SAGE Open Medical Case Reports
Volume 11: 1–4

DOI: 10.1177/2050313X231186496
journals.sagepub.com/home/sco
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A case of Chopra-Amiel-Gordon syndrome with a novel heterozygous variant in the *ANKRD17* gene: A case report

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Abstract

Chopra-Amiel-Gordon syndrome (OMIM: 619504) is an autosomal dominant neurodevelopmental disorder characterized by developmental delay, intellectual disability, speech delay, epilepsy, dysmorphic craniofacial features, ophthalmological abnormalities, and recurrent infections. It is caused by heterozygous loss-of-function pathogenic variants in the *ANKRD17* gene, which codes for an ankyrin repeat-containing protein. Currently, about 35 cases of Chopra-Amiel-Gordon syndrome are described in the medical literature. We report on a 4-year-old female patient with a novel heterozygous variant in the *ANKRD17* gene.

Keywords

Chopra-Amiel-Gordon syndrome, ANKRD17, neurodevelopmental syndrome, developmental delay

Date received: 25 March 2023; accepted: 20 June 2023

Introduction

Chopra-Amiel-Gordon Syndrome (CAGS; OMIM: 619504) also called *ANKRD17*-related neurodevelopmental syndrome is an ultra-rare autosomal dominant disorder that manifests with developmental delay (DD) and/or intellectual disability (ID)—especially affecting speech, behavioral disorders, epilepsy, ophthalmologic abnormalities, growth delay, recurrent infections, gait and/or balance disturbances, and dysmorphic facial features.[1] Facial dysmorphism includes triangular face, high anterior hairline, deep-set and/or almond-shaped eyes, full cheeks, thick nasal alae and flared nostrils, thin vermilion of the upper lip, and low-set ears. Infrequent but reported features include cleft palate with Pierre Robin sequence, scoliosis and renal agenesis.[1] A single case of ruptured cerebrovascular aneurysm occurring during the neonatal period has been also reported in CAGS.[2] CAGS is caused by heterozygous loss-of-function pathogenic variants in the *ANKRD17* (NM_032217.4) located on chromosome 4q13. *ANKRD17* encodes ankyrin repeat domain-containing protein 17 (ANKRD17). This motif is present in many proteins and have wide functions including signal transduction, transcriptional regulation, cytoskeletal organization, and formation and/or maintenance of blood vessels.[3,4] CAGS is inherited in an autosomal dominant pattern. Majority of cases represent de novo mutations; however several instances of familial inheritance has been also described.[1,2] Here, we report an additional case of CAGS in a patient with previously unreported heterozygous missense variant in *ANKRD17* gene. Detailed description of clinical manifestations and diagnosis are presented.

Case presentation

A 4-year-old girl was referred for genetic counseling because of DD, ophthalmologic abnormalities, and dysmorphic craniofacial features. She was born to a 29-year-old G2P2 mother at 34 weeks of gestation by cesarean section. There was no history of consanguinity, and she had a healthy 6-year-old brother. Family history was unremarkable. Pregnancy was uneventful. Birth weight was 1900 g (0th percentile), length 49 cm (47th percentile) and occipitofrontal circumference (OFC) 31 cm (2.4th percentile). Neonatal period was complicated by cyanosis and hypoxia shortly after birth requiring oxygen support. She had a prolonged neonatal intensive care

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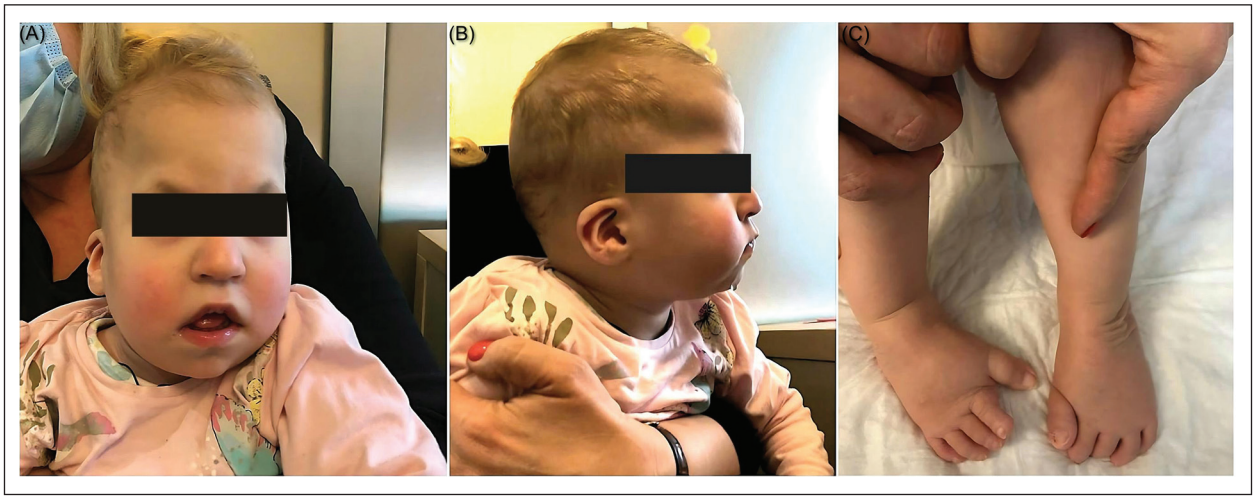

Figure 1. (a) Characteristic dysmorphic facial features including high anterior hairline and full cheeks; (b) low-set ears; (c) bilateral clubfoot.

unit stay due to persistent oral feeding difficulties requiring nasogastric tube placement. She was discharged at 4 months of age after restoration of oral feeding. Post-discharge body weight gain was age appropriate. At time of birth, the patient had bilateral clubfoot requiring Achilles tendon lengthening surgical procedure at the age of 6 months. Foot abduction bracing was initiated after surgery which led to a significant improvement in position.

The patient had significant DD. She started holding her head steady without support from 5 months, was able to sit independently from 27 months, began standing with support from 2 years. Currently, speech development is severely delayed, she is not able to say words but can produce some syllables with doubling. Upon request, she is able to respond to her name-calling, but not always. She can stand independently but is not able to walk.

Ophthalmological evaluation at the age of 6 months revealed bilateral microphthalmia, microcornea, iris dysplasia, pupil dislocation, and lens subluxation. Additionally, retinal dysplasia, congenital chorioretinal coloboma and optic nerve hypoplasia was detected in the left eye. At the time of our evaluation, she had decreased vision and myopia.

Brain magnetic resonance imaging performed at the age of 7 months showed nonspecific findings including subependymal gray matter heterotopia with nodules seen in the region of the trigones and occipital horns. At the age of 2 years the patient developed epileptic spasms. Electroencephalogram (EEG) showed modified hypsarrhythmia with background encephalopathic pattern. She was treated with vigabatrin with full remission. Abdominal and renal ultrasound were normal.

Physical examination showed prominent dysmorphia with elongated face, full cheeks, high anterior hairline, upslated palpebral fissures, strabismus, low-set ears, thick nasal alae and flared nostrils (Figure 1(a)–(c)). Two focal superficial hemangiomas were present in the inner thighs. Current weight is 14 kg (15th percentile), length 95 cm (10th percentile) and head circumference 48 cm (15th percentile).

Basic metabolic workup, including serum lactate, ammonia, amino acids, organic acids, total homocysteine, was normal. Lymphocyte chromosome analysis at the 550-band level showed a normal female karyotype 46,XX. Whole exome sequencing (WES) revealed a novel heterozygous variant c.7778A>C, p.His2593Pro in the *ANKRD17* (NM_032217.4) classified as variant of unknown significance.[5] Subsequent parental segregation analysis confirmed *de novo* status of the detected variant. Based on the clinical findings and WES results CAGS was diagnosed. Currently the patient is under the multidisciplinary team care involving ophthalmologist, neurologist and pediatric specialists. She is undergoing physical, occupational, behavior, and speech therapy.

Discussion

In this report, we give clinical and genetic characterization of a previously unreported heterozygous c.7778A>C, p.His2593Pro variant in the *ANKRD17* (NM_032217.4) in a patient demonstrating symptoms of CAGS. This variant is absent in gnomAD. Detected missense variant replaces basic and polar histidine with neutral and non-polar proline. Most of *in silico* tools (Mutation Tester, SIFT, PolyPhen) predict the variant to be damaging. The detected variant is located in exon 34 which is outside of known functional domains. In addition, Chopra and colleagues described presence of two missense variants, c.5638T>C (p.Ser1880Pro) and c.7300C>G (p.Arg2434Gly), that are also located outside of functional domains.[1] This region is evolutionary conserved

across *ANKRD17* orthologs suggesting the likely functional significance of these less unexplored regions.

The protein encoded by *ANKRD17* (NM_032217.4) is a member of the family of ankyrin repeat-containing proteins and contains two distinct arrays of ankyrin repeats in its amino-terminal region. It also has a nuclear export signal, nuclear localization signal, and a cyclin-binding RXL motif.[6] Ankyrin repeats are present in multiple proteins with functions that include cell signaling, transcription, cell cycle progression, tissue growth, and inflammatory response.[3,4,7–9] Ankyrin repeat domain 17 is also speculated to be important for the formation and/or maintenance of blood vessels.[4] ANKRD17-deficient mice models demonstrated abnormalities of embryonic development and hemorrhages with lethality.[4] Silverstein et al.[2] reported a male neonate with a heterozygous missense de novo variant in *ANKRD17* who experienced subarachnoid hemorrhage from a ruptured aneurysm. However, further functional analyses are needed to confirm its role in causation of cerebrovascular malformations and hemorrhages.

Chopra and colleagues identified 34 patients with *ANKRD17* mutations which included 21 truncating or canonical splice site variants, 9 missense variants, 1 in-frame indel, and 1 chromosomal microdeletion including *ANKRD17* along with other genes.[1] All nine missense variants identified occur at amino acids that are highly conserved across vertebrate *ANKRD17* orthologs. Based on the structural predictions most of the missense mutations disrupted the stability of ankyrin repeats. Although roles for ANKRD17 protein have been proposed and damaging effects of its mutations are shown, it is yet unclear how the disruption leads to the clinical phenotype in humans. Further studies and appropriate animal models for loss-of-function effect studies are warranted.

Our patient presented with bilateral clubfoot—a feature that has not been previously reported in the literature. Genomic testing did not evidence any significant findings to explain clubfoot. Additionally, there was no history of oligohydramnios or other prenatal complications. This finding expends the phenotypic spectrum of CAGS.

Many characteristics of the neurodevelopmental syndrome caused by *ANKRD17* pathogenic variants are nonspecific and highly variable that makes the diagnosis of CAGS challenging. More studies are needed to understand the precise molecular mechanisms and the existence of a genotype-phenotype correlation.

Conclusion

We described additional case of an ultra-rare CAGS caused by a novel heterozygous c.7778A>C, p.His2593Pro missense variant in the *ANKRD17* gene. Differentiating CAGS from other neurodevelopmental syndromes can be challenging based on the clinical phenotype alone, highlighting the importance of WES as a first-line investigation in individuals with DD, ID and congenital malformations. Timely diagnosis aids in appropriate medical intervention, coordinated multidisciplinary care and genetic counseling.

Acknowledgements

Tinatin Tkemaladze examined and investigated the patient and provided clinical information. Elene Abzianidze conceptualized the report. Tinatin Tkemaladze, Kakha Bregvadze, Mikheil Gogoberishvili and Tamari Sopromadze-Diebold wrote the manuscript. All co-authors reviewed and approved the submitted version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Because all findings were a consequence of routine clinical evaluation and diagnostics, and further research did not require further, individual investigations, ethical review board evaluation was not required. Written and oral consent was obtained from LAR.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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