Two Siblings with Kaufman Oculocerebrofacial Syndrome Resembling Oculoauriculovertebral Spectrum

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Established Facts

- Kaufman oculocerebrofacial syndrome (KOS) is an autosomal recessive disorder characterized by intellectual disability and dysmorphic facial features with ocular involvement.
- KOS is included in the differential diagnosis of blepharophimosis-mental retardation syndromes.

Novel Insights

- Clinical features associated with oculoauriculovertebral spectrum, including epibulbar dermoids and auricular abnormalities, such as microtia and preauricular skin tags, may be accompanying findings in KOS.

Keywords

Kaufman oculocerebrofacial syndrome · *UBE3B* ·
Blepharophimosis-mental retardation syndromes ·
Intellectual disability · Oculoauriculovertebral spectrum

Abstract

Kaufman oculocerebrofacial syndrome is a rare autosomal recessive disorder which represents a phenotype mainly involving craniofacial and neurodevelopmental manifesta-

tions due to *UBE3B* gene mutations. The vast majority of the affected individuals exhibit microcephaly, eye abnormalities, and typical facial gestalt including blepharophimosis, ptosis, telecanthus, upslanting palpebral fissures, dysplastic ears, and micrognathia. We encountered 2 siblings in whom severe psychomotor delay, distinctive facial features, hearing loss, and respiratory distress were observed. Some clinical manifestations of the patients, including epibulbar dermoid, microtia, and multiple preauricular tags, were reminiscent of the oculoauriculovertebral spectrum. However, 2 affected

siblings exhibited a similar clinical picture consisting of microcephaly, severe developmental and cognitive disabilities, failure to thrive, and dysmorphic features, which were not fully consistent with oculoauriculovertebral spectrum. Also, hypoplastic nails, considered as a core manifestation of Coffin-Siris syndrome, were present in our patients. Therefore, whole-exome sequencing was carried out in order to identify the underlying genetic alterations, contributing to the complex phenotype shared by the 2 siblings. A homozygous pathogenic mutation was found in both affected siblings in the *UBE3B* gene which caused Kaufman oculocerebrofacial syndrome. Kaufman oculocerebrofacial syndrome should be considered among the autosomal recessive causes of blepharophimosis-mental retardation syndromes, particularly in populations with a high rate of consanguineous marriages, even if there are dysmorphic facial features that are not typically associated with the phenotype. © 2021 S. Karger AG, Basel

Introduction

Kaufman oculocerebrofacial syndrome (KOS), also known as blepharophimosis-ptosis-intellectual disability syndrome, is a rare autosomal recessive disorder featuring intellectual disability and distinctive craniofacial dysmorphisms. KOS was first described by Kaufman et al. [1971] in 4 siblings with intellectual disability, microcephaly, ophthalmologic abnormalities, and distinctive facial features, suggesting autosomal recessive inheritance. Since the original description, 31 cases diagnosed with KOS have been reported [Galarreta et al., 2019]. The condition is classified in the group of blepharophimosis-mental retardation syndromes (BMRS), characterized by horizontal narrowing of the palpebral fissures, intellectual disability, and miscellaneous systemic malformations [Yilmaz et al., 2018]. The disorders arise from biallelic mutations of the gene encoding ubiquitin-protein ligase E3B (*UBE3B*; MIM 608047) located at chromosome 12q24 [Basel-Vanagaite et al., 2012]. Herein, we report on 2 additional patients from one family harboring a rare pathogenic *UBE3B* variant.

Case Presentation

Patient 1

A 2-month-old boy presented to our clinic with a preliminary diagnosis of oculoauriculovertebral spectrum (OAVS), previously known as Goldenhar syndrome, based on the dysmorphic features. The family denied consanguinity; however, the parents

originated from the same geographic region. He was born after a full-term pregnancy with a birth weight of 3,050 g by caesarean section. At birth, he was hospitalized in the neonatal intensive care unit for one week due to feeding problems and laryngomalacia. At initial admission, his weight was 3,100 g (−3.71 SD), his length 55 cm (−1.9 SD), and his occipitofrontal circumference (OFC) was 35 cm (−3.11 SD). On examination, an epibulbar dermoid in the left eye, left microtia with a preauricular pit, bilateral auricular abnormalities involving helix and tragus along with multiple preauricular skin tags, single transverse palmar crease on the left hand, and inguinal hernia were observed. He had conductive hearing loss, due to the absence of the auditory canal on the left side, as well as bilateral sensorineural deafness. After 3 years of age, he had multiple episodes of febrile seizures responsive to anticonvulsants, and EEG revealed no epileptic discharges. On the most recent clinical examination at the age of 13, he presented with dysmorphic findings such as prominent forehead, smooth supraorbital ridges, bilateral blepharophimosis, depressed nasal bridge with anteverted nostrils, micrognathia, pectus carinatum, scoliosis, bilateral pes cavus, and hypoplastic fifth toenails. He achieved head and neck control at around 10 months of age. He has not attained developmental milestones properly, such as sitting without support, and standing and walking by the age of 13. Also, he was not able to speak any meaningful words and demonstrated severe intellectual disability with stereotyped repetitive movements. Radiological assessments included brain MRI, echocardiography, and renal ultrasonography, neither of these showing significant abnormalities. Conventional cytogenetic studies demonstrated a normal karyotype of 46,XY. Microarray analysis was performed (Affymetrix® CytoScan Optima platform, Santa Clara, CA, USA) and revealed no genomic imbalances.

Patient 2

The proband's sister presented at the age of 16 days, the third live-born child of the family, who clinically resembled the proband. She was born at term with a birth weight of 2,700 g after an uneventful pregnancy. She was kept in the neonatal intensive care unit to ensure proper nutrition and was discharged with a nasogastric tube to overcome feeding difficulties. On admission, her weight was 2,750 g (−1.92 SD) and OFC was 32 cm (−3.06 SD). Dysmorphic facial features included prominent forehead, hypertelorism, bilateral preauricular skin tags, a preauricular pit on the left side, high-arched palate, and microretrognathia. Talipes calcaneus deformity of the left foot and hypoplastic fifth fingernails were also noted. She had significant psychomotor developmental delay. Bilateral severe sensorineural hearing impairment was detected, requiring hearing aids. Ophthalmologic examination was normal. Echocardiography revealed a small secundum atrial septal defect with mild hypertrophy of the left ventricle. Abdominal ultrasound showed no abnormal findings. The clinical course deteriorated because of feeding difficulties and respiratory insufficiency at the age of 4 months, and tracheostomy was performed to maintain adequate ventilation. During a 2-year follow-up, she required no respiratory support, allowing tracheostomy decannulation. The auxological parameters when she was re-evaluated at the age of 3 years were: weight 9.6 kg (−3.75 SD), height 89 cm (−1.26 SD), and OFC 43 cm (−3.35 SD). She could not sit without support and was unable to speak.

Methods and Results

Based on a similar clinical presentation in 2 siblings of different gender, born to healthy parents, an autosomal mode of inheritance was assumed, and exome sequencing was carried out on a research basis. Whole-exome sequencing (WES) was performed by using Ion Ampliseq Exome RDY kit and Ion Proton sequencer. For variant filtering, common variants were discarded (minor allele frequency, MAF >0.01). After that, exonic and nonsynonymous substitutions were selected. We performed homozygosity mapping by using WES data in order to identify regions of homozygosity shared by the 2 affected siblings. A total of 2 candidate variants, associated with a phenotype or not, were detected in 2 different homozygous regions (online suppl. Table 1; for online suppl. material, see www.karger.com/doi/10.1159/513078). One of these was a pathogenic variant according to the ACMG guidelines (c.556C>T; p.Arg186Ter) in the *UBE3B* gene. For heterozygous variants, we used an additional filtering step which filtered out when the variant was reported in gnomAD. At the end of this filtering, 91 variants in 57 genes common to the 2 siblings remained, and these are listed in online supplementary Table 2. None of them were related to the disease phenotype. Also, there were no de novo heterozygous deleterious variants that could potentially contribute to the phenotypic features of the patients. Sanger sequencing was performed in order to validate this nonsense *UBE3B* variant and analyze the segregation. The parents were found to be heterozygous carriers of this mutation. The phenotypic information and the variant details were submitted to ClinVar database [Landrum et al., 2014].

Discussion

KOS is a subtype of the syndromes classified as BMRS disease spectrum and has been assigned to mutations in the *UBE3B* gene, which encodes an E3 ubiquitin ligase containing a HECT domain [Basel-Vanagaite et al., 2012; Flex et al., 2013]. Patients with KOS have a high prevalence of ocular abnormalities that include microcornea, microphthalmia, coloboma, optic atrophy, refractive errors, astigmatism, strabismus, nystagmus, entropion, and nasolacrimal duct stenosis, besides facial characteristics such as hypertelorism, telecanthus, epicanthal folds, blepharophimosis, ptosis, and upslanting palpebral fissures [Basel-Vanagaite and Borck, 2016; Galarreta et al., 2019]. However, Basel-Vanagaite et al., [2014] reported a

Fig. 1. Clinical pictures of patient 1 (a) and patient 2 (b). Please note: prominent forehead, smooth supraorbital ridges, sparse eyebrows, hypertelorism, bilateral blepharophimosis, epibulbar dermoid in the left eye, depressed nasal bridge, left microtia, and bilateral abnormal helices with preauricular skin tags (a), and abnormal helix with a preauricular pit, skin tags, and microretrognathia (b).

patient with 2 missense mutations disrupting a region outside the HECT domain, who exhibited slight dysmorphism and lacked blepharophimosis, which is quite characteristic of the condition. The present patients exhibit severe clinical features consistent with a nonsense mutation located upstream to the HECT domain which truncates protein before this critical domain.

Other craniofacial dysmorphisms include depressed nasal bridge with broad nasal base, anteverted nares, low-set and malformed ears, preauricular skin tags, long philtrum, small mouth, and micrognathia [Figuera et al., 1993; Basel-Vanagaite and Borck, 2016; Galarreta et al., 2019]. Our patients had many characteristic findings of the syndrome (Fig. 1). Neurological manifestations are mainly hypotonia, intellectual disability, epilepsy, microcephaly, and central nervous system abnormalities [Basel-Vanagaite and Borck, 2016; Galarreta et al., 2019]. Developmental delay, intellectual disability, and microcephaly were observed in both siblings and patient 1 also suffered from recurrent febrile seizures, whereas no central nervous system abnormalities were present. Skeletal abnormalities including chest wall deformities, hip dysplasia, scoliosis, slender fingers, polydactyly, fifth finger clinodactyly, hypoplastic distal phalanges, and metatarsus adductus have been associated with KOS [Basel-Vanagaite and Borck, 2016; Galarreta et al., 2019]. Congenital heart diseases, respiratory distress, laryngomalacia, genitouri-

Table 1. Comparison of clinical features in KOS and OAVS

Phenotypes	KOS	OAVS	Patient 1	Patient 2
Failure to thrive	+	+	+	+
Microcephaly	+	+	+	+
<i>Ear abnormalities</i>				
Simple ears	–	+	+	+
Low-set ears	+	+	–	+
Microtia/anotia	+	+	+	–
External auditory canal atresia	+	+	+	–
Preauricular tags/pits	+	+	+	+
Hearing loss	+	+	+	+
<i>Ocular anomalies</i>				
Microphthalmia/anophthalmia	+	+	–	–
Upslanted palpebral fissures	+	+	–	+
Ptosis	+	+	+	–
Blepharophimosis	+	+	+	–
Epibulbar dermoid	+	+	+	–
Coloboma	+	+	–	–
Strabismus	+	+	–	–
Hypertelorism	+	+	+	+
<i>Facial dysmorphism</i>				
Prominent forehead	+	+	+	+
High-arched eyebrows	+	–	+	Mild
Depressed nasal bridge with anteverted nares	+	–	+	+
Facial asymmetry	+	+	+	+
Microretrognathia	+	+	+	+
Palate anomalies	+	+	+	+
Macrostomia	–	+	–	–
Small mouth	+	–	–	–
Thin columella	–	–	+	+
Prominent central incisors	–	–	+	NA
<i>Vertebral anomalies</i>				
Vertebral anomalies	+	+	+	–
Limb abnormalities	+	+	+	+
Hypoplastic nails	+	–	+	+
Laryngomalacia	+	+	+	+
Feeding difficulties	+	+	+	+
Lung hypoplasia	–	+	–	–
Cardiac malformations	+	+	–	+
Urogenital anomalies	+	+	+	+
Inguinal hernia	+	+	+	–
Brain abnormalities	+	+	–	NA
Seizure	+	+	+	–
Developmental delay/intellectual disability	+	+	+	+

KOS, Kaufman oculocerebrofacial syndrome; OAVS, oculoauriculovertebral spectrum; NA, not available. +, present; –, absent.

nary malformations, hearing loss, constipation, and ectodermal abnormalities such as sparse hair, thin and dry skin, small teeth and nail dysplasia have been described in some patients [Basel-Vanagaite and Borck, 2016; Galarreta et al., 2019]. Clinical features exhibited by our patients such as skeletal deformities, respiratory distress, laryngo-

malacia, hearing loss, and nail dysplasia were similar to those described in cases with KOS. Additionally, abnormally decreased concentrations of serum cholesterol values have been documented in approximately half of individuals with KOS, while that was not assessed in our patients [Basel-Vanagaite and Borck, 2016].

Ubiquitination is a type of post-translational modification that allows the addition of ubiquitin to proteins. The role of ubiquitination is to provide the stability of proteins by attaching ubiquitin to misfolded proteins for degradation [Ottis et al., 2017]. This process is catalyzed by enzymes called an activating enzyme (E1), a conjugating enzyme (E2), and a ligase (E3) [Ottis et al., 2017]. The *UBE3B* gene encodes an E3 ubiquitin ligase involving a HECT domain. Alternative splicing produces 2 main proteins differed by the presence or elimination of the HECT domain, which determines functionality [Gong et al., 2003].

Deficiency in protein ubiquitination and proteasomal degradation of proteins underlie the pathogenesis of a wide variety of diseases, including neurodegenerative disorders [Basel-Vanagaite et al., 2012]. *UBE3B* is expressed most highly in the central nervous system, digestive tract, heart, lung, skeletal muscle, skin, and soft tissues [Flex et al., 2013]. An animal model revealed that the *Ube3b* knockdown mice displayed phenotypic profiles consistent with KOS [Basel-Vanagaite et al., 2012]. *UBE3B* missense variants involving HECT domain or nonsense and frameshift mutations raising a premature stop codon that can result in truncated protein lacking crucial domains or nonsense-mediated mRNA decay have been demonstrated as responsible for the disorder [Basel-Vanagaite et al., 2012].

The phenotypic traits of KOS resemble those of BMRS including chromosome 3pterp25 deletion syndrome, Ohdo syndrome, Say-Barber/Biesecker/Young-Simpson syndrome (SBBYSS), Maat-Kievit-Brunner syndrome, and blepharophimosis-mental retardation syndrome, Verloes type, to some extent [Verloes et al., 2006]. The contiguous gene deletion at chromosome 3pterp25 can be distinguished with the presence of trigonocephaly. Short philtrum, proteinuria, normal growth, and absence of anomalies involving extremities and nose are characteristic for Ohdo syndrome. SBBYSS and Maat-Kievit-Brunner syndrome exhibit distinctive facial gestalts that are useful for diagnosis. Hypsarrhythmia, adducted thumbs, and genital anomalies are significant signs in differential diagnosis for blepharophimosis-mental retardation syndrome, Verloes type [Verloes et al., 2006].

Some clinical features of the patients reported herein, including ocular involvement, facial asymmetry, and auricular abnormalities with preauricular skin tags are consistent with OAVS [Tasse et al., 2005]. Epibulbar dermoid, seen in our patient 1, is not an essential feature in KOS, while it is accepted as a hallmark of OAVS. How-

ever, it is not a pathognomonic sign for OAVS. Our patients presented with microcephaly, severe developmental delay, failure to thrive, and dysmorphic features, including blepharophimosis and hypertelorism which were not commonly reported among the typical findings of OAVS. Both siblings exhibited significant developmental and cognitive disabilities and a clinical phenotype including depressed nasal bridge with anteverted nares and hypoplastic nails besides characteristics of OAVS (Table 1). Nail hypoplasia on fifth finger or toe, seen in our patients, is a common presentation of Coffin-Siris syndrome; however, there were no sufficient facial characteristics that suggest Coffin-Siris syndrome. Previously, heterozygous truncating mutations in the *ZNF148* gene have been identified in 4 patients with dysmorphic facial features, intellectual disability, short stature, feeding difficulties, microcephaly or macrocephaly, corpus callosum hypoplasia, and systemic malformations, similar to those seen in KOS [Stevens et al., 2016]. In that report, facial appearance described in the affected individuals included coarse face, prominent columella, wide mouth, and pointed chin, and these were not present in our patients. The constellation of dysmorphic features led us to focus on disorders associated with BMRS. WES was elected as a convenient diagnostic approach for the present family in an attempt to practically disclose the genetic etiology, given the confusing phenotypic overlap and challenging clinical diagnosis. WES identified a Sanger-validated pathogenic variant ascertained as the causal genetic defect.

This report emphasizes the utility of WES in unveiling the definitive genetic diagnosis of disorders within a broad phenotypic spectrum. Besides, establishing an accurate diagnosis by the detection of the causative variants enable us to offer comprehensive genetic counseling for prognosis and subsequent pregnancies. Some clinical features reminiscent of OAVS such as epibulbar dermoids, facial asymmetry, and preauricular skin tags may be present in KOS, particularly when a developmentally delayed patient with blepharophimosis results from a consanguineous union.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki Principles.

Written informed consent was obtained from the parents for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

G.E. Utine, P.Ö. Şimşek-Kiper, and G. Ürel-Demir constructed the idea for research and designed the study. G.E. Utine, P.Ö. Şimşek-Kiper, and K. Boduroğlu supervised the course of the research. G. Ürel-Demir, E.Z. Taşkıran, B. Aydın, B. Karaosmanoğlu, and Ö. Akgün-Doğan took responsibility in conducting of the experiments and patients' follow-up. G. Ürel-Demir, E.Z. Taşkıran, B. Karaosmanoğlu, G.E. Utine, and P.Ö. Şimşek-Kiper analyzed and interpreted the data. G. Ürel-Demir and Ö. Akgün-Doğan were responsible for literature review. G. Ürel-Demir wrote the paper. G.E. Utine, P.Ö. Şimşek-Kiper, and K. Boduroğlu revised and finalized the manuscript.

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