Report of an Asian–Indian patient with Okur–Chung Syndrome and comparison of the clinical phenotype in different ethnic groups

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List of key features

Frontal upsweep of hair
Eversion of lateral third of lower eyelid
High arched eyebrows
Hypertelorism, exotropia and lagophthalmos
Single transverse palmar crease
Bilateral talipes equinovarus

Introduction

Okur–Chung syndrome is a neurodevelopmental disorder (OCNDS,OMIM#617062) characterised by intellectual disability, variable dysmorphic features, behaviour abnormalities, cortical malformations and multisystem involvement associated with heterozygous mutation in the *CSNK2A1* gene (Okur *et al*., 2016). Around 60 patients worldwide have been diagnosed with this condition till now. The phenotypic spectrum of this rare disease is still evolving showing a high degree of interpatient variability (Trinh *et al*., 2017). The features most consistent with this disorder include hypotonia and feeding difficulty at birth followed by developmental delay and significant speech delay (not necessarily leading to intellectual disability), in infancy and childhood. Significant dysmorphism is noted in most patients in the form of hypertelorism, arched eyebrows, synophrys, low-set ears, broad nasal bridge and high arched palate (Owen *et al*., 2018). However, dysmorphism varies across various age groups and ethnicity. Some children have had congenital heart disease (Tetralogy of Fallot, atrial septal defects, dysplastic pulmonary valve), constipation and gastroesophageal reflux (Chiu *et al*., 2018). Behavioural abnormalities are also noted in the form of temper tantrums, volatile mood, hand flapping and hyperactivity (Martinez-Monseny *et al*., 2020). MRI abnormalities include cortical neuronal migration defects (Akahira-Azuma *et al*., 2018).

We report a female patient of Asian–Indian origin with mild intellectual disability and facial dysmorphism, in whom exome sequencing showed a previously reported p.Arg47Gln variant in the *CSNK2A1* gene. Previously reported children with OCNDS due to c.140G>A (p.Arg-47Gln) variant in *CSNK2A1* had a significant intellectual disability, whereas our patient had only mild intellectual disability. The presence of milder intellectual disability, an unusual pattern of scalp hairs making hairs difficult to comb, eversion of lower eyelids, lagophthalmos, club feet, apnoeic spells and MRI findings suggestive of subcortical hypomyelination are not previously reported with this syndrome, adding to the phenotypic spectrum of this rare disorder.

Clinical report

This female child, the second born to a nonconsanguineously married couple, first presented to us at the age of 2 years and 8 months with mild global developmental delay and bilateral talipes treated in infancy. She was born at term by normal vaginal delivery and her birth weight was 3 kg (30th centile). Her perinatal period was uneventful. She achieved head control at 6 months, and recognition of her mother at 5–6 months. She was sitting without support at 8 months and walking without support after 2 years (delayed walking might be contributed to by the talipes deformity and its management). She could feed with a spoon with spillage by 6 years, could say monosyllables with meaning at 3–4 years and three-word sentences by 7 years and she could understand the concepts of good and bad by 7 years. She is still unable to pedal a tricycle (>7 years).

On examination at age 2 years 8 months, she had a head circumference of 41.8 cm (–3 to –4SD) and height of 82 cm (–2 to –3 SD). Facial features included a frontal upsweep of hair with an unusual pattern of scalp hair making it difficult to comb, a palpable sagittal ridge, round face, high forehead, sparse thin arched eyebrows, telecanthus, mild lateral eversion of lateral one-thirds of the lower eyelids bilaterally, low-set ears, small nose with

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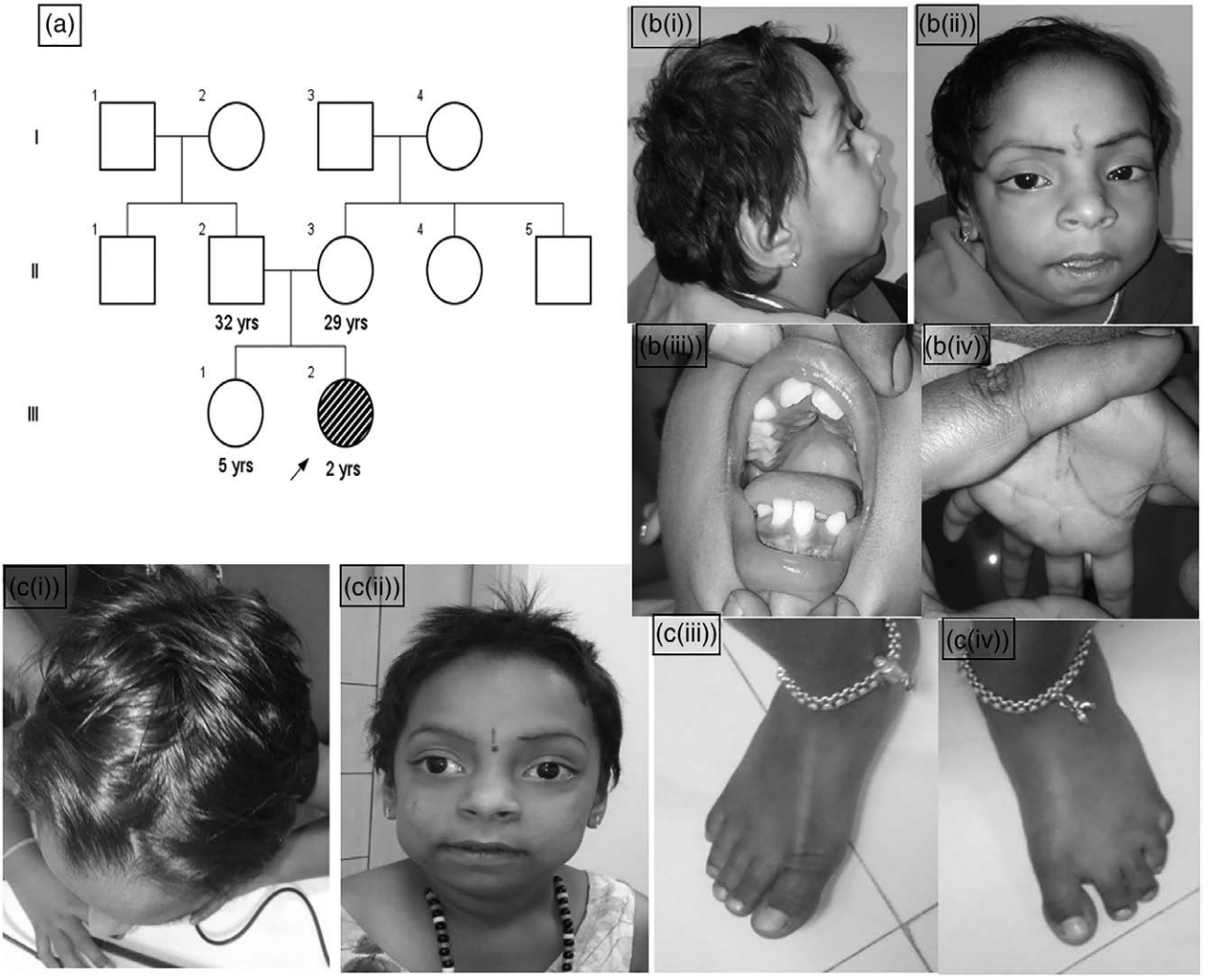
flared nares, long philtrum, wide mouth, high arched palate and micro-retrognathia. In addition, she had a single palmar transverse crease in her left hand, bilateral fifth finger clinodactyly and persistence of Mongolian spots. The left foot showed residual talipes deformity and the right foot was normal (Fig. 1). Central nervous system examination showed generalised hypotonia with normally elicitable deep tendon reflexes. Eye examination showed intermittent alternating exotropia with bilateral nocturnal lagophthalmos.

The initial evaluation at 2 years 8 months of age included 2D echocardiography, thyroid function tests, skeletal survey and standard karyotyping, all of which were normal. MRI brain was done and showed subcortical hypomyelination.

No specific aetiological diagnosis could be made initially, although clinically the hair patterning was similar to that in Johanson–Blizzard syndrome, and eversion of the lateral one-third of the lower eyelids was reminiscent of Kabuki syndrome (Fig. 1).

On follow-up at the age of 5 years, she had undergone bilateral adenotonsillectomy for chronic adeno-tonsillitis. At age 6 years, her head circumference was 44.5 cm (–4 to –5 SD) and height was 114 cm (–2 to –3SD). She was also noted to have behaviour abnormalities with breath-holding spells. Her formal IQ measurement could not be completed because of her behavioral issues during assessment but her overall IQ was estimated to be in the range of 50–70, suggestive of mild intellectual disability. A spine radiograph repeated at the age of 6 years was normal.

Fig. 1



(a) Three generation family pedigree, (b(i)) Facial features at 2 years 8 months showing retrognathia with low-set ears. (b(ii)) Round face, high wide forehead, frontal upsweep, hypertelorism, sparse thin arched eyebrows, lower eyelids lateral 1/3rd eversion, long palpebral fissure, small nose with flared nares, long wide philtrum and wide mouth. (b(iii)) High arched palate. (b(iv)) Single palmar crease, fifth finger clinodactyly. (c(i),(ii)) Unusual pattern of scalp hairs, facial features at 6 years age. (c(iii),(iv)) Residual CTEV.

Table 1 **Comparison of clinical features of previously reported patients with p.R47Q with our patient**

Feature	Okur *et al* (2016)	Chiu *et al.* (2018)	Owen *et al.* (2018)	Our patient (2021)
Age	6 years	2 → 6 years	6years	2 → 6 years
Gender	Female	Female	Male	Female
Mutation	p.Arg47Gln	p.Arg47Gln	p.Arg47Gln	p.Arg47Gln
Intellectual disability	Significant	Significant with predominant speech delay	Significant with predominant speech delay	mild
Behaviour	Temper tantrums, hyperactivity, ataxia	Sleep apnoea, seizure	Normal	Breath-holding spells
Microcephaly	+	+	+	+
Short stature	–	+	+	+
MRI	Pachygyria	Vermis hypoplasia with thin non-dysplastic corpus callosum	Normal	Subcortical hypomyelination
Cardiac involvement	–	Dystrophic pulmonary valve	–	–
Immunodeficiency	–	–	–	–
Clinodactyly/camptodactyly	+	+	–	+
Single palmar crease	+	–	–	+
Congenital talipes equinovarus	–	–	–	+
Others	Umbilical hernia at birth, palmar erythema and cutis marmorata	Butterfly vertebrae, advanced bone age, feeding difficulties, cholesteatoma surgery	Flexion deformity, umbilical hernia, feeding difficulty and pes planus	Congenital talipes equinovarus

Note: +, present; –, absent.

Table 2 **Facial dysmorphology of previously reported patients with p.R47Q with our patient**

Dysmorphism	Percentage of cases with OCNDS with dysmorphism in the cohort studied by (Okur *et al*., 2016; Chiu *et al*., 2018; Owen *et al*., 2018)	Okur *et al.,* (2016)	Chiu *et al.,* (2018)	Owen CI *et al*., (2018)	Our patient (2021)
Frontal upsweep with unusual pattern of scalp hairs	-	-	-	-	Present
Prominent forehead	21%	-	Present	-	Present
Hypertelorism	21%	Present	Present	Present	Present
Eversion of lateral eyelid	-	-	-	-	Present
Arched eyebrows	29%	Present	Present	Present	Present
Partial Ptosis, lagophthalmos, exotropia	21%	-	-	-	Present
Low-set ears	29%	Present	Present	Present	Present
Broad nasal bridge	43%	-	-	Present	-
High arched palate	21%	Present	-	-	Present
Thin upper lip	21%	-	-	Present	-
Retrognathia	29%	Present	Present	Present	Present

Note: -, not reported.

Chromosomal microarray done using the Affymetrix CytoScan 750K platform Thermo Fisher Scientific (Affymetrix, Santa Clara, California, USA) showed no clinically significant copy number variants. Whole exome sequencing was done on the Illumina NextSeq500 platform after library preparation and capture using Illumina Nextera Rapid Capture Exome Kit V1.2. (Illumina Inc., San Diego, California, USA). Bioinformatics analysis was done using the pipeline based on Burrows–Wheeler Aligner (BWA-MEM) program (http://bio-bwa.sourceforge.net/), Picard tools (https://broadinstitute.github.io/picard/), the Genome Analysis Toolkit (GATK; https://gatk.broadinstitute.org/hc/en-us) and Annovar (https://annovar.openbioinformatics.org/). A heterozygous missense variant c.140G>A (p.Arg47Gln) in *CSNK2A1* (NM_177559.3) was detected in the proband. This variant is not present in population databases (1000G and gnomAD). The variant is previously reported as a pathogenic/likely pathogenic variant in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/; accession number VCV000224796) by multiple submitters, although no functional evidence for this variation has been presented. This variant is reported to be deleterious by various in silico prediction tools (Mutation Taster, Provean, SIFT, Polyphen2, FATHMM and LRT) and classified as a pathogenic variant by InterVar, as per the American College of Medical Genetics & Genomics and the Association for Molecular Pathology (ACMG-AMP) 2015 guidelines. Targeted variant testing through Sanger sequencing of exon 3 was performed for both parents and the patient, using specific primers to amplify the targeted region by PCR followed by bidirectional sequencing on ABI3130 sequencer (Applied Biosystems, Thermo Fisher Scientific). This validated the result in the proband and confirmed the absence of the variant in both parents.

Discussion

Casein kinase 2 (CK2) is a serine/threonine protein kinase that phosphorylates acidic proteins such as casein. It exists as a tetramer with two alpha and two beta subunits. *CSNK2A1* encodes for the alpha subunit that contains the catalytic site. Somatic mutations are implicated in various cancers whereas the germline mutations are known to cause Okur–Chung neurodevelopmental

syndrome (Wirkner *et al*., 1998). The *CSNK2A1* 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. In the recent study, a cell-based assay of *CSNK2A1* missense variants showed reduced kinase activity and abnormal localization of CK2α responsible for OKNDS (Dominguez *et al*., 2021). The variant p.Arg47Gln resides in the glycine-rich ATP binding loop, the subunit of CK2. The residue p.Arg47 is highly conserved across species and this p.Arg47Gln variant has been previously reported as causative for OCNS in three different cohort studies (Okur *et al*., 2016; Chiu *et al*. 2018; Owen *et al*., 2018).

A comparison of the clinical features of previously reported patients with p.Arg47Gln with that of our patient has been given in Table 1,2. This variant was first reported in a 6-year-old female child by Okur *et al*., 2016. Subsequently, the variant was also reported by Chiu *et al*. in 2018 and Owen *et al*. in 2018. Although the age of presentation of these patients was similar to that of our patient, there are some distinct differences. The previously reported three children had significant intellectual disability (likely severe), and in our patient the ID was mild. Behavioural abnormalities including temper tantrums and attention deficit hyperactivity disorder were noted in two patients (Okur *et al*., 2016; Chiu *et al*., 2018), but were not present in our patient and the patient reported by Owen *et al*. in 2018. Cardiac and skeletal abnormalities were present in one child (Chiu *et al*., 2018) but not seen in the other two or in our patient. Sleep apnoea and seizures were previously reported in one patient (Chiu *et al*., 2018), but not apnoeic or breath-holding spells as seen in our patient. The presence of talipes, eversion of lateral eyelids, an unusual pattern of scalp hair, lagophthalmos and MRI findings of subcortical hypomyelination have not previously been reported in children with OCNDS, although delayed myelination has been reported in two patients (Akahira-Azuma *et al*., 2018, Owen *et al*., 2018). There was significant overlap in the facial dysmorphology with hypertelorism, low-set ears, high arched palate, arched eyebrows and micrognathia seen in all cases. The facial phenotype in our patient was more characteristic at 2 years of age than at 6 years of age (Fig. 1) and showed resemblance to the patient reported by Owen *et al*., 2018. A prominent forehead, thin arched eyebrows, epicanthic fold and ear fold abnormalities appear to be more common in younger age groups (<2 years old) (Chiu *et al*., 2018; Owen *et al*., 2018; Martinez-Monseny *et al*., 2020).

The majority of children with OCNDS have a head circumference at the lower end of the normal range. Significant microcephaly (defined as < −2SD) is seen in only approximately 30% of reported patients (Source PubMed) and sometimes microcephaly can be progressive. Our patient had significant progressive microcephaly.

Conclusion

Careful and detailed case reporting from different ethnic backgrounds helps in defining the phenotypic spectrum of Okur–Chung neurodevelopmental syndrome, and may help to establish clinical diagnostic criteria for this rare syndrome which displays phenotypic heterogeneity and interpatient variability.

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Conflicts of interest

There are no conflicts of interest.

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