). Other reported features included plagiocephaly, flat face, almond-shaped eyes, intermittent esotropia, iris coloboma/anisocoria, high palate, thin upper lip, retrognathia/micrognathia, prominent tongue, 2 rows of teeth and large upper incisors.

3.4 | Molecular genetics

To date, there have been several cohorts reporting *CSNK2A1* variants in neurodevelopmental disorders. Okur et al,[7] first reported 5 *CSNK2A1* variants in 2016 among all 4102 neurodevelopmental cases. About a year later in 2017, in the DDD study[9] another 8 individuals with *CSNK2A1* variants were reported among 4293 neurodevelopmental cases in their cohort. And most recently, Trinh et al[8] added another case report on a *CSNK2A1* variant. Including the 8 additional variants in our cohort, we performed a summary of all 22 subjects and 16 reported variants in the gene (Figure 1, Table 2 and Table S1).

The *CSNK2A1* gene consists of 1 large protein kinase domain spanning exons 4 to 12, and Okur et al suggested several important subunits including an ATP/GTP binding loop, a basic cluster, an active site and an activation segment containing a "p + 1 loop." Of all variants in our cohort, 2 variants fall outside of this protein kinase domain, namely p.(Glu27Lys) (Subject 2) and p.(Met1Val) (Subject 3) which leads to a start loss (Figure 1 and Table 2). All other missense variants are within protein kinase domain and is most densely clustered on exon 9. Variants clustering on exon 9 include p.(Lys198Arg) (Subject 1) from the current cohort, 8 cases involving 5 variants (p.(Ile174Met), p.(Trp176Arg), p.(Arg191Gln), p.(Phe197Ile), p.(Lys198Arg) from DDD cohort, and 2 variants (p.(Lys198Arg) and p.(Asp175Gly)) were reported from Okur et al (-Table S1). Particularly, p.(Lys198Arg) is the most frequently observed variant in *CSNK2A1* and it is possibly a mutation hotspot. Furthermore, the arginine at position 191 belongs to "p + 1 loop" of the activation site and is thus important for recognition of acidic residues in phosphorylation. Among the other 3 reported variants in this report, the p.(Arg47Gln) variant (Subject 6) and p.(Ser51Arg) (Subject 8) are located within the glycine-rich ATP/GTP binding loop, clustered around p.(Arg47Gln) and p.(Tyr50Ser) from Okur et al (Figure 1). Next, the p.(Val73Glu) variant (Subject 5) was found in the same exon as the p.(Arg80His) variant from DDD, in the basic cluster region of the protein kinase domain. Finally, p.(Pro231Arg) (Subject 4) is found in exon 10, whereas p.(Arg312Gln) and p.(Arg312Trp) (Subject 7 and another subject from DDD) are found in exon 12 of the protein kinase domain.

The *CSNK2A1* gene is very well conserved especially at the ATP/GTP binding loop and the basic cluster. The 8 variants in our cohort had a GERP (genomic evolutionary rate profiling) score of 4.52 to 5.24, which shows that they are all highly conserved. Furthermore, the *CSNK2A1* gene has a high constraint *Z*-score of 3.89 for missense variants on Exome Aggregation Consortium (ExAC), which means it is highly intolerant to missense variants, with the observed no. of variants (n = 42) much lower than expected (n = 134.2) (Table S2A).

Seven out of 8 variants found in our cohort were novel. The p.(Met1Val) variant (Subject 4) affects the start codon and is predicted to lead to a loss of protein from Position 1 to 137, the position of the next in-frame start-codon. Variant p.(Glu27Lys), identified in Subject

3, is predicted to affect the protein by in silico analysis, and is in close contact with glycine-rich basic stretch of the N-terminal,[16] which is responsible for substrate recognition.[17] Subject 2 carries mutation p.(Pro231Arg). The amino acid Pro231 forms a stable *cis*-peptide with the loop region of the C-terminal helical domain, which is likely to be the result of *cis/trans*-isomerization of the peptide bond.[18] This process has been implicated as a "molecular switch" in controlling the amplitude and duration of cellular processes.[19] Subject 5 carries the mutation p.(Val73Glu) and is located in the protein kinase domain within the N-terminal region of the protein. All of them alter highly conserved amino acids with important roles in stabilization and substrate recognition and are likely disruptive. Subject 7 carries the mutation p.(Arg312Gln), at which the same position was reported to have mutation p.(Arg312Trp) in DDD cohort. Subject 8 carries the p.(Ser51Arg) and falls within the ATP/GTP binding loop which was postulated as a mutation hotspot by Okur et al.

In a 3D simulated CSNK2A1 peptide model, all variants except p.(Arg312Gln), reported in this study were found to be located at the same spatial region (Figure 3A), at the protein kinase domain (amino acid residue 39 to 231) of the holoenzyme. Similar localization for the previously reported variants was also observed (Figure 3B). The simulation also predicted the changes in protein stability by delta-delta *G* value. All variants were predicted to have a delta-delta *G* value greater than 0 indicating these variants are responsible for stabilizing the CSNK2A1 protein fold (Table S3).

4 | DISCUSSION

CSNK2A1 encodes the α subunit of the CK2 protein, which is a serine/threonine kinase consisting of 2 catalytic subunits (either 2 α or 2 α′ or one of each) and 2 regulatory β subunits, using either GTP or ATP as a phosphate donor in the kinase reaction (MIM #115440). It is ubiquitously expressed in various tissues and has an important role in cellular growth, proliferation and apoptosis.[20] Increased expression of *CSNK2A1* has also been reported in various cancers,[20–22] and frequent somatic intragenic deletions of *CSNK2A1* were found in T cell leukemia.[23] CK2 also promotes development of myeloid-derived suppressor cells,[24] which suppresses adaptive immune response and regulate immune responses.[25] This may explain the frequent occurrence of immunological abnormalities in affected individuals with Okur-Chung syndrome. Furthermore, human RNA-Seq analysis in RIKEN-FANTOM5 CAGE (cap analysis of gene expression) project revealed that *CSNK2A1* is expressed in different parts of the brain, as well as the left ventricle of the heart, lymph nodes, kidney, spleen and ovary.[26] All these expressed tissues correlate with the clinical features observed in affected individuals.

In our study we report 8 variants, including 6 novel variants and 2 previously reported variants. In the previous publication, variants were mostly related to either the ATP binding site of the N-terminal (position 46-51) or the activation site of the C-terminal within the alpha subunit (position 175-201). In comparison, 5 out of 8 subjects in our current cohort carry variants outside these regions (Figure 1) but nonetheless are likely disruptive by altering highly conserved amino acids with important roles in stabilization and substrate recognition. This is further supported by the high CADD score in the 9 variants reported, ranging from 24.1 to 35, indicating these variants were predicted to be the top 1% of genetic changes with deleterious effect. Furthermore, the delta-delta *G* values of the variants are all greater than 0, suggesting impaired protein interaction with the ligands with disruption of normal kinase function.

Although CK2 is well known for its roles on various cellular functions, such as metabolic control, gene expression, cell cycle and cell proliferation, the exact molecular mechanism underlying is unknown. Nevertheless, literature reports can give us some insights on its potential molecular mechanism. *CSNK2A1* homologous knock-out mice, despite being embryonically lethal, was showed to have neural tube defect, smaller head size as well as retarded limb bud development and unfused branchial arches,[10] which draw similarities with clinical type of our patients and suggest potential loss of function properties in observed variants. *CSNK2A1* also has a pLi value of 1.0 in the ExAC database (Table S2A), suggesting that the gene is loss-of-function intolerant. We thus postulate loss-of-function as a possible mechanism underlying *CSNK2A1* variations in Okur-Chung syndrome. However, without functional studies we are not able to exclude other mechanisms at work, especially because protein kinase inactivated *CSNK2A1* has been shown to interfere with CK2 activity in a dominant negative manner, thus affecting normal cellular function on growth and cell cycle progression.[27] In addition, most of the reported variations are located on the surface of the molecule, and are associated with non-haploinsufficient mechanisms.[28]

Two variants were found recurrently in both cohorts. First, the p.(Lys198Arg) variant was found in Subject 2 from Okur et al and Subject 1 from the current series. The previously published individual had global developmental delay, started walking at the age of 2 and was able to speak 2 single words at the age of 22 months. He was reported to have hypotonia and abnormal gait requiring braces. Severe gastrointestinal abnormalities including severe gastroesophageal reflux and significant oromotor delay with failure to thrive requiring a gastrostomy tube were present. Furthermore, hypogammaglobulinaemia was mentioned. In contrast, our subject was remarkably less severely affected. He had normal cognitive abilities, with only mild language delay and normal gross motor development. Despite hyperlaxity of the joints and dilated renal pelvis, his medical history was otherwise unremarkable. Second, the p.(Arg47Gln) variant was found in Subject 1 from the Okur et al cohort and Subject 6 from the current cohort. These 2 subjects had more clinical features in common. Both subjects had microcephaly and global developmental delay. They also share unique dysmorphic features, including hypertelorism, single palmer crease, retrognathia, as well as flexion deformity of the fifth finger. The previous subject had a fifth finger clinodactyly whereas Subject 6 from the current series had left camptodactyly. The differences between the 2 include ADHD and pachygyria on MRI brain, which was not present in Subject 6. On the other hand, Subject 6 had a dystrophic pulmonary valve, butterfly vertebrae, cholesteatoma, conjunctival gray spots, frontal bossing, anteverted nares, feeding difficulties, gingival hypertrophy, generalized joint laxity, kyphosis and advanced bone age.

In this series, we report 8 additional subjects with de novo variants in *CSNK2A1* in addition to cases from Okur et al[7] (5 female

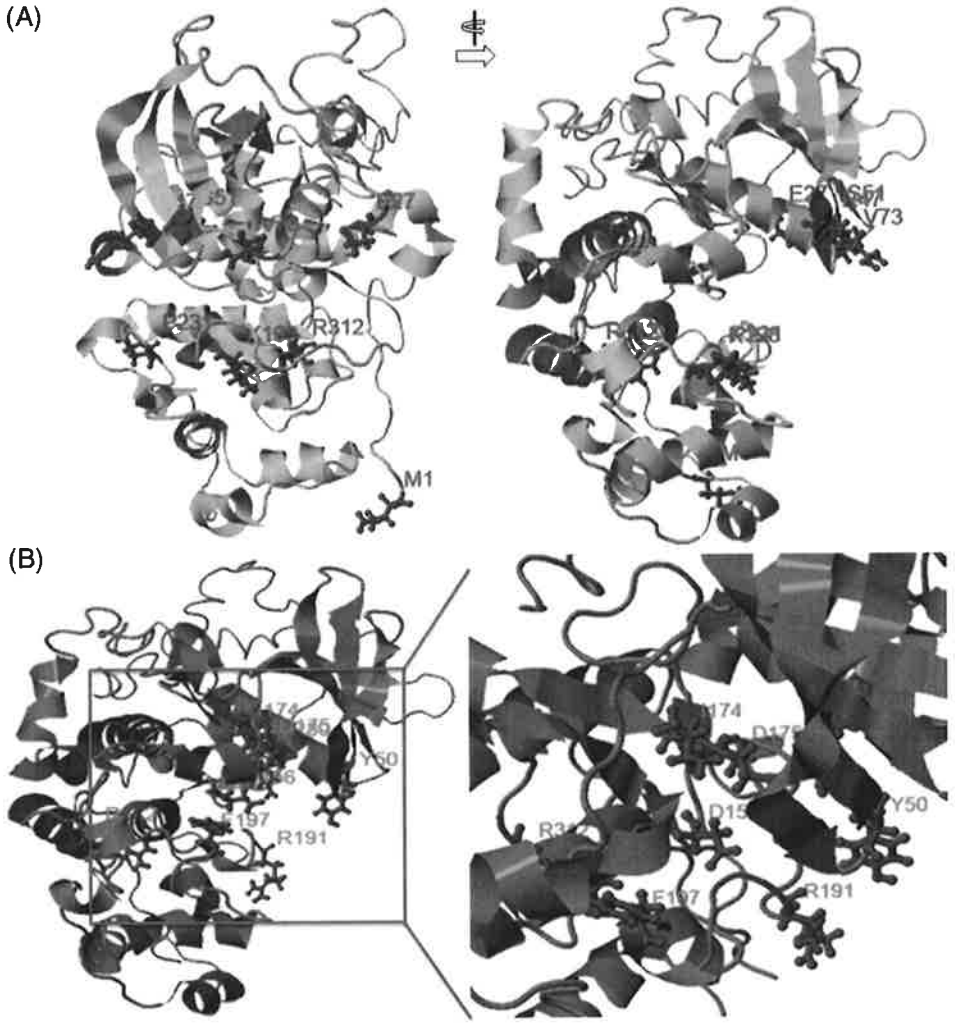

FIGURE 3 3D simulation of the α subunit, CSNK2A1, using STRUM (a method for structure-based stability change prediction upon single-point variant). (A) 3D modeling of the CSNK2A1 monomer with the spatial relationship of all variant sites reported in our cohort indicated. All mutations, except p.(Arg312Gln), were found to be located at the same spatial region of the holoenzyme, where the protein kinase functional domain is located. A more clear representation of the spatial relationship was shown on the right. (B) 3D simulation of other reported CSNK2A1 variants. A magnified view of the peptide was shown on the right. [Color figure can be viewed at wileyonlinelibrary.com]

subjects), Trinh et al[8] (1 male subject) and the DDD cohort[9] (4 male and 4 female affected individuals). The male to female ratio is 1:1. Both males and females are affected equally as it would be expected in an autosomal variation. Taking this into account, and given the fact that *CSNK2A1* is located at chromosome 20 and not at the X-chromosome, it is unlikely that variable X-chromosome inactivation contributes to the phenotypic variability between individuals, as suggested before.[7]

We included clinical photographs from Subjects 1, 2, 6, 7 and 8 in this series. The combined clinical photographs from all 5 subjects of different ages helps to highlight the recognizable facial features of this syndrome. We also report new clinical features in association with *CSNK2A1*, including ASD, idiopathic increase in intracranial pressure requiring ventriculoperitoneal shunting, thin corpus callosum, pes planus, 2 rows of teeth, butterfly vertebra and dysplastic pulmonary valve. In addition, isolated features from the Okur et al[7] series were found to recur in our cohort, including ptosis, sleep problem, loose joints, inguinal hernia and recurrent upper respiratory infections.

With an expanded case series, the overall phenotypic heterogeneity is better characterized. It should be noted, however, that owing to the small number of subjects available for analysis, the phenotypic spectrum of Okur-Chung neurodevelopmental syndrome is not fully understood. As such we cannot provide clinical diagnostic criteria for the syndrome at this stage. Of particular note, despite >90% of patients showing intellectual disability, Subject 1 was able to enter mainstream primary school and perform satisfactorily. This has important implications on genetic counseling and clinical management, in that special education is not necessarily required.

4.1 | Management recommendation

Reviewing the clinical manifestation of reported children with Okur-Chung neurodevelopmental syndrome, we make the following recommendations on management of children with the condition:

1. Assessment by clinical geneticist

Clinical and molecular information should be reviewed by a clinical geneticist in the diagnosis of this syndrome, and appropriate genetic counseling should be made. Caution should be made regarding the prognosis of this condition. While this is expected to be an autosomal dominant condition, it is a new pathogenic variant and no relative or inheritance of the disorder has been observed.

2. Comprehensive neurodevelopmental assessment and multidisciplinary training

Neurodevelopmental abnormality is the most consistent feature of the syndrome. Comprehensive neurodevelopmental assessment should be provided in combination with early intervention and appropriate referrals to physiotherapist, occupational therapist, speech therapist for further training. Those suspected to have ASD or ADHD should be referred to clinical psychologist and/or child psychiatrist for further assessment. Should the subject be older than 6 years of age, intellectual assessment should be considered with appropriate educational support.

3. Serial measurement of growth, nutrition and skeletal malformation

Yearly surveillance on growth and skeletal malformation is recommended. Even though *CSNK2A1* is associated with growth abnormalities these children are susceptible to increased risk of gastrointestinal problems such as oromotor dysfunction, esophageal reflux, which are treatable causes of undernutrition and should not be overlooked. Imaging and/or referral to orthopedic surgeon should be considered if clinical/ skeletal abnormalities are detected.

4. Serial measurement of head circumference

Head circumference should be monitored serially. As 60% of the children have microcephaly, increase in head circumference may need to prompt early imaging for hydrocephalus. Brain imaging should be contemplated in case of abnormal neurological findings such as seizures, ataxia or significant hypotonia, and electroencephalogram (EEG) in case of seizures or abnormal movement.

5. Immunological workup

Should there be any suspicion of frequent or severe infection, a baseline immunoglobulin pattern and referral to immunologist should be considered.

Special attention should also be made regarding occurrence of umbilical and inguinal hernia with timely referral to pediatric surgeon for consideration of surgery.

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Conflict of interest

The authors do not have any conflict of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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