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CASE REPORT

The phenotypic spectrum of the Cornelia de Lange-like "Alazami-Yuan syndrome": A case report of the 7th diagnosed individual and review of the literature

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Key Clinical Message

We present a 17-year-old female with a childhood clinical diagnosis of Cornelia de Lange Syndrome (CdLS), however later genetic testing identified compound heterozygous variants in *TAF6*, consistent with AYS. This case report adds to the phenotypic spectrum observed in AYS, and draws connections to transcriptional pathways between CdLS and AYS.

KEYWORDS

Alazami-Yuan syndrome, Cornelia de Lange-like syndrome, TAF6, transcriptomopathies

1 | INTRODUCTION

Alazami-Yuan syndrome (AYS) is an autosomal recessive Cornelia de Lange-like syndrome caused by loss of function variants in *TAF6*.[1–4] *TAF6* encodes a TATA-binding protein associated factor (TAF) included in the transcription factor II D (TFIID) multiprotein complex that mediates interactions with transcriptional activators and epigenetic markers during early steps of gene transcription.[5] Cornelia de Lange syndrome (CdLS) and AYS have significant phenotypic overlap, including similar dysmorphic facial features, intellectual disability, growth restriction, limb abnormalities, sensorineural hearing loss, and feeding difficulties. However, none of the six AYS individuals reported to date have met clinical criteria to confer a clinical diagnosis of classic CdLS. Here, we report the 7th individual with AYS.

2 | CASE HISTORY

The individual is a 17-year-old female presenting with CdLS-like features including dysmorphic facial features, slowed growth, and sensorineural hearing deficits that led to a clinical diagnosis of CdLS in early childhood. However, genetic testing later in life revealed compound heterozygous variants in *TAF6* consistent with AYS.

There were no recognized maternal complications during pregnancy, and the individual's family history was non-contributory. She was born at 36 weeks gestation via c-section due to preterm labor and breech presentation. She was small for gestational age (1.79 kg, <3%ile for age) and remained in the NICU for 2 weeks for management of poor feeding and a congenital left cataract. At 6 months of age, she developed aspiration pneumonia prompting nasogastric placement. By that time, she had multiple

Annie Pappas, Mary Mooney, and Katherine Kohnen made equal contributions as co-first authors.

dysmorphic features including thick arched eyebrows, long eyelashes, widely spaced teeth, and microcephaly, leading to a clinical diagnosis of CdLS. Genetic testing was pursued and resulted with nondiagnostic karyotype, microarray, *NIPBL* and *SMC1A* sequencing, and *NIPBL* deletion/duplication testing. At 11 months of age, she had a G-tube placed with a simultaneous nissen fundoplication for severe reflux. Global developmental delay was evident by 12 months of age, with further workup demonstrating bilateral mild to moderate sensorineural hearing loss.

At 23 months of age, she had a brain and lumbar sacral MRI only notable for borderline decreased myelination for age. She was enrolled in early intervention services, with an emphasis on learning sign language and the use of other forms of non-verbal communication.

At age 9, she began having episodes of painful, bilateral #2–3 distal interphalangeal and #3 proximal interphalangeal joint swelling and articular erythema that lasted up to 4 days before resolving spontaneously. Episodes occurred 3–4 times each year. She also had transient discoloration of fingers and toes 2–5 that typically lasted 1 hour before resolving without known triggers. Further evaluation showed an elevated erythrocyte sedimentation rate (44; reference range: 0–20 mm/hour). At age 16, she was diagnosed with palindromic rheumatism. Antibody testing was positive for SS-B, prompting ongoing monitoring for Sjogren's syndrome. In the same year, she was diagnosed with generalized joint hypermobility and lumbar scoliosis (15°).

At age 16, she was again evaluated by genetics. Her physical exam was notable for a friendly female with microcephaly, arched eyebrows, broad nasal bridge, prominent chin, hypertrichosis on her abdomen and back, and thinned hair on her head with a receding hairline (Figure 1).

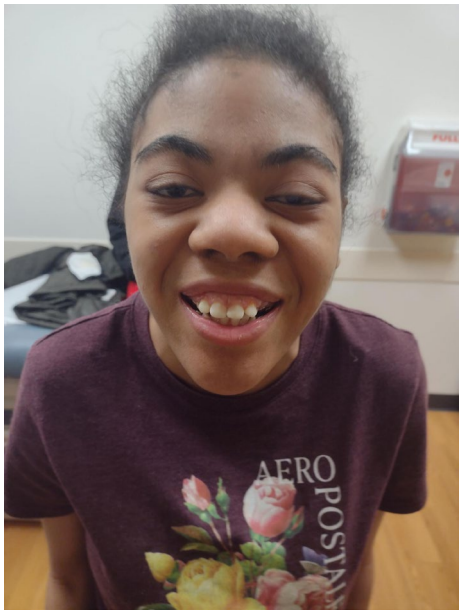

FIGURE 1 Patient image at age 16.

3 | METHODS

A 2775-gene sequencing panel for autism spectrum disorder/developmental disability (DD)/intellectual disability (ID) was obtained from the individual and her parents, and the trio analysis revealed two likely pathogenic variants in a compound heterozygous state in *TAF6*: paternally inherited NM_005641.3:c.212T>C p.(Ile71Thr) and maternally inherited NM_005641.3:c.1863dup p.(Thr622HisfsTer?) (also known as c.323T>C p.(Ile108Thr) and c.1974dup p.(Thr659HisfsTer?) in NM_001190415.1). Other CdLS genes (*NIPBL*, OMIM 122470; *BRD4* (Alesi et al, 2019); *SMC3*, OMIM 610759; *RAD21*, OMIM 614701;, *SMC1A*, OMIM 300590; and *HDAC8*, OMIM 300882) and CdLS-like genes (*AFF4*, OMIM 616368;, *ANKRD11*, OMIM 148050; *ASXL1*, OMIM 605039; *EP300*, OMIM 613684; and *TAF1*, OMIM 300966) are included in this panel, but there were no reportable variants detected in these genes.

Since her symptoms were specific for a CdLS-like syndrome in which she was known to be a compound heterozygote with likely pathogenic *TAF6* variants, she was given a clinical diagnosis of Alazami-Yuan syndrome.

4 | CONCLUSION

Now at 17 years of age, she continues to demonstrate small stature (weight 41.7 kg, 0.74%ile; height 152.4 cm, 4.96%ile; HC 48.8 cm, <0.01%ile). She has a progressive left cataract with anticipated surgical removal planned in the next year. Endocrinology is monitoring her hair loss. A recent video swallow study showed moderate intermittent vestibular penetration with thin liquids without tracheal aspiration, though most nutrition continues to be taken orally with use of her G-tube about once per month. Her scoliosis has remained unchanged at 15 degrees without intervention. She remains nonverbal, but with hearing aids she can respond to speech with sign language. She receives speech, occupational, and physical therapy services through school, and she has not demonstrated regression of skills.

5 | DISCUSSION

Alazami-Yuan syndrome was first reported in 2015, and there are six individuals with this syndrome from four families reported in literature to date. This individual represents the seventh case of AYS, with biallelic likely pathogenic presumed loss of function variants in *TAF*6. The likely pathogenic c.212T>C p. (Ile71Thr) variant

identified in this individual has been previously reported in a homozygous state in four individuals from two families with AYS and segregated with the disease (Table 1). In vitro functional studies indicated that this variant resulted in disruption between *TAF6* and other TFIID components which may lead to instability of the overall protein complex.[2] The c.1863dup variant has not been previously reported in the literature or in the ClinVar

TABLE 1 Features of Alazami-Yuan syndrome individuals in comparison to classic CdLS individuals.[8]

	Reported individual	Lin et al, 2022	Tuc et al, 2020	Yuan et al, 2015	Yuan et al, 2015	TAF6 Individuals		CdLS Individuals[c]
Sex	F	M	M	M	2M/1F[a]	NA		NA
Impacted Gene	TAF6	TAF6	TAF6	TAF6	TAF6			
Allele 1	c.212T>C	c.1052delT	c.212T>C	c.136C>T	c.212T>C			
	p.Ile71Thr	p.I351Tfs*40	p.Ile71Thr	p.Arg46Cys	p.Ile71Thr			
Allele 2	c.1863dup	c.76>T	c.212T>C	c.136C>T	c.212T>C			
	p.Thr622HisfsTer?	p.Met26Leu	p.Ile71Thr	p.Arg46Cys	p.Ile71Thr			
Age	17	11	18	4	NR			
Craniofacial								
Low hairline	−	NR	−	+	3/3	5/7	71%	NR
Synophrys	−	−	+	+	3/3	5/7	75%	98%
Arched eyebrows	+	+	+	+	3/3	7/7	100%	97%
Prominent nasal bridge	−	+	+	+	3/3	6/7	88%	NR
Long eyelashes	+	NR	+	+	2/2[b]	5/5	100%	>90%
Ptosis	+	−	−	NR	NR	1/3	33%	60%
Long philtrum	+	−	−	+	0/2[b]	2/7	29%	91%
Microcephaly	+	−	+	+	NR	3/4	60%	>90%
Thin upper lip	−	+	+	+	2/2	5/6	71%	>90%
Hypertrichosis	+	−	−	+	3/3	5/7	71%	>80%
Micrognathia	−	−	−	NR	2/2	2/5	33%	80%
High arched palate	−	NR	+	NR	NR	1/2	67%	30%
Neurologic								
Developmental delay	+	−	+	+	3/3	6/7	88%	>95%
Intellectual disability	+	−	+	+	3/3	6/7	88%	>95%
Hypotonia	+	−	NR	NR	NR	½	67%	NR
Epilepsy	−	−	−	NR	NR	0/3	0%	25%
Growth								
Prenatal growth failure	+	+	−	NR	NR	2/3	75%	94%
Postnatal growth failure	+	−	−	+	NR	2/4	40%	>95%
CDH	−	−	−	−	NR	0/4	0%	5%–20%
Musculoskeletal								
Scoliosis	+	+	NR	NR	NR	2/2	100%	33%
Oligodactyly	−	−	−	NR	0/3	0/6	0%	25%
CHD	−	−	−	NR	NR	0/3	0%	30%
Hearing loss	+	−	−	NR	NR	1/3	25%	80%
Consanguinity	−	−	+	+	3/3	5/7	75%	NA
Other symptoms	Palindromic rheumatism	−	Inguinal hernia, nystagmus	Cryptorchidism	NR			

Abbreviations: CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; NA, not applicable; NR, feature not reported.

[a]Limited phenotypic information available, so 3 indviduals from same family grouped into one column.

[b]Features assessed from photos of 2 males included in study; no image of female was available.

[c]Data from GeneReviews unless otherwise cited.

database, nor has it been reported in any large population databases such as the genome aggregation database (gnomAD). This 1-bp duplication variant in the last exon is thought to disrupt the reading frame and extend the coding region by replacing the last 56 amino acid codons with 115 new amino acid codons. The new stop codon at the end of the 3′ untranslated region results in mRNA without a 3′ UTR and canonical polyadenylation site, where the poly(A) tail is added. The 3′ UTR plays an important role in directing mRNA translation, stability, localization, protein abundance, protein–protein interaction, as well as protein function.[6] The subsequent blood transcriptome analysis specific to this targeted variant, c.1863dup, showed the mRNA sequence is consistent with heterozygous c.1863dup variant, without significant changes in transcript levels or splicing patterns in this gene comparing to controls. This suggests the variant does not trigger mRNA decay and its effect is more likely at the protein translation initiation, protein stability, or protein function level. Additional functional studies at the protein level may provide evidence to further characterize this variant.

Table 1 provides a phenotype comparison of this individual, the six previously reported individuals with AYS, and individuals with classic CdLS. Arched eyebrows and long eyelashes were the only universal findings among AYS individuals, though a low hairline, synophrys, prominent nasal bridge, thin upper lip, hypertrichosis, DD/ID, and prenatal growth failure were frequently seen. Prominent nasal bridge and low hairline were the only features in AYS individuals not reported in CdLS individuals. In contrast, no individuals with AYS had a short nose with a concave nasal ridge, hand anomalies, or congenital diaphragmatic hernia that are more specific features of CdLS. While no other reported individuals with AYS had sensorineural hearing loss, it is reported in up to 40% of patients with CdLS,[7,8] implying a role of sensorineural hearing loss in AYS as well, or another area of potential overlap between the conditions. This case further supports significant phenotypic overlap between AYS and CdLS while maintaining that these are two clinically distinct conditions. This is supported by the CdLS clinical scoring system.[7] Table 2 demonstrates that all AYS indiviuals have enough symptoms to merit CdLS testing, though none meet enough criteria for a clinical diagnosis of classic CdLS. Only one individual with AYS would qualify for a non-classic CdLS diagnosis, primarily based on his facial features.[2]

Autoimmune disease has not been previously described in patients with AYS, but may be a new finding associated with the disease. Palindromic Rheumatism/Sjogren's Disease has not previously been reported as a feature of CdLS. It is possible that autoimmunity may

TABLE 2 Clinical CdLS score of Alazami-Yuan syndrome individuals.

	Reported individual	Lin et al, 2022	Tuc et al, 2020	Yuan et al, 2015 Individual	Yuan et al, 2015 Family[a]
Cardinal features (2 points)					
Synophrys and/ or thick eyebrows	+	−	+	+	+
Short nose, concave nasal ridge, and/or upturned nasal tip	−	−	−	−	−
Long and/or smooth philtrum	+	+	−	+	−
Thin upper lip vermilion and/or downturned corners of mouth	−	+	−	+	+
Hand oligodactyly and/or adactyly	−	−	−	−	−
Congenital diaphgragmatic hernia	−	−	−	−	−
Suggestive Features (1 point)					
Global developmental delay and/or intellectual disability	+	−	+	+	+
Prenatal growth retardation	+	+	−	−	NR
Postnatal growth retardation	+	−	−	+	NR
Microcephaly	+	−	+	+	NR
Small hands and/or feet	−	−	−	−	NR
Short fifth finger	−	−	−	−	NR
Hirsutism	−	−	−	+	+
Clinical score	**8**	**5**	**4**	**10**	**6**

Note: >11 points, of which at least three are cardinal: classic CdLS. 9 or 10 points, of which at least two are cardinal: non-classic CdLS. 4–8 points, of which at least one is cardinal: molecular testing for CdLS indicated. <4 points: insufficient to indicate molecular testing for CdLS.

[a]Insufficient information to report the three members of this family independently.

be a unique feature of AYS, or that this patient may have comorbid autoimmune disease. Patients with CdLS are more likely to present with immunodeficiencies such as antibody deficiency rather than autoimmune conditions.[7] Interestingly, TFIID does mediate epigenetic interactions in early gene transcription,[5] and epigenetic changes have been shown to play a role in autoimmune diseases such as Sjogren's Syndrome.[9] CD4+ T cells and costimulatory molecules both have been described to be epigenetically altered, potentially contributing to systemic autoimmune rheumatic diseases.

A connection between congenital cataract and TAF6 is not known, and has not yet been documented in patients with AYS. Cataracts are a rare but previously described feature of CdLS.[7] Congenital cataracts have been known to be associated with pathogenic variants in transcription factor genes such as *HSF4*, *FOXE3*, *MAF*, and *PITX3*,[10] so it is possible that dysfunction of the TFIID complex through its role in transcriptional regulation has an implication in congenital cataracts. This role has not yet been described, but is intriguing.

CdLS is considered a cohesinopathy caused by pathogenic variants in multiple genes in the cohesin pathway, including *NIPBL*, *SMC1A*, *SMC3*, *RAD21*, and *HDAC8*. Cohesin mediates interactions between sister chromatids and is involved in critical cellular processes such as repairing DNA, gene expression, and gene transcription.[11] While *TAF6* does not directly impact cohesins, it does play significant roles in transcription through stabilization of the TFIID complex. This shared widespread disruption of gene transcription may provide the link between CdLS and AYS. This is supported by evidence that other genes that play direct roles in gene transcription such as *AFF4*, *ANKRD11*, *EP300*, and *TAF1* also cause a CdLS-like phenotype[12] while lacking sufficient features to consider these as true causes of CdLS. Overall, this suggests that the "cohesinopathies" that explicitly impact cohesin function cause a classic CdLS phenotype, while the "transcriptomopathies" that more explicitly impact transcription leads to a CdLS-*like* phenotype. More research is needed to better understand the distinction between pathogenic genetic changes that impact cohesins and transcription proteins.

In conclusion, this individual represents the seventh reported case of Alazami-Yuan syndrome. Her clinical course further supports that loss of function of *TAF6* leads to symptoms similar to, but ultimately distinct from CdLS, with this similarity likely driven by transcription dysregulation that occurs in both conditions.

AUTHOR CONTRIBUTIONS

Annie Pappas: Writing – original draft; writing – review and editing. **Mary Mooney:** Writing – original draft; writing – review and editing. **Katherine Kohnen:** Writing – original draft; writing – review and editing. **Wenying Zhang:** Supervision; writing – review and editing. **Robert J. Hopkin:** Supervision; writing – original draft; writing – review and editing. **Joshua W. Owens:** Project administration; supervision; writing – review and editing. **Amelle Shillington:** Conceptualization; formal analysis; methodology; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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