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A novel *ARCN1* splice-site variant in a Chinese girl with central precocious puberty, intrauterine growth restriction, microcephaly, and microretrognathia

Guoying Chang[1,2†], Fan Yang[2†], Lingwen Ying[1], Qianwen Zhang[1], Biyun Feng[1], Yao Chen[1], Yu Ding[1], Tingting Yu[3], Ruen Yao[3], Kana Lin[4], Juan Li[1*] and Xiumin Wang[1*]

Abstract

The *ARCN1* gene encodes the delta subunit of the coatomer protein complex I (COPI), which is essential for mediating protein transport from the Golgi complex to the endoplasmic reticulum. Variants in *ARCN1* are associated with clinical features such as microcephaly, microretrognathia, intrauterine growth restriction, short rhizomelic stature, and developmental delays. We present a case of a patient exhibiting intrauterine growth restriction, preterm birth, microcephaly, micrognathia, and central precocious puberty. Whole-exome sequencing identified a novel splice-site variant, NM_001655.5: c.1241 + 1G > A, in the *ARCN1* gene. To our knowledge, this is the first documented case of ARCN1-related syndrome associated with central precocious puberty, contributing to the understanding of the disease phenotype.

Keywords ARCN1-related syndrome, *ARCN1* variant, Central precocious puberty

Introduction

ARCN1-related syndrome (OMIM: 617164) is characterized by intrauterine growth restriction (IUGR), short postnatal stature often rhizomelic, and micrognathia. Additional common features include developmental delays, microcephaly, preterm birth, and genitourinary malformations. Some patients may also experience transient liver dysfunction, glycosylation abnormalities, hepatoblastoma, giant cell hepatitis, and cataracts [1–4]. The phenotypic severity of the syndrome varies significantly among individuals and families, ranging from mild manifestations to intrauterine death or stillbirth.

The *ARCN1* gene, located in the 11q23.3 region, encodes a protein that is a key component of the coatomer, a cytosolic protein complex that binds to dilysine motifs and associates reversibly with Golgi

†Guoying Chang and Fan Yang contributed equally to this work.

*Correspondence:
Juan Li
ljuan_scmc@126.com
Xiumin Wang
wangxiumin1019@126.com
[1]Department of Endocrinology and Metabolism, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, 1678 Dongfang Road, Shanghai 200127, China
[2]Department of Clinical Research Ward, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China
[3]Department of Medical Genetics and Molecular Diagnostics laboratory, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China
[4]Department of Clinical Research Center, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

non-clathrin-coated vesicles. This complex mediates the reverse transport of proteins from the Golgi apparatus through the endoplasmic reticulum (ER) [3, 5, 6]. Prior functional studies have demonstrated that loss-of-function variants in *ARCN1* lead to defective type I collagen transport and reduced collagen secretion, corroborating its role as the delta subunit of the coat protein complex I (COPI) involved in intracellular protein transport [3].

In the present study, whole-exome sequencing (WES) was performed on DNA samples from a Chinese girl presenting with IUGR, preterm birth, microcephaly, micrognathia, and central precocious puberty (CPP). A novel heterozygous variant of the *ARCN1* gene was identified, resulting in a diagnosis of ARCN1-related syndrome. This case represents the first documented instance of an *ARCN1* heterozygous mutation in China and the first reported case of the CPP phenotype associated with this syndrome worldwide.

Clinical reports

General information

The patient was referred to the Department of Endocrinology and Metabolism at Shanghai Children's Medical Center, Shanghai Jiaotong University School of Medicine, for evaluation of precocious puberty and microretrognathia. Comprehensive counseling was provided to the proband and her parents, and informed consent was obtained. The study was approved by the ethics committee of the Shanghai Children's Medical Center.

The patient was born preterm at 35 weeks of gestation, with a birth weight of 1.3 kg and a length of 38 cm. The postnatal course was uncomplicated. She is the second child of a healthy, nonconsanguineous couple, who also have a 15-year-old healthy son. The couple had previously experienced four spontaneous abortions. The patient was referred to our department at 7 years and 3 months of age due to early breast development. Physical examination revealed Tanner stage II breast development and Tanner stage I pubic hair development. Her height and weight were within the normal range for her age (height: 122 cm, 25th-50th percentile; weight: 23.5 kg, 50th percentile). Her body mass index (BMI) was 15.7 kg/m^2 (25th-50th percentile), and her head circumference measured 49.8 cm (less than the third percentile). Notable physical features included a bulbous nasal tip, microcephaly, micrognathia, and brachydactyly (Fig. 1a、1b).

Blood biochemical tests, including assessments of blood glucose, liver function, and kidney function, were normal. Endocrine evaluations showed normal thyroid function and the following hormone levels: insulin-like growth factor-1 (IGF-1) at 279.0 ng/ml (reference range: 68.6-352.2), cortisol at 14.08 μg/dl (reference range: 6.4–22.8), carcinoembryonic antigen (CEA) at 0.53 μg/L (reference range: 0.0–5.0), alpha-fetoprotein (AFP) at < 2.00 ng/ml (reference range: 0.0-8.8), and β-Human Chorionic Gonadotropin (β-HCG) at < 0.50 mIU/ml (reference range: 0.0–5.0). Basal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were 0.87 mIU/ml and 3.62 mIU/ml, respectively. The gonadotropin-releasing hormone (GnRH) stimulation test demonstrated a pubertal response, with peak LH and FSH values of 5.97 mIU/ml and 11.99 mIU/ml, respectively (Table 1). Bone age assessment indicated advancement to 11 years (Fig. 1c). Pelvic ultrasound revealed increased sizes of both the uterus (21 × 9 × 19 mm) and ovaries (right ovary: 27 × 11 × 12 mm, left ovary: 24 × 12 × 13 mm), with bilateral ovarian follicles (Fig. 1d and e). Abdominal and cardiac ultrasonography, as well as brain magnetic resonance imaging (MRI), were unremarkable.

Genetic analysis

Genomic DNA was extracted from peripheral blood samples collected from the patient and her parents, using a QIAamp Blood DNA Mini Kit (Qiagen GmbH, Hilden, Germany). Whole exome sequencing and data analysis were performed, as previously described [7]. All suspected variants were confirmed using Sanger sequencing and were validated by parental testing. Manual classification of these variants was then completed using the method recommended by the American College of Medical Genetics and Genomics (ACMG) [8]. The potential pathogenicity of the novel variants was determined using three in silico prediction methods, including MutationTaster (http://www.mutationtaster.org/). We focused on genes associated with central precocious puberty (CPP), such as *MKRN3*, *DLK1*, and *MECP2*. In addition to analyzing allelic variation, we also performed copy number variation (CNV) analysis.

Results

High-throughput sequencing results and sanger sequencing verification

Whole-exome sequencing of the proband and her parents identified a de novo variant in the ARCN1 gene: Chr 11 (GRCh37): g.118464414G > A (NM_001655.5: c.1241 + 1G > A). Sanger sequencing confirmed that this variant was present exclusively in the proband and not in her parents (Fig. 2). This variant has not been previously reported in the Human Genome Mutation Database or in control databases such as the Genome Aggregation Database, Exome Aggregation Consortium, NHLBI Exome Sequencing Project, or the 1000 Genomes Project, indicating it is extremely rare. It has been previously reported in a fetal case in the literature, but no functional validation or parental testing was described in that context.

It may affect the editing processing or expression of mRNA. Based on the American College of Medical

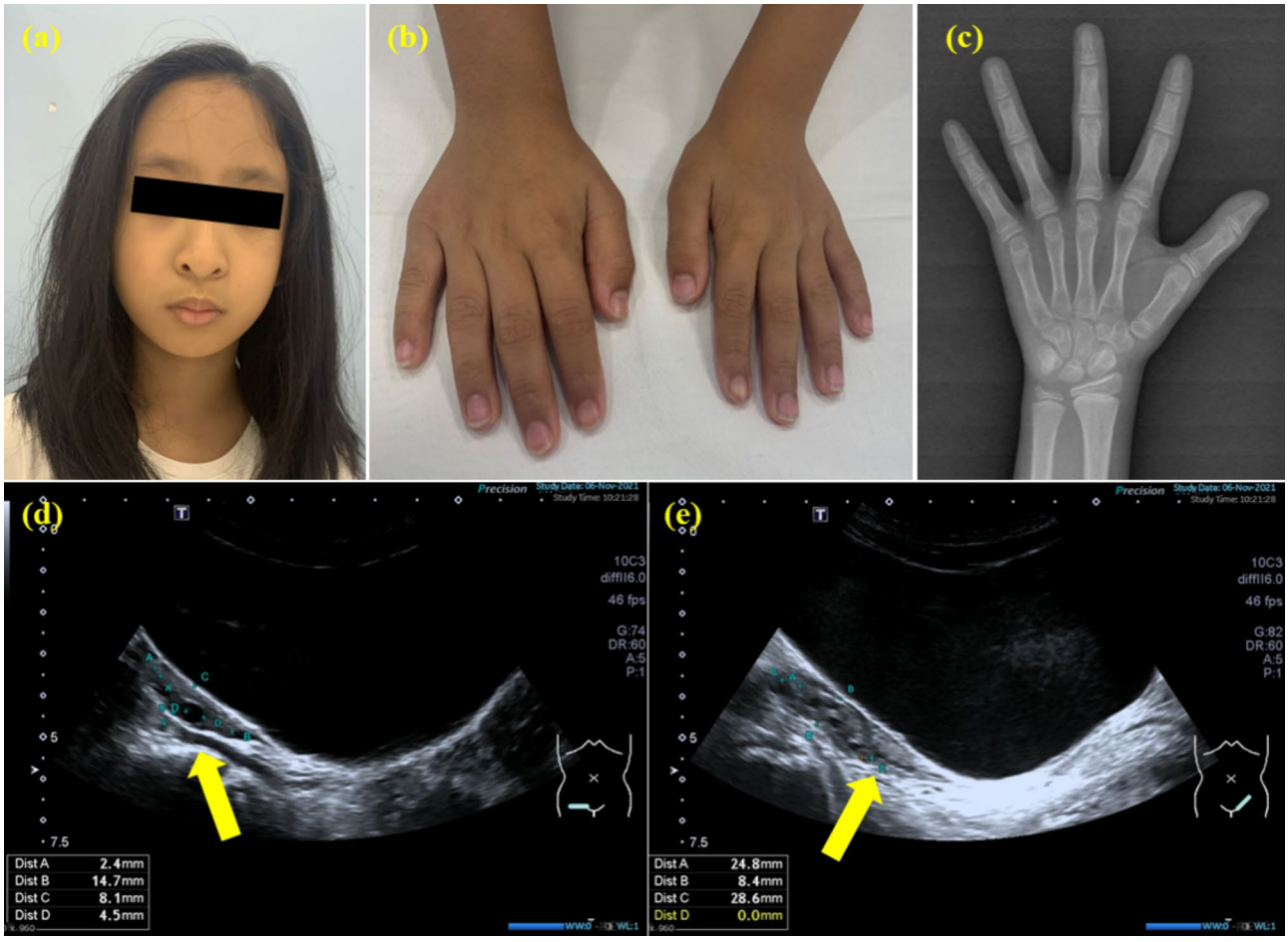

Fig. 1 Clinical characteristics of the patients with ARCN1-related syndrome. (**a**). Facial characteristics including bulbous nasal tip, microcephaly, and micrognathia. (**b**). Brachydactyly. (**c**). The patient's advanced bone age was 11 years, as assessed by the Greulich and Pyle atlas (G&P) method. (**d**) and (**e**). Pelvic ultrasound revealed a 21 × 9 × 19 mm uterus, a 24 × 12 × 13 mm (1.96 ml) left ovary, and a 27 × 11 × 12 mm (1 ml) right ovary. Both ovaries had several follicles, with the largest being greater than 4 mm

Table 1 The results of GnRH stimulation test

Time (min)	LH (mIU/mL)	FSH (mIU/mL)
0	0.13	1.56
30	5.97	9.85
60	4.95	11.43
90	4.19	11.99

Genetics and Genomics (ACMG) variant classification criteria, this variant is classified as "Likely Pathogenic."

Diagnosis, treatment, and follow-up

The clinical, radiological, and laboratory findings supported a diagnosis of impaired final height due to CPP and ARCN1-related syndromes, characterized by intrauterine growth restriction (IUGR), preterm birth, micrognathia, microcephaly, and rhizomelic shortening. To delay epiphyseal closure and preserve growth potential, at 7 years and 6 months old, the patient was given a subcutaneous injection of 3.75 mg leuprorelin acetate for treatment, with the drug administered once every 4 weeks. Meanwhile, recombinant human growth hormone (rhGH) was administered at a dose of 0.1–0.15 U/kg/day for treatment.

During the follow-up period of two years and ten months, sex hormone levels were significantly reduced, and no significant acceleration in bone age was noted (Fig. 3). The patient's annual growth rate averaged approximately 7 cm. At her last visit, at age 10 years and 5 months, her height was 144.9 cm (75th percentile), weight was 38.7 kg (50th-75th percentile) (Fig. 4), and BMI was 18.53 kg/m^2 (50th-75th percentile).

Clinical phenotypes of ARCN1-related syndrome

We present data on 16 patients, including our case and 15 previously reported cases, as well as 6 fetuses from 4 families (Table 2) [1–4, 9]. These cases encompass 16 pathogenic variants in the *ARCN1* gene (Fig. 5). Among these, three variants were recurrent in unrelated patients: c.934 C > T (p.Arg312*), observed in 3 cases; c.654–15 A > G, observed in 2 cases; and c.157_158del

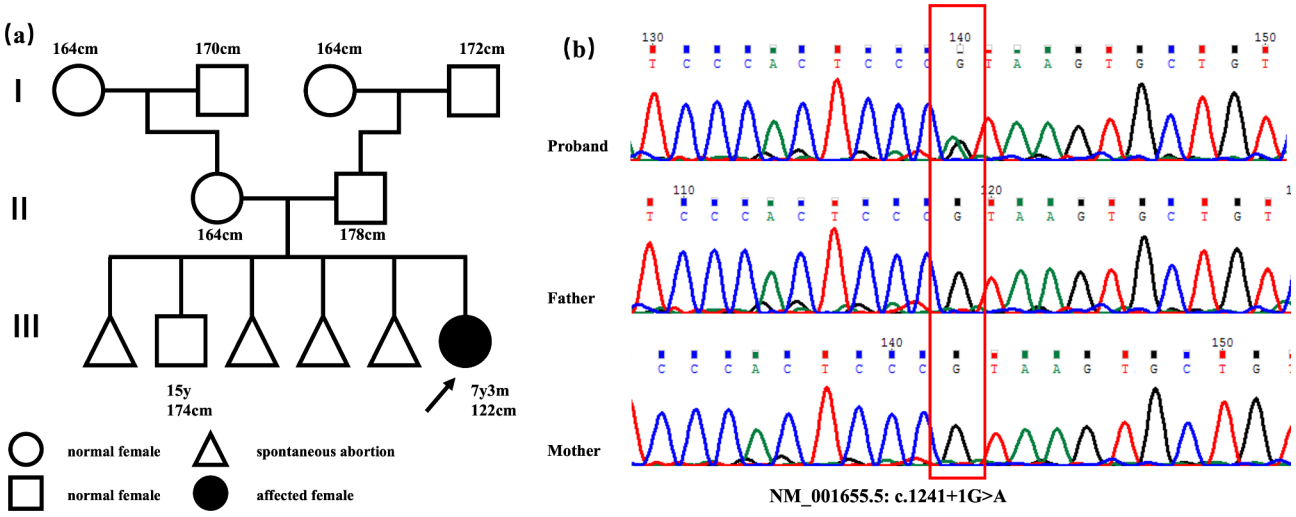

Fig. 2 The patient's family pedigree and results of *ARCN1* gene sequencing. Family pedigree. (**b**) Chromatogram of Sanger sequencing showing a de novo heterozygous *ARCN1* c.1241 + 1G > A mutation in the patient; her parents were normal. The corresponding sequences in which the mutation was found are indicated in a red box

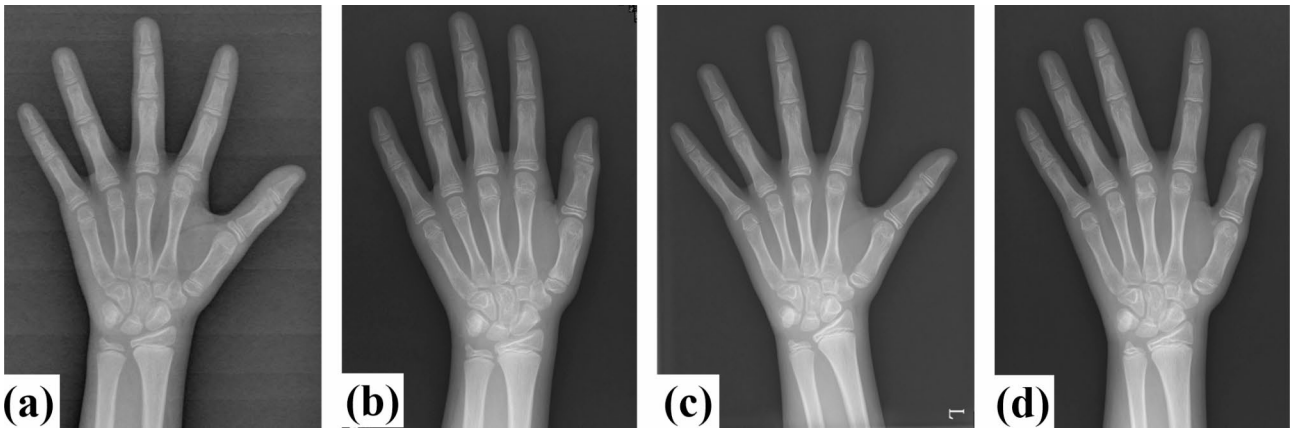

Fig. 3 The patient's age corresponds to changes in bone age. Chronological age was 8 years and 3 months (**a**), 9 years and 3 months (**b**), 9 years and 11 months (**c**), and 10 years and 5 months. There was no significant increase in bone age during the follow-up period

(p.S53C*39), also observed in 2 cases. The c.1241 + 1G > A variant has been previously reported in fetuses in the literature and is also identified in the patients described in this case. Two fetuses exhibited core features of ARCN1-related syndrome, but no *ARCN1* variants were identified in these cases. All 16 patients and 6 fetuses with ARCN1-related syndromes presented with intrauterine growth restriction (IUGR), micrognathia, and short stature. A majority of the patients (12/16, 75%) were born preterm (before 37 weeks of gestation), with an average gestational age of 34.5 weeks (range: 26–40 weeks). Of these patients, 3 (20%) required tracheotomy due to respiratory failure, often associated with micrognathia and preterm birth.

Discussion

In this report, we describe a novel likely pathogenic variant of the *ARCN1* gene identified through whole-exome sequencing (WES), which is associated with ARCN1-related syndromes. The clinical manifestations of the proband—namely intrauterine growth restriction (IUGR), preterm birth, microcephaly, and micrognathia—are consistent with previously documented cases of ARCN1-related syndrome [1].

We describe a novel splice-site variant in *ARCN1*, c.1241 + 1G > A. This variant adds to the *ARCN1* gene profile and enhances the ARCN1-related gene database, facilitating more accurate clinical genetic counseling.

The presence of the same *ARCN1* variant in patients with varying phenotypic severities complicates the establishment of clear genotype-phenotype correlations in this cohort. Prior research suggests that both genetic factors

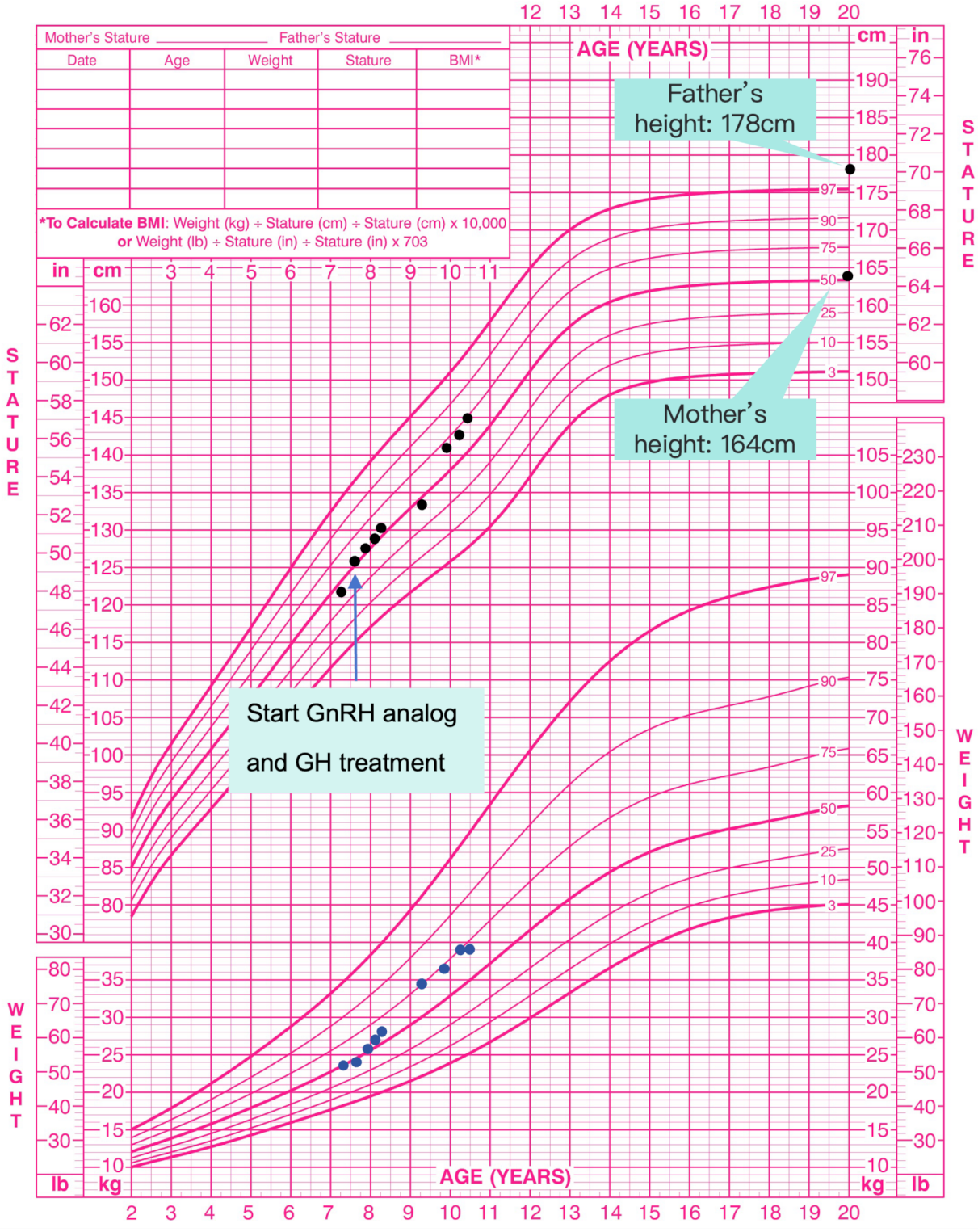

Fig. 4 The growth chart of the patient with ARCN1-related syndrome. The height and weight of the patient ranged from 7 years 4 months to 10 years 5 months. Combined therapy with a GnRH analog and growth hormone was initiated at age 7 years 7 months

Table 2 Clinical features of fetal cases with ARCN1-related syndrome

Clinical feature	Our case	Previously reported cases	Total (%)
Core features			
born prematurely	+	11/15	12/16 (75)
Intrauterine growth restriction	+	21/21[a]	22/22 (100)
Micrognathia	+	21/21[a]	22/22 (100)
Microcephaly	+	17/21[a]	18/22 (81.8)
Cleft palate	-	7/21[a]	7/22 (31.8)
Tracheostomy	-	3/15	3/16 (18.8)
Congenital anomalies			
Congenital heart disease	-	5/21[a]	5/22 (22.7)
Genitourinary anomalies	-	9/21[a]	9/22 (40.9)
Musculoskeletal			
Short stature	+[b]	15/15	16/16 (100)
Rhizomelic shortening	+	13/21[a]	14/22 (63.6)
Joint laxity	-	4/15	4/16 (25)
Neurologic/ development			
Developmental delay/ intellectual disability	-	11/15	11/16 (68.8)
Autism	-	2/15	2/16 (12.5)
Seizure	-	2/15	2/16 (12.5)
Novel features			
Cataract	-	4/15	4/16 (25)
Carbohydrate deficient transferrin abnormalities	-	4/15	4/16 (25)
Giant cell hepatitis	-	3/15	3/16 (18.8)
Liver function abnormalities	-	6/15	6/16 (37.5)
Hepatoblastoma	-	1/15	1/16 (6.25)
Central precocious puberty	+	0/15	1/16 (6.25)

[a] The data of 15 previously reported patients and 6 fetuses were summarized

[b] Short stature was judged according to bone age in our case

and environmental influences may affect the phenotypic outcomes of ARCN1-related syndromes. While associations between *ARCN1* loss-of-function variants and features such as micrognathia, short stature, and developmental delays have been identified, the impact of *ARCN1* missense variants on clinical phenotypes remains uncertain. The lower-than-expected frequency of missense variants in the *ARCN1* gene, compared to genome aggregation databases, suggests that such variants may be associated with milder forms of ARCN1-related syndromes.

Skeletal manifestations of ARCN1-related syndrome primarily affect the appendicular skeleton, with short stature being universally observed. Three patients, including our own, received growth hormone therapy during early childhood, which initially improved height velocity. Over half of the patients (9/16, 56.3%) exhibited rhizomelic shortening and facial dysmorphisms, such as downslanting palpebral fissures, a bulbous nasal tip, and prominent ears. Although 68.8% (11/16) of patients showed developmental delays, these were generally mild, as assessed by neuropsychological tests. The higher rate of preterm births in this cohort may have influenced these developmental outcomes. Micrognathia was present in all patients and fetuses, but only 7 out of 22 individuals (31.8%) had a cleft palate. Congenital heart disease was observed in 5 cases (22.7%), and genitourinary anomalies were found in 9 cases (40.9%). The identification of multiple fetuses with severe ARCN1 pathogenic variants, often leading to intrauterine fetal demise, suggests a potentially broader clinical spectrum than previously recognized. Several rare but notable complications were observed, including cataracts (4/16, 25%), transient liver dysfunction (6/16, 37.5%), glycosylation anomalies (4/16, 25%), giant cell hepatitis (3/16, 18.8%), and hepatoblastoma (1/16, 6.25%) (Table 2). The presence of central precocious puberty (CPP) in this patient has not been previously reported. CPP is an endocrine disorder characterized by the early development of secondary sexual characteristics and accelerated growth and bone maturation before the normal age of puberty (7.5 years for girls and 9 years for boys). It will be of interest to investigate whether CPP is a feature observed in other patients with ARCN1 mutations [10].

ARCN1 encodes the exosome subunit delta protein, a component of the COPI complex. COPI consists of seven subunits: alpha, beta, beta-prime, gamma, delta, epsilon, and zeta-COPs. A primary function of COPI is retrograde vesicular transport of luminal and membrane proteins from the Golgi apparatus back to the endoplasmic reticulum (ER), including the retrieval of resident ER glycoproteins [3, 6, 11]. Other COPI components include the exosome subunits alpha (encoded by COPA) and beta (encoded by COPB2). Pathogenic variants in COPA are associated with autoimmune interstitial lung, joint, and kidney diseases [12, 13], while loss-of-function variants in COPB2 are linked to developmental delays and osteoporosis [14]. Despite their roles as COPI components, ARCN1, COPA, and COPB2 mutations lead to distinct clinical outcomes, suggesting that these COPI subunits may have additional, atypical functions beyond their involvement in COPI.

Phenotypic overlap has been noted between ARCN1-related syndrome and Stickler syndrome (OMIM: 108300), including features such as micrognathia, short stature, and joint laxity, although neurological, ocular, and audiological symptoms can differ. Stickler syndrome is caused by heterozygous loss-of-function mutations in COL2A1 and other collagen genes [15, 16]. The similarities between ARCN1-related and Stickler syndromes may be attributed to impaired cellular collagen secretion. Lzumi et al. demonstrated that *ARCN1* plays a direct role in the intracellular transport of type I collagen and that defects in collagen transport are not secondary to ER stress, underscoring the

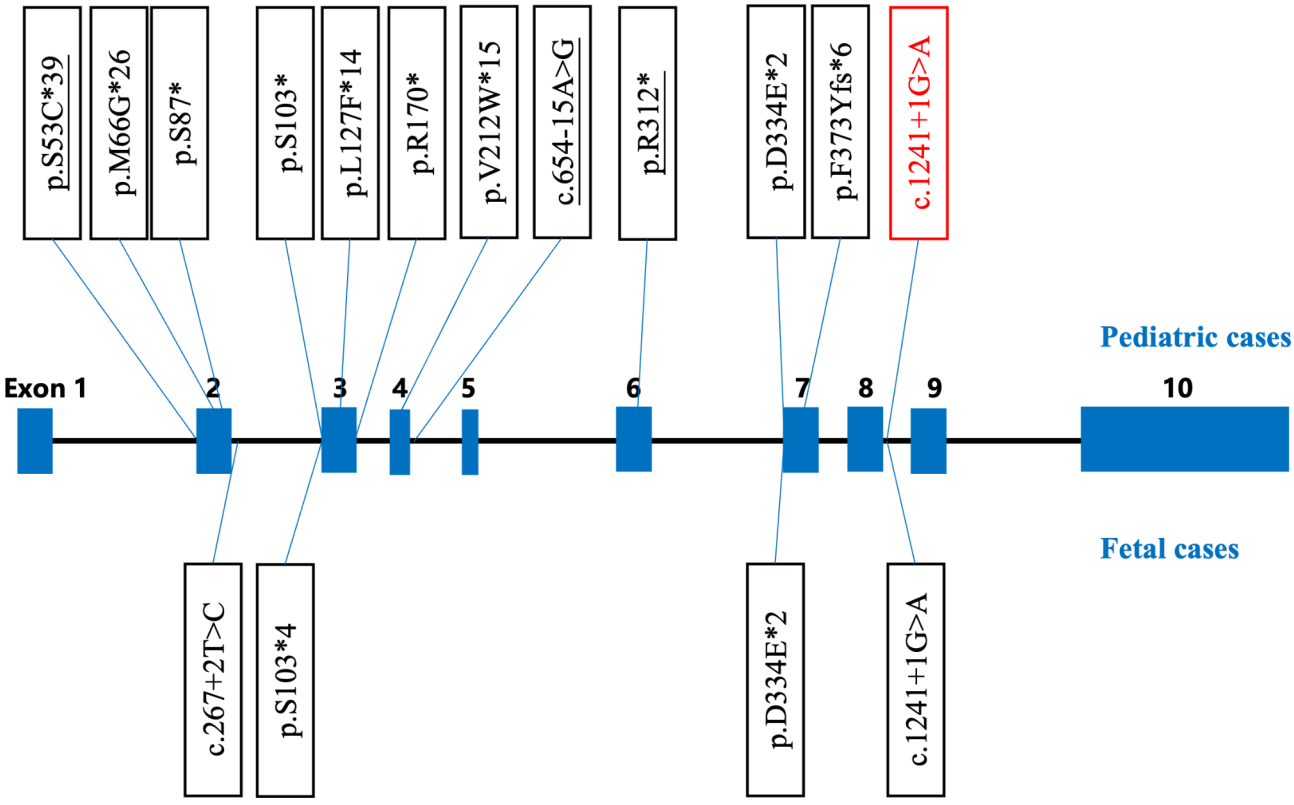

Fig. 5 Structure of *ARCN1* (NM_001655) and the location of the previously-identified *ARCN1* variations. Schematic diagram of the distribution of 15 reported variants, including 12 pediatric cases, and 3 fetal cases

critical role of COPI transport in skeletogenesis, particularly in mandibular bone formation [3].

In contrast to our observation of premature skeletal maturation, we hypothesize that *ARCN1* may also regulate chondrocyte maturation, leading to accelerated bone development. However, further research is needed to validate this hypothesis and clarify the role of *ARCN1* in bone maturation.

Conclusion

In conclusion, this study presents the first case of ARCN1-related syndrome in a Chinese patient and identifies a novel variant, thereby expanding the known genotype spectrum. Notably, the occurrence of central precocious puberty (CPP) in our patient has not been previously documented. As sequencing technologies continue to advance and become more widely applied, we anticipate the identification of additional variants associated with this phenotype. However, the precise genotype-phenotype correlations and the specific underlying mechanisms remain unclear. Further research is needed to determine whether *ARCN1* plays a role in regulating chondrocyte maturation.

Abbreviations

ACMG	American College of Medical Genetics and Genomics
AFP	Alpha-fetoprotein
BMI	Body Mass Index
CEA	Carcinoembryonic Antigen
COPI	Component of the coat protein complex I
CPP	Central Precocious Puberty
ER	Endoplasmic Reticulum
FSH	Follicle-Stimulating Hormone
GnRH	Gonadotropin-releasing hormone
IGF-1	Insulin Like Growth Factor-1
IUGR	Intrauterine growth restriction
LH	Luteinizing Hormone
MRI	Magnetic Resonance Imaging
WES	Whole-Exome Sequencing
rhGH	Recombinant Human Growth Hormone
β-HCG	β-Human Chorionic Gonadotropin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-024-05329-2.

Supplementary Material 1

Acknowledgements

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Author contributions

G.C. and F.Y. conceived and designed the study. L.Y. and Q.Z. performed the clinical evaluations and collected patient data. R.Y. and T.Y. conducted the genetic analyses and interpreted the results. B.F. and Y.C. were responsible for preparing and analyzing the figures. Y.D. and K.L. contributed to the manuscript drafting and critical revisions. J.L. and X.W. provided overall guidance and supervised the research. All authors reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
This study was approved by the ethics committee of Shanghai Children's Medical Center, Shanghai Jiaotong University School of Medicine. All methods were performed in accordance with the relevant guidelines and regulations [International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva.
Council for International Organizations of Medical Sciences (CIOMS); 2016]. Informed consent for publication was obtained from all of the families of individual participants included in the study.

Consent for publication
Written informed consent for publication of their clinical details and clinical images was obtained from the patient's parent of the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests
The authors declare no competing interests.

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Publisher's note