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# Extending the phenotype associated with the CSNK2A1-related Okur–Chung syndrome—A clinical study of 11 individuals

Ceris I. Owen<sup>1</sup> | Ramsay Bowden<sup>2</sup> | Michael J. Parker<sup>3</sup> | Jo Patterson<sup>3</sup> |  
Joan Patterson<sup>2</sup> | Sue Price<sup>4</sup> | Ajoy Sarkar<sup>5</sup> | Bruce Castle<sup>6</sup> |  
Charulatha Deshpande<sup>7</sup> | Miranda Splitt<sup>8</sup> | Neeti Ghali<sup>9</sup> |  
John Dean<sup>10</sup> | Andrew J. Green<sup>11</sup> | Charlene Crosby<sup>12</sup> |  
Deciphering Developmental Disorders Study<sup>13</sup> | Katrina Tatton-Brown<sup>12,14</sup>

<sup>1</sup> Medical Research Council, London Institute for Medical Sciences, Hammersmith Hospital, London, UK

<sup>2</sup> East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

<sup>3</sup> Sheffield Children's NHS Foundation Trust, Sheffield Clinical Genetics Service, Sheffield, South Yorkshire, UK

<sup>4</sup> Department of Clinical Genetics, Oxford University Hospitals NHS Trust, Oxford, UK

<sup>5</sup> Department of Clinical Genetics, Nottingham University Hospitals NHS Trust, Nottingham, UK

<sup>6</sup> Peninsula Genetics Service, Royal Devon and Exeter Hospitals NHS Trust, Exeter, UK

<sup>7</sup> South East Thames Regional Genetics Unit, Guys and St Thomas NHS Trust, London, UK

<sup>8</sup> Northern Genetics Service, Newcastle Upon Tyne Hospital NHS Foundation Trust, Newcastle, UK

<sup>9</sup> North West Thames Regional Genetics Service, North West London Healthcare NHS Trust, Harrow, UK

<sup>10</sup> Department of Clinical Genetics, NHS Grampian, Aberdeen, UK

<sup>11</sup> National Centre for Medical Genetics, Our Lady's Hospital, Dublin, Republic of Ireland

<sup>12</sup> South West Thames Regional Genetics Service, St George's University Hospitals NHS Foundation Trust, London, UK

<sup>13</sup> Deciphering Developmental Disorders Study, Wellcome Trust Sanger Institute, Cambridge, UK

<sup>14</sup> St George's University of London, London, UK

## Correspondence

Katrina Tatton-Brown, South West Thames Regional Genetics Service, St George's University Hospitals NHS Foundation Trust, Cranmer Terrace, London SW17 0RE, UK.  
Email: k.tattonbrown@nhs.net

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Variants in the Protein Kinase CK2 alpha subunit, encoding the CSNK2A1 gene, have previously been reported in children with an intellectual disability and dysmorphic facial features syndrome: now termed the Okur–Chung neurodevelopmental syndrome. More recently, through trio-based exome sequencing undertaken by the Deciphering Developmental Disorders Study (DDD study), a further 11 children with de novo CSNK2A1 variants have been identified. We have undertaken detailed phenotyping of these patients. Consistent with previously reported patients, patients in this series had apparent intellectual disability, swallowing difficulties, and hypotonia. While there are some shared facial characteristics, the gestalt is neither consistent nor readily recognized. Congenital heart abnormalities were identified in nearly 30% of the patients, representing a newly recognized CSNK2A1 clinical association. Based upon the clinical findings from this study and the previously reported patients, we suggest an initial approach to the management of patients with this recently described intellectual disability syndrome.

## KEYWORDS

CSNK2A1, DDD study, intellectual disability, Okur-Chung, protein kinase CK2

## 1 | INTRODUCTION

Genetic disorders associated with an intellectual disability are estimated to affect approximately 0.5% of children (Ropers, 2010). Since the introduction of massively parallel sequencing technologies, the genetic cause of many intellectual disability syndromes has been identified (DDD-Study, 2015; de Ligt et al., 2012; Gilissen et al., 2014; Rauch et al., 2012). The Deciphering Developmental Disorders Study (DDD study) has investigated over 13,600 children with an undiagnosed intellectual disability and has undertaken trio-based exome sequencing in over 33,000 individuals (patients and parents), recruited from Clinical Genetics centers in the United Kingdom and the Republic of Ireland (DDD-Study, 2015; Firth et al., 2009; Firth & Wright, 2011). The DDD study recently reported 94 genes as being enriched in de novo variants including CSNK2A1, which encodes the Protein Kinase CK2 (casein kinase 2) alpha sub-unit (McRae, 2017).

Protein Kinase CK2 is a ubiquitously expressed, constitutively active serine/threonine and tyrosine kinase, with a diverse range of substrates (Meggio & Pinna, 2003). The CK2 holoenzyme is a heterotetramer, comprised of two catalytic alpha subunits (CK2 $\alpha$  or CK1 $\alpha$ , either  $\alpha/\alpha$ ,  $\alpha/\alpha'$ , or  $\alpha'/\alpha'$ ) and two regulatory beta subunits (CK2 $\beta$ ) (Niefind, Guerra, Ermakowa, & Issinger, 2001). The alpha subunits are encoded by two homologous genes: CSNK2A1, which encodes CK2 $\alpha$  (Wirkner, Voss, Lichter, Ansoerge, & Pyerin, 1994) and CSNK2A2, which encodes CK2 $\alpha'$  (Ackermann, Neidhart, Gerber, Waxmann, & Pyerin, 2005). The beta subunit is encoded by CSNK2B (Albertella, Jones, Thomson, Olavesen, & Campbell, 1996). Protein kinase CK2 is widely expressed in the mammalian brain (Diaz-Nido, Mizuno, Nawa, & Marshak, 1994), with CK2 $\alpha$  predominating over CK2 $\alpha'$  (Ceglia, Flajolet, & Rebholz, 2011).

The CSNK2A1 gene spans 70 kb and comprises 13 exons, encoding a 391 amino acid polypeptide with three conserved, functional domains: an N-terminal ATP/GTP binding motif, a basic cluster and a C-terminal activation domain (Niefind et al., 2001; Wirkner, Voss, Ansoerge, & Pyerin, 1998) (Figure 1).

To date six patients with CSNK2A1 variants have been reported. An initial series included five patients with de novo heterozygous CSNK2A1 missense or consensus splice site variants and variable combinations of intellectual disability, hypotonia, speech problems, gastrointestinal problems, immune dysfunction, pachygyria, and dysmorphic facial features (Okur et al., 2016). Subsequent to this report, the condition was eponymously named the Okur-Chung neurodevelopmental syndrome (OMIM 617062). More recently, a further child with a de novo heterozygous CSNK2A1 missense variant and features of intellectual disability, progressive microcephaly, and subtle dysmorphic facial features has been described (Trinh et al., 2017).

Here we have undertaken a clinical study of 11 patients with de novo CSNK2A1 variants and thereby expand and provide further detail on the Okur-Chung syndrome phenotype.

## 2 | METHODS

De novo CSNK2A1 variants were identified by the DDD study using a trio-based exome sequencing strategy as described (McRae, 2017). The study was approved by the UK Research Ethics Committee (10/H0305/83, granted by the Cambridge South REC, and GEN/284/12 granted by the Republic of Ireland REC).

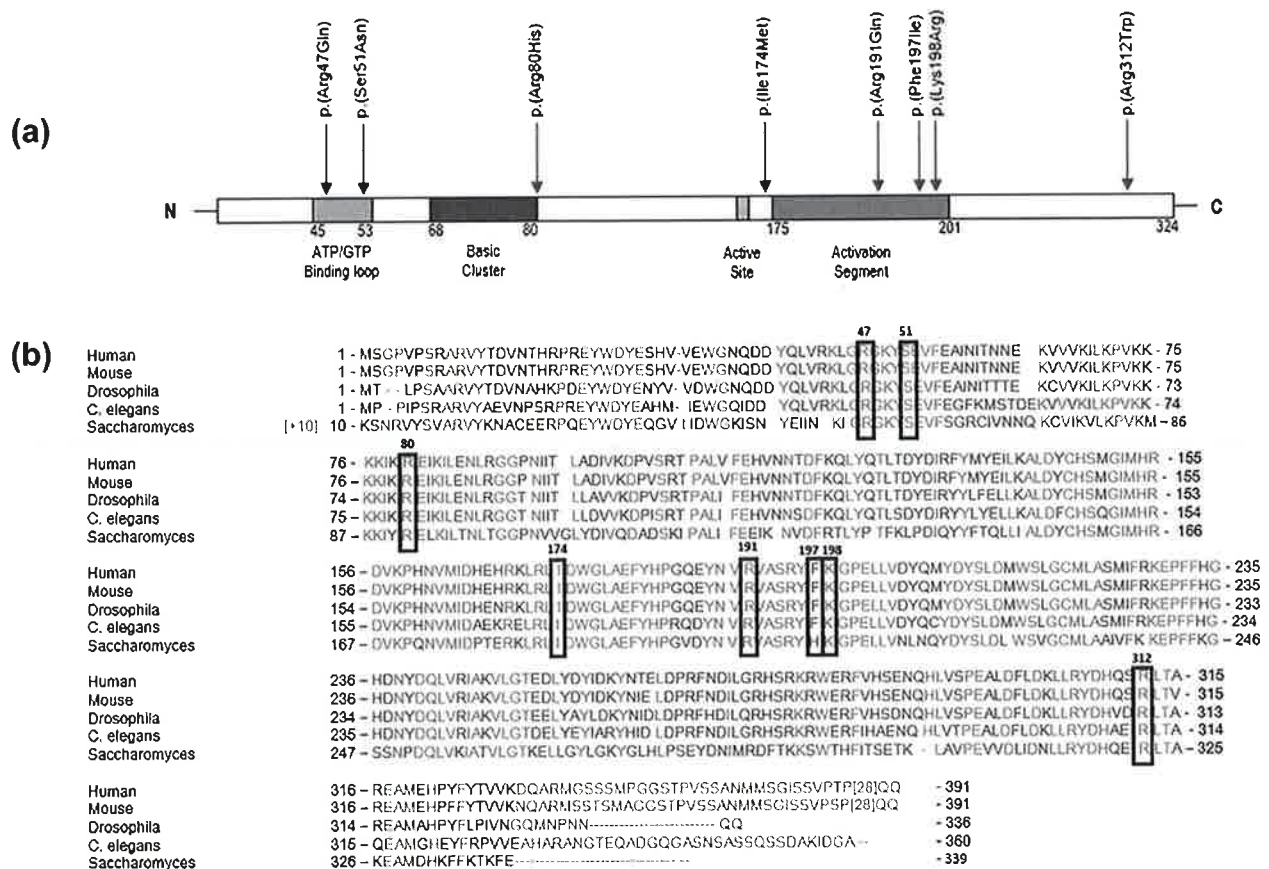
All patients had been reviewed in clinic by at least one of the authors and phenotypic data were obtained from all patients using a standardized form. Photographs with accompanying consent for publication was requested from all and obtained from the families of eight patients.

## 3 | RESULTS

In total, eight distinct CSNK2A1 variants, identified in 11 unrelated individuals, were identified and were considered likely pathogenic variants. Pathogenicity assignment was based upon the American College of Medical Genetics and Genomics and the Association of Molecular Pathology Criteria: PS2, PM2, PP2, and PP3 criteria were met for each of the variants with evidence detailed below (Richards et al., 2015).

All of the CSNK2A1 variants had arisen de novo through exome sequencing that confirmed maternity and paternity (PS2). None of the eight CSNK2A1 variants were identified in the GnomAD population database where coverage at all bases was greater than 30 $\times$  for genome and/or exome data (PM2). The CSNK2A1 constraint score (as reported by the ExAC study) was significant (expected number of missense variants was 134.2 compared to the observed number of 42.0, z-score = +3.89) (Lek et al., 2016) (PP2) and multiple lines of computational evidence support a deleterious effect on the gene/gene product (PP3) (Table 1). In addition, all of the amino acids altered by these variants are evolutionarily conserved across species to at least the nematode *Caenorhabditis elegans*, with seven of the eight mutated amino acids conserved to *Saccharomyces cerevisiae* (Figure 1, Table 1). Three of the variants targeted the evolutionarily conserved activation domain of CSNK2A1, one variant fell one amino acid N-terminal to this domain, one variant targeted the final amino acid of the basic cluster domain and two further variants lay within the ATP/GTP binding domain (Figure 1).

The clinical features reported in the 11 affected patients are summarized in Table 2 and detailed in the supplementary data. Of note,



**FIGURE 1** Domains and comparative sequence alignment of the CK2α protein. (a) Schematic of CK2α protein domains with missense variants represented by predicted amino acid alterations shown by arrows above the protein. (b) Comparative sequence alignments from Human to Yeast, (amino acids conserved across all species shown by the black boxes). [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

all 11 patients had apparent intellectual disability. Formal evaluation of the degree of intellectual disability was not undertaken but details of developmental attainments are described in the supplementary data. Mean values for developmental milestones were 11.5 months for sitting unaided, 30.5 months for walking, and 44.0 months for first words.

Additional clinical features, reported in at least three affected individuals, included neonatal hypotonia (seven patients); autistic spectrum traits including repetitive behaviors, mannerisms, and self-injurious behavior (four patients); swallowing difficulties (three patients) and congenital heart disease (three patients; two with septal

defects and one with tetralogy of Fallot). The 11 patients were generally of short stature with a mean postnatal height of ~1.8 standard deviations (Table 2). Microcephaly, defined as an occipito-frontal circumference (OFC) at least two standard deviations below the mean, was described in just one of the 11 patients although the mean OFC was one standard deviation below the mean. Although there were some shared facial characteristics including malar flattening, depressed nasal bridge, short nose, thin upper lip vermillion, epicanthus, short philtrum, and widely spaced teeth, there was neither a consistent nor recognizable facial gestalt (Figure 2). Recurrent infections were not reported (and therefore further immunological evaluation had not

**TABLE 1** In silico prediction of pathogenicity for the eight CSNK2A1 missense variants identified in this study

| Variant                 | Chr 20 co-ordinates (GRCh37) | Polyphen          | SIFT     | Mutation taster (v2013) | PROVEAN     |
|-------------------------|------------------------------|-------------------|----------|-------------------------|-------------|
| c.140G>A, p.(Arg47Gln)  | g.485835C>T                  | Possibly damaging | Damaging | Disease causing         | Deleterious |
| c.152G>A, p.(Ser51Asn)  | g.485823C>T                  | Possibly damaging | Damaging | Disease causing         | Deleterious |
| c.239G>A, p.(Arg80His)  | g.480553C>T                  | Possibly damaging | Damaging | Disease causing         | Deleterious |
| c.522A>G, p.(Ile174Met) | g.472997T>C                  | Probably damaging | Damaging | Disease causing         | Deleterious |
| c.572G>A, p.(Arg191Gln) | g.472947C>T                  | Probably damaging | Damaging | Disease causing         | Deleterious |
| c.589T>A, p.(Phe197Ile) | g.472930A>T                  | Probably damaging | Damaging | Disease causing         | Deleterious |
| c.593A>G, p.(Lys198Arg) | g.472926T>C                  | Possibly damaging | Damaging | Disease causing         | Deleterious |
| c.934C>T, p.(Arg312Trp) | g.468110G>A                  | Probably damaging | Damaging | Disease causing         | Deleterious |

**TABLE 2** Clinical characteristics of patients with CSNK2A1 missense variants

| Patient number          | 1  | 2  | 3   | 4   | 5                                | 6                        | 7   | 8                        | 9                        | 10                       | 11   |
|-------------------------|--|--|---|---|----------------------------------|--------------------------|---|--------------------------|--------------------------|--------------------------|--|
| <b>Patient details</b>  |  |  |   |   |                                  |                          |   |                          |                          |                          |  |
| Age (years)             | 6.1  | 11.1   | 10.7  | 10.9  | 10.0                             | 8.0                      | 7.3   | 10.9                     | 18.3                     | 18.7                     | 6.0  |
| Sex                     | Male   | Female   | Male  | Male  | Female                           | Female                   | Female  | Male                     | Male                     | Female                   | Female   |
| <b>Mutation details</b> |  |  |   |   |                                  |                          |   |                          |                          |                          |  |
| Nucleotide              | c.140G>A   | c.152G>A                                       | c.239G>A  | c.522A>G  | c.572G>A                         | c.589T>A                 | c.593A>G  | c.593A>G                 | c.593A>G                 | c.593A>G                 | c.934C>T   |
| Amino acid              | p.(Arg47Gln)                                     | p.(Ser51Asn)                                   | p.(Arg80His)                                    | p.(Ile174Met)                                       | p.(Arg191Gln)                    | p.(Phe197Ile)            | p.(Lys198Arg)   | p.(Lys198Arg)            | p.(Lys198Arg)            | p.(Lys198Arg)            | p.(Arg312Trp)                                      |
| Inheritance             | De novo  | De novo  | De novo   | De novo   | De novo                          | De novo                  | De novo   | De novo                  | De novo                  | De novo                  | De novo  |
| <b>Growth</b>           |  |  |   |   |                                  |                          |   |                          |                          |                          |  |
| BW/kg (SD)              | 2.27 (-2.1)                                      | 2.88 (-1.9)                                    | 3.69 (-0.8)                                     | 1.84 (-0.5)   | 3.57 (+1.0)                      | 2.78 (+0.4)              | 3.81 (+0.8)   | 3.02 (-0.8)              | 2.92 (-1.0)              | 2.80 (-1.3)              | 2.70 (-0.7)  |
| Age/years               | 5.6  | 11.1   | 9.3   | 2.1   | 5.5                              | 3.3                      | 5.8   | 7.7                      | 7.3                      | 10.0                     | 5.3  |
| Ht/cm (SD)              | 105.8 (-1.9)                                     | 111 (-5.1)                                     | 124.5 (-1.7)                                    | 89.6 (+1.4)   | 108 (-0.6)                       | 85 (-2.8)                | 102.7 (-2.1)  | 113.4 (-1.3)             | 110 (-2.5)               | 129 (-1.4)               | 100.3 (-2.2)                                       |
| Wt/kg (SD)              | 16.2 (-2.0)                                      | 17.6 (-4.7)                                    | 38.8 (1.4)                                      | 13.3 (-0.6)   | 19 (0.0)                         | 12.1 (-1.6)              | 16.2 (-1.5)   | 21.8 (-0.2)              | 17.6 (-2.5)              | 24.8 (-1.7)              | 15.3 (-1.6)  |
| OFI/cm (SD)             | 49.5 (-1.5)                                      | 51.5 (-0.9)                                    | 56.0 (2.50)                                     | 48.0 (-0.9)   | 48.3 (-1.9)                      | 46.5 (-1.5)              | 50.0 (-0.5)   | 49.2 (-1.9)              | 50.5 (-1.2)              | 49.5 (-2.1)              | 49.4 (-1.1)  |
| <b>Development</b>      |  |  |   |   |                                  |                          |   |                          |                          |                          |  |
| Sitting                 | 6 months   | 7 months                                       | 30 months                                       | 18 months   | 12 months                        | 6 months                 | 15 months   | 6 months                 | 11 months                | 24 months                | 10 months  |
| Walking                 | 22 months  | 24 months                                      | 30 months                                       | 30 months   | 18 months                        | 24 months                | 49 months   | 40 months                | 24 months                | 48 months                | 27 months  |
| Speech                  | First words at 12 months, lost by aged 24 months | First words at 36 months, 36 months, 36 months | First words at 60 months                        | First words at 18 months                            | First words at 36 months         | First words at 48 months | First words at 48 months                                    | First words at 96 months | First words at 72 months | First words at 14 months | First words at 14 months                           |
| <b>Behavior</b>         |  |  |   |   |                                  |                          |   |                          |                          |                          |  |
| No issues               | No issues  | No issues                                      | Challenging behaviors, autistic traits, anxiety | Autistic traits, mannerisms and obsessions, anxiety | Passive, easily frustrated       | No issues                | Autistic traits, repetitive behaviors, verbal & motor ticks | No issues                | No issues                | No issues                | Autistic traits, self-injurious (biting), tantrums |
| <b>Medical problems</b> |  |  |   |   |                                  |                          |   |                          |                          |                          |  |
| Neonatal hypotonia      | No   | No   | Yes   | Yes   | Yes                              | No                       | Yes   | No                       | Yes                      | Yes                      | Yes  |
| Swallowing difficulties | Yes  | No   | No  | Yes   | Yes-slow eater and chokes easily | No                       | No  | No                       | No                       | No                       | No   |
| Seizures                | No   | No   | No  | No  | No                               | No                       | 3 × febrile seizures  | No                       | ? absence seizures       | No                       | No   |
| Cardiac                 | Echocardiogram not tolerated                     | Tetralogy of Fallot                            | No  | No  | Large ASD                        | No                       | No  | No                       | No                       | No                       | ASD  |
| Brain MRI               | Normal   | Not done                                       | Normal  | Not done  | Not done                         | Normal                   | Normal  | Normal                   | Not done                 | Delayed myelination      | Not done   |

(Continues)

TABLE 2 (Continued)

| Patient number | 1  | 2  | 3                                      | 4 | 5          | 6                           | 7                      | 8      | 9   | 10                                   | 11         |
|----------------|--|--|--|---|------------|-----------------------------|------------------------|--------|---|--------------------------------------|------------|
| Other issues   | Asthma, flexion deformity of right 2nd–3rd fingers, umbilical hernia, pes planus, GERD | Severe infantile scoliosis from age 8 months | Hypermobile joints, painful leg cramps |   | Tongue tie | Absent left sided ear canal | Post-axial polydactyly | Eczema | Mild cutaneous syndactyly digits 1–4 in hands | Duplex right renal collecting system | Pes planus |

ASD, atrial septal defect; BW, birth weight; Ht, height; GERD, gastro-esophageal reflux disease; ID, intellectual disability; MRI, magnetic resonance imaging;

OFC, occipito-frontal circumference; SD, standard deviations; Wt, weight.

\*Genomic co-ordinates as per GRCh37 construct.

been undertaken in any of the patients) and a brain MRI scan had been undertaken in six of the 11 patients: this was normal in five patients and demonstrated delayed myelination in the sixth.

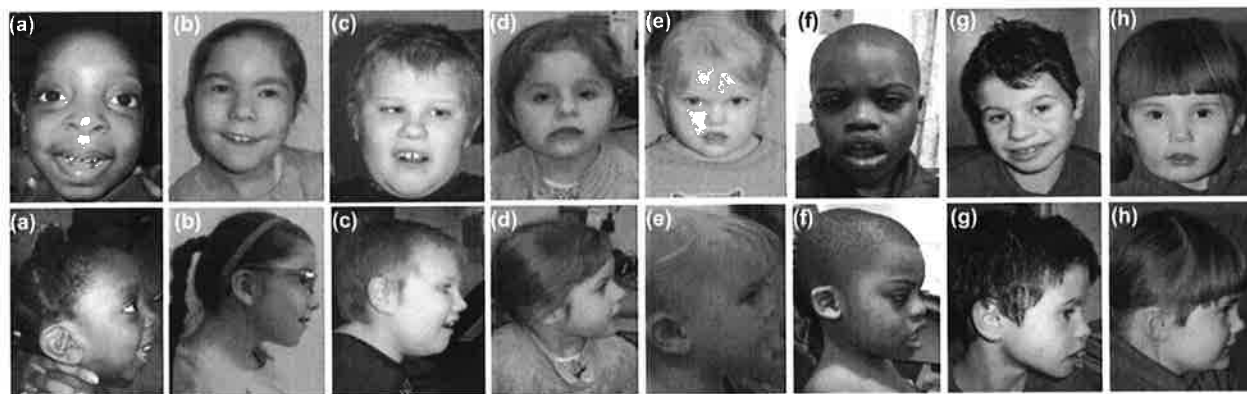
Other clinical features, reported in a single individual, are shown in Table 2 and include polydactyly, syndactyly, pes planus, scoliosis, absent ear canal, and a duplex renal collecting system. Until greater numbers of patients with Okur–Chung syndrome are identified, it is unclear whether these single clinical findings are true associations of the condition or coincidental.

## 4 | DISCUSSION

*CSNK2A1* variants were first reported as causative of an intellectual disability and a range of medical problems in 2016: this report led to the eponymous designation of the condition as the Okur–Chung neurodevelopmental syndrome (Okur et al., 2016). Subsequently an additional patient with a de novo *CSNK2A1* missense variant and an intellectual disability has been reported (Trinh et al., 2017). The current report includes 11 unrelated patients, identified through trio-based exome sequencing, undertaken by the DDD study. This ascertainment of patients with *CSNK2A1* variants through genotype rather than phenotype allows the unbiased evaluation of the *CSNK2A1*-associated cognitive, behavioral, and medical profile.

Eight different de novo *CSNK2A1* missense variants were identified in 11 unrelated patients. Two of these variants had previously been reported (c.140G>A (p.(Arg47Gln)) and c.593A>G (p.(Lys198Arg)) (Okur et al., 2016)). The majority of variants were identified in only one individual, other than the c.593A>G (p.(Lys198Arg)) variant which was identified in four unrelated individuals in the study suggesting a hotspot at this location (Figure 1). The mechanism whereby germline missense variants cause the Okur–Chung neurodevelopmental disorder has not yet been elucidated but it is of interest that missense variants are the primary variant type constituting 16 of the 17 variants identified to date. Functional assays to investigate the effect of the variants on the encoded protein are required to evaluate this, however due to the highly pleiotropic nature of the targets of protein kinase CK2, a global phosphoproteomic approach may be the optimal strategy to investigate the effects of these mutations, which is beyond the scope of this study. All currently identified variants have arisen de novo and germline mosaicism has not been described. This suggests that the recurrence risk for future pregnancies of unaffected parents is low.

There is some overlap between the *CSNK2A1* clinical associations reported in our series, the Okur et al. (2016) series, and the Trinh et al. (2017) patient. Notably, all patients were claimed to have moderate or severe intellectual disability, but only the patient reported by Trinh et al. (2017) was formally tested. In addition, autistic spectrum traits or other behavioral issues, swallowing difficulties, and hypotonia were frequently reported. Although shared facial features were present (malar flattening, depressed nasal bridge, short nose, thin upper lip vermillion, epicanthus, short philtrum, and widely spaced teeth), there is not a recognizable gestalt and patients with the Okur–Chung syndrome can be difficult to



**FIGURE 2** Facial characteristics of individuals with de novo missense *CSNK2A1* variants variably demonstrating malar flattening, depressed nasal bridge, short nose, thin upper lip vermillion, epicanthus, short philtrum, and widely spaced teeth. (a) Patient 1; aged 5 years 11 months, c.140G>A, p.(Arg47Gln). (b) Patient 2; aged 11 years 1 months, c.152G>A, p.(Ser51Asn). (c) Patient 3; aged 9 years 10 months, c.293G>A, p.(Arg80His). (d) Patient 4; aged 3 years 4 months, c.589T>A, p.(Phe197Ile). (e) Patient 7; aged 2 years 9 months, c.593A>G, p.(Lys198Arg). (f) Patient 8; aged 5 years 0 months, c.593A>G, p.(Lys198Arg). (g) Patient 9; aged 9 years 0 months, c.593A>G, p.(Lys198Arg). (h) Patient 11; aged 4 years 5 months, c.934C>T, p.(Arg312Trp). [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

identify/distinguish clinically. In contrast to the initial report of Okur–Chung syndrome, none of the six patients investigated with a brain MRI scan had pachygyria. In addition, recurrent infections, requiring further immunological investigations, were not reported in any of the 11 patients. However, three of the patients in our series presented with congenital heart disease, a previously unrecognized association.

The current study adds to our knowledge of the Okur–Chung neurodevelopmental syndrome by increasing the number of affected individuals from 6 to 17. Based upon clinical data from this and the previous Okur–Chung and Trinh studies and given there are few discriminators to allow clinical stratification to more targeted gene sequencing, we conclude that *CSNK2A1* sequencing represents a suitable addition to a multigene panel investigation of intellectual disability disorders. In addition, as well as providing more detail on this new intellectual disability syndrome, the current study highlights that cardiac anomalies are a new likely association of the Okur–Chung neurodevelopmental syndrome. In order to ensure consistency of management for children with the Okur–Chung neurodevelopmental syndrome and based upon the evidence from the 17 individuals, we suggest in addition to standard care, a detailed echocardiogram to investigate for congenital heart disease; referral to speech and language therapy for swallow assessment; referral to physiotherapy if hypotonia is present and early referral and formal cognitive evaluation for an assessment of educational needs. Although recurrent infections were not reported in our series of 11 patients, we also recommend a low threshold for immunological investigation of recurrent infections and a brain MRI scan where clinically indicated, for instance if a patient developed seizures. However, with increasing accessibility to exome sequencing, additional individuals with the Okur–Chung syndrome are likely to be identified over the coming years. Therefore, once additional and longitudinal data are available, these management suggestions should be updated and revised.

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This study makes use of data generated by the DECIPHER community. A full list of centers who contributed to the generation of the data is available from <http://decipher.sanger.ac.uk> and via email from [decipher@sanger.ac.uk](mailto:decipher@sanger.ac.uk). Funding for the project was provided by the Wellcome Trust. The views expressed in this work are those of the authors and do not represent the views of the Wellcome Trust or the department of Health. We are grateful to the healthcare practitioners involved in the care of the patients and, in particular, we are grateful to the families and patients who participated in this and the DDD study. The DDD study presents independent research commissioned by the Health Innovation Challenge Fund [grant number HICF-1009-003], a parallel funding partnership between the Wellcome Trust and the Department of Health, and the Wellcome Trust Sanger Institute [grant number WT098051]. The views expressed in this publication are those of the author(s) and not necessarily those of the Wellcome Trust or the Department of Health. The study has UK Research Ethics Committee approval (10/H0305/83, granted by the Cambridge South REC, and GEN/284/12 granted by the Republic of Ireland REC). The research team acknowledges the support of the National Institute for Health Research, through the Comprehensive Clinical Research Network.

## WEB RESOURCES

The URLs for data presented herein are as follows:

Cobalt alignment tool; [https://www.ncbi.nlm.nih.gov/tools/cobalt/re\\_cobalt.cgi](https://www.ncbi.nlm.nih.gov/tools/cobalt/re_cobalt.cgi)

DDD study; <https://www.ddduk.org/>

Elements of morphology; <https://elementsofmorphology.nih.gov/>

ExAC browser; <http://exac.broadinstitute.org/>

GnomAD browser; <http://gnomad.broadinstitute.org/>

Variant taster; <http://www.varianttaster.org/>

Online Mendelian Inheritance in Man (OMIM); [www.ncbi.nlm.nih.gov/omim](http://www.ncbi.nlm.nih.gov/omim)

Polyphen; <http://genetics.bwh.harvard.edu/pph2/>

PROVEAN; <http://provean.jcvi.org/index.php>

SIFT; <http://sift.jcvi.org/>

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ORCID

Ceris I. Owen  <http://orcid.org/0000-0002-6065-0959>

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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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## **SUPPLEMENTAL DATA**

### **Individual Case Presentations:**

#### **Patient 1**

Patient 1 is a six year old boy. There were no issues in pregnancy and he was born at term weighing 2.27kg (-2.1SD). He met his motor milestones within the normal range (he sat unaided at 6 months and walked independently at 22 month), and spoke his first words aged one year. However by the age of two he had lost all speech and at age six, he had no words and cannot sign. He communicates his needs through actions and his mum uses Makaton but is unsure of his understanding of this.

Patient 1 is a happy and affectionate boy. He is very active, preferring solitary play although doesn't interact with toys. He loves to chew things. Sleep is problematic in that he finds it hard to get sleep and will sleep for fewer than 8 hours, although this has improved since an adenoidectomy aged 4. He needs help with dressing, and continues to wear nappies.

Patient 1 had several episodes of bronchiolitis in early childhood. He had an umbilical hernia which was surgically repaired aged 18 months. He has developed contractures of the 2<sup>nd</sup> and 3<sup>rd</sup> fingers on the right hand which were surgically released aged three years. He has a history of gastro-esophageal reflux disease, which has improved with age. He had swallowing difficulties in early childhood and although this has improved he continues to eat a soft diet at the age of six.

#### **Patient 2**

Patient 2 is an 11 year old girl. She was born at 42 weeks following a normal delivery weighing 2.88kg (-1.9SD). She required resuscitation at birth and was transferred to

the neonatal intensive care unit where she was subsequently diagnosed with a tetralogy of Fallot for which we underwent surgery at aged 1 month, three years, and six years. At aged eight months she developed a severe infantile scoliosis, ultimately, at the age of eight, requiring anterior and posterior spinal fusion T2 - L3.

Patient 2 sat unsupported at seven months, and walked independently at 24 months. Her first intelligible words were at aged 36 months. She is currently attending a mainstream school, with one to one educational support, however she is significantly behind in all educational areas.

### **Patient 3**

Patient 3 is a ten year old boy. He was born at 42 weeks by emergency caesarean section due to breech presentation, following a pregnancy complicated by polyhydramnios from 20 weeks. He weighed 3.69kg (-0.8SD). He was jittery and hypoglycaemic at birth for which he was treated on the special care baby unit for 48 hours. In addition, he was noted to have hypotonia with persistent head lag.

He first smiled at seven weeks, but was delayed in motor development walking unaided at 30 months. He had no expressive language until aged five years. At the age of 11 he talks in short phrases and uses Makaton signs, but is unable to hold conversations.

Patient 3 attends a school for special educational needs. He needs help with dressing and toileting, and wears nappies at night. Although generally happy, he can have challenging behaviour, with defiance and temper tantrums often stemming from frustration at his communication difficulties. He can also be anxious, and has repetitive behaviours.

Patient 3 has hypermobile joints, and poor co-ordination. He has nocturnal muscle cramps for which a trial of Baclofen did not improve the symptoms. He has been investigated with creatinine kinase and electroencephalograms, both of which were normal.

#### **Patient 4**

Patient 4 is a ten year old boy. He was born following a premature delivery at 33 weeks, weighing 1.84kg (-0.5 SD). The pregnancy was complicated by gestational diabetes from 20 weeks. He was admitted to the special care baby unit for five weeks for prematurity, and had hypotonia and difficulty swallowing liquids throughout this period with dribbling of fluids.

Patient 4 first smiled at 5 weeks (corrected). He was delayed in his motor development, sitting unaided at 18 months, and walking with support at 30 months. His first words were at 18 months, but he has limited speech and receives specialist speech and language support. Although generally happy, he can have challenging behaviour, has mannerisms and obsessions and can become anxious. He is otherwise in good general health.

#### **Patient 5**

Patient 5 is a ten year old girl. She was born at term following an uncomplicated pregnancy weighing 3.57kg (+1.0SD). She was delivered by forceps for apparent fetal distress. Meconium was present at delivery. However she had normal Apgar scores, and normal cord gasses. She had mild central and peripheral hypotonia. She had a tongue tie which was diagnosed late, and now she is a slow eater and chokes easily.

Patient 5 was able to sit unsupported at 12 months, and walked independently at 18 months. Her first words were at 36 months. She currently attends a mainstream school with some educational support. She has a short attention span and is significantly behind in all educational areas although her speech is improving. She is a happy child, but does get frustrated. She is vulnerable with no real awareness of danger. She has poor co-ordination and joint laxity, and frequently falls over.

She was diagnosed with a large atrial septal defect at four months of age, and this was monitored until the age of four years when she underwent a surgical closure, from which she recovered well. In early childhood she had bronchiolitis, but is otherwise in good health.

#### **Patient 6**

Patient 6 is an eight year old girl. She was born at 36 weeks by emergency caesarean section for failure to progress. She was well in the immediate post-natal period and did not need specialist care. Her birth weight was 2.78 Kg (+0.4SD).

Patient 6 sat unsupported at 6 months, cruised at 20 months and walked independently at 2 years. Her language was delayed, with first words at four years. Aged five her expressive language was limited to a few short sentences. Currently she is unable to hold a conversation, but she can count to five, and is beginning to recognise some words. She is able to dress and toilet without help.

She is generally a happy child, with no behavioural issues. She is in generally good health. Although she has a congenital absence of the left ear canal, her hearing on the right side is normal.

#### **Patient 7**

Patient 7 is a seven year old girl. She was born after a normal delivery at term, weighing 3.81kg (+ 0.8 SD). The pregnancy was complicated by oligohydramnios detected at the 20 week scan. This apparently resolved over the course of the pregnancy, although her mother was given steroids at 25 weeks as a precautionary measure in case of prematurity. Mild neonatal hypotonia was noted, but this was self-resolving.

Her parents first became concerned about her development when she was one year of age and her motor milestones were delayed: she sat unsupported at 15 months, crawled at 24 months, used a knee walker at 37 months and walked independently at 49 months. She is currently unable to climb stairs, jump or hop. Her language development was delayed, and she communicated with Makaton until her first words at four years of age. She currently attends a mainstream school with educational support and is continuing to develop her language skills, but is significantly behind in all educational areas. She performs repetitive behaviours and has verbal and motor ticks with unusual head movements and grunting noises.

In early childhood she had three febrile seizures, all of which were self-terminating, and she has not required treatment with antiepileptic medication. She has otherwise been in good health. She has a surgical procedure to remove a fifth finger skin tag on right hand and small bony prominence on right fifth toe aged 12 months.

### **Patient 8**

Patient 8 is a ten year old boy. He was born at term following an uncomplicated pregnancy, weighing 3.02kg (-0.8 SD). There were no concerns in the neonatal period and he was established on bottle and breast feeding without problems.

He first sat independently at 6 months, but did not walk unaided until 40 months. At the age of nine he was unable to run or jump. His language development was delayed with no expressive language until aged eight. He currently has a few words, and is able to follow two-stage commands. He attends a school for special educational needs, and is able to use a number line. He requires help with dressing and undressing, and continues to wear nappies. He is a generally good natured and happy boy, who likes to play alone, or watch television. He is otherwise in good health, but does have mild eczema, for which he uses topical emollients.

### **Patient 9**

Patient 9 is an 18 year old man. He was born at term following an uncomplicated pregnancy, weighing 2.92kg (SD -1.0). He had a mild neonatal hypotonia.

His early motor milestones were mildly delayed: he sat unsupported at 11 months and walked independently at 24 months. He attended a mainstream school with educational support. At the age of 18 years he attends college to help support him with life skills. He speaks in simple phrases and requires help with his self-care. He can make a sandwich, but cannot manage money, and does not live independently. He has a calm, trusting and kind personality. In early childhood he may have had some absence seizures, although he never received treatment and these resolved. He is currently seizure free and does not take anti-epileptic medication. He is otherwise in good health.

### **Patient 10**

Patient 10 is an 18 year old woman. She was born at term weighing 2.80kg (-1.3 SD). She was immediately unwell in the neonatal period with low Apgar scores and poor respiratory effort, and was admitted to the neonatal intensive care unit for

ventilation. She was extubated after five days and made a steady recovery from this admission. She was noted to have neonatal hypotonia, which resolved without physiotherapy.

She was delayed in her milestones, sitting unaided at 24 months and walking unaided at 48 months. Her first words were at 72 months. At the age of 18 years she is able to speak in sentences, but is not literate or numerate. She requires help with self-care, including dressing, toileting and to a lesser extent feeding. She does not live independently.

She has limited mobility, but is able to get around the house, although she cannot go for long walks. A renal ultrasound for recurrent urinary tract infections demonstrated a right duplex renal collection system, but she is otherwise in good health.

### **Patient 11**

Patient 11 is a six year old girl. She was born following a normal delivery at term weighing 2.70kg (-0.7 SD). The pregnancy was complicated by gestational diabetes diagnosed at 24 weeks. She was well in the immediate neonatal period although she did have mild hypotonia.

Patient 11 was delayed in her motor milestones, sitting unsupported at 10 months, and walking independently at 27 months. Her first words were at 14 months. At the age of six she attends a mainstream school with one-to-one support. She is unable to dress herself and sometimes needs assistance with toileting. She stopped using nappies in the daytime aged five, and at night aged six. She struggles with co-ordination and finds it difficult to use a pen at school.

She becomes easily frustrated and has tantrums, with breath-holding episodes when she is upset. She has some self-injurious behaviours, biting her hands and arms,

particularly when she is stressed. She also has mannerisms when she is upset, particularly arm flapping. She is vulnerable, and has no stranger danger or safety awareness. Socially she has a few friends, and is very affectionate with people she knows.

In terms of general health she has an atrial septal defect detected in early childhood which closed spontaneously. She also had a number of seizures as a baby, however these have subsequently resolved and she does not take antiepileptic medication. She suffers from constipation and will intermittently take laxatives for this. She has bilateral pes planus and weak ankles and wears orthotic shoes.