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Expanding the phenotype of alopecia–contractures–dwarfism mental retardation syndrome (ACD syndrome): description of an additional case and review of the literature

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Abstract Alopecia–contractures–dwarfism mental retardation syndrome (ACD syndrome; OMIM 203550) is a very rare genetic disorder with distinct features. To our knowledge, there have been four cases documented to date. In addition, another three patients, previously described as having IFAP syndrome (OMIM %308205), may also have ACD syndrome. We report on one patient with short stature, total alopecia, ichthyosis, photophobia, seizures, ectrodactyly, vertebral anomalies, scoliosis, multiple contractures, mental retardation, and striking facial and other features (e.g. microdolichocephaly, missing eyebrows and eyelashes, long nose, large ears) consistent with ACD syndrome. Results of laboratory testing in the literature case reports were normal, although in none of them, array-CGH (microarray-based comparative genomic hybridization) analysis was performed. In conclusion, the combination of specific features, including total alopecia, ichthyosis, mental retardation, and skeletal anomalies are suggestive of ACD syndrome. We propose that children with this syndrome undergo a certain social pediatric protocol including EEG diagnostics, ophthalmological investigation, psychological testing, management of dermatologic and orthopedic problems, and genetic counseling.

Keywords ACD syndrome · Total alopecia · Ichthyosis · Ectodermal dysplasia · Contractures · Skeletal anomalies

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Introduction

Alopecia–contractures–dwarfism mental retardation syndrome (ACD syndrome; OMIM 203550 [9]) is a very rare genetic disorder first described by Schinzel in a 17-year-old female patient [16]. To date, four cases in total have been documented to our knowledge [5, 17]. Findings included mental retardation, short stature, microcephaly, total alopecia or, in one case, sparse hair suggesting subtotal alopecia, ichthyosis, photophobia, skeletal anomalies, limb anomalies including anomalies of fingers and toes, multiple contrac-

tures and a distinct facial appearance including large ears and long nose. Cytogenetic analyses were performed in three of these cases with normal results.

Though ACD syndrome shares some features with other syndromes such as Karsch-Neugebauer syndrome (OMIM 183800), alopecia-mental retardation syndromes (APMR) 1, 2, and 3 (OMIM %203650, OMIM %610422, Woodhouse-Sakati syndrome OMIM %241080), and alopecia-mental retardation syndrome with convulsions and hypergonadotropic hypogonadism (OMIM 601217), the combination of findings observed in ACD syndrome represents—as previously suggested by Schinzel [16]—a well-defined and recognizable clinical pattern within the large and heterogenous group of ectodermal dysplasias characterised by major skeletal involvement (EDSs) [15]. These include ectrodactyly–ectodermal dysplasia–cleft lip/palate syndrome (EEC; OMIM %129900, #604292), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT; OMIM #103285), limb mammary syndrome (LMS; OMIM #603543), Rapp-Hodgkin syndrome (anhidrotic ectodermal dysplasia with cleft lip/palate; OMIM #129400), ankyloblepharon–ectodermal defects–cleft lip/palate syndrome (AEC; OMIM #106260), ectodermal dysplasia-ectrodactyly-macular dystrophy syndrome (EEM; OMIM #225280), tricho-dento-osseous syndrome (TDO; OMIM #190320), Ellis-van Creveld syndrome (EvC; OMIM #225500), lacrimo-auriculo-dento-digital

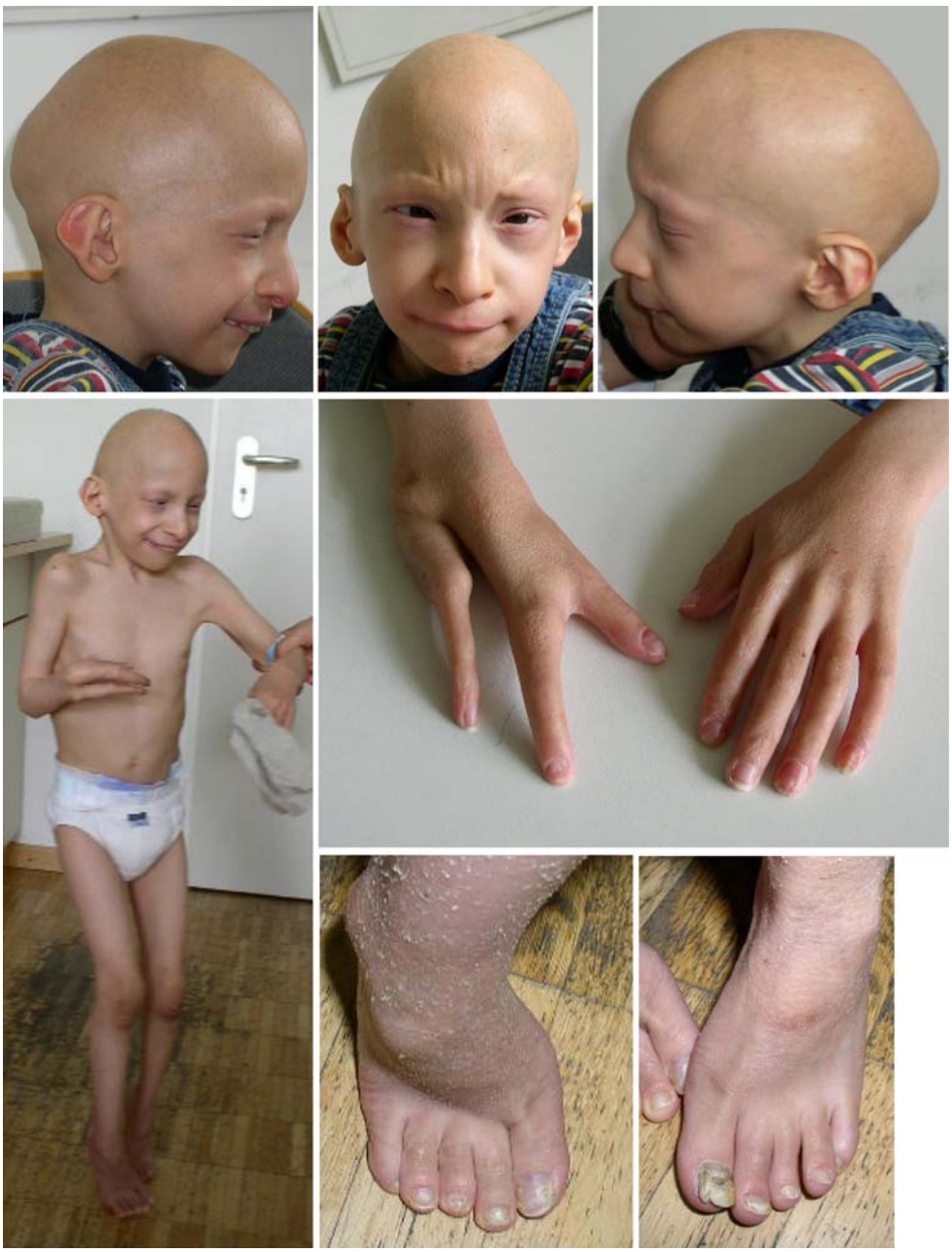

Fig. 1 Patient at the age of 10 years 1 month showing distinct dysmorphic features, including microdolichocephaly, high forehead, total alopecia, absent eyebrows and eyelashes, photophobia, hypertelorism, slightly upslanting palpebral fissures, nystagmus, strabismus convergens, hypolacrimation, long nose, short and flat philtrum, thin upper and lower lip, low-set, broad ears, ichthyosis, hyperkeratotic area at the back, ectrodactyly of the right hand, long fingers, zygodactyly of the second and third toes, contractures of knees and hips, and pes equinus

syndrome (LADD; OMIM #149730), cranio–ectodermal dysplasia (OMIM %218330), and ichthyosis follicularis alopecia and photophobia (IFAP; OMIM %308205) syndrome.

The patient described by Martino 1992 [13] with ichthyosis follicularis alopecia and photophobia (IFAP; OMIM %308205) syndrome as well as the two brothers reported by Mégarbané 2004 [14] with IFAP syndrome may have been misdiagnosed and instead have ACD syndrome, because these three patients share skeletal findings consistent with ACD syndrome. Cytogenetic results in these patients were normal.

Clinical report

The index patient is the first child of unrelated healthy parents from Turkey. The boy was delivered after an uneventful pregnancy at 37 weeks of gestation. His birth length (42 cm), and his birth weight (2,160 g) were below the normal range (< p 10). Information about his head circumference at birth is not available. He had breathing difficulties after birth necessitating respiratory assistance. Feeding problems due to muscular hypotonia in the neonatal period required tube feeding. He had ectrodactyly

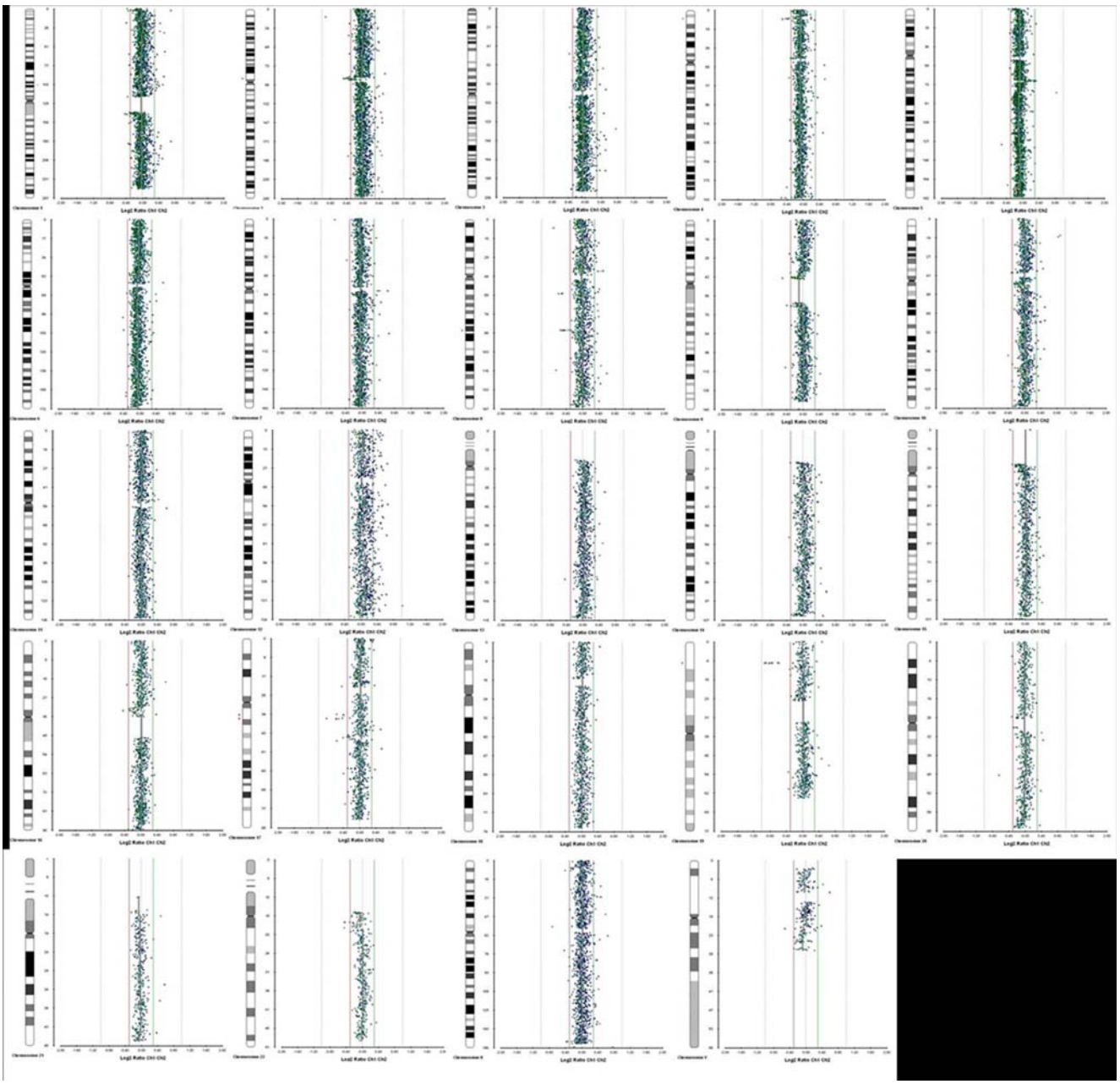

Fig. 2 Array-CGH profile in our patient. Six aberrations were detected including deletions of 2p11.2, 4p16.1, 8q21.2, 17q12, and 19p13.2 as well as duplication of 7q11.1. However, all of these aberrations can be classified as genomic variants [4]

of the right hand. Eye findings consisted of nystagmus, strabismus convergens, and hypolacrimation. No other ocular abnormalities were described in the ophthalmological examination, especially no macular pathology. The child's further development was severely delayed. He started sitting at the age of 7 years. He was able to stand with assistance on the tips of his toes and could crawl at the age of 10 1/12 years. Though he was not able to speak at the age of 10, he was friendly, and communicated with gestures.

The boy had recurrent respiratory infections including bronchitis at the age of 4 1/2 months. At this age, microcephaly, total alopecia, and ichthyosis congenita confirmed by electron microscopical examination were noted. Cryptorchidism was present. Laboratory investigations

Table 1 Comparison of the main findings of the literature cases with ACD syndrome and the present case (M: male; F: female; + : trait is present; −: trait is absent; ?: not-informative, i.e. trait was described neither as present nor as absent in the patient)

	Patient							
Trait	1	2	3	4	5	6	7	8
Gender	F	M	M	M	M	M	M	M
Mental retardation	+	+	+	+	+	+	+	+
Alopecia/sparse hair	+	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	+	+	+
Dolichocephaly	−	+	−	−	?	?	?	+
Brachycephaly	+	−	+	+	?	?	−	−
Turricephaly	−	+	−	−	−	−	−	+
High forehead	+	+	−	−	+	+	+	+
Short stature	+	+	+	+	+	+	+	+
Ichthyosis	+	−	+	+	+	+	+	+
Hyperkeratosis	+	−	+	+	+	+	+	+
Hypohidrosis	−	−	−	+	+	−	−	−
Ocular findings	?	+	+	+	+	+	+	+
Photophobia	−	?	+	−	+	+	+	+
Absent eyebrows	+	+	+	−	+	+	+	+
Absent eyelashes	+	+	+	−	+	+	+	+
Hypertelorism	−	+	+	?	+	−	?	+
Long, prominent nose	+	+	+	+	+	+	?	+
Hypolacrimation	?	?	+	−	?	−	−	+
Short philtrum	+	+	+	+	+	+	+	+
Flat philtrum	+	+	−	−	+	?	?	+
Thin upper lip	+	+	−	−	?	+	?	+
Thin lower lip	−	+	−	−	−	−	?	+
Teeth findings	−	+	+	+	+	−	−	−
Low-set ears	−	+	+	+	−	−	−	+
Broad ears	+	+	−	+	?	+	+	+
Posteriorly rotated ears	+	+	+	−	?	?	+	+
Multiple contractures	+	+	−	+	−	−	−	+
Skeletal abnormalities	+	+	+	+	+	+	?	+
Kyphosis/ scoliosis	+	+	+	+	+	?	?	+
Limb anomalies	+	+	?	?	−	−	+	+
Cryptorchidism	?	+	−	+	?	+	?	+
Recurrent respiratory infections	?	?	+	+	+	?	?	+
Seizures	−	−	−	−	+	+	−	+
Brain abnormalities	?	?	?	?	+	?	?	?
Syringomyelia	?	?	?	?	?	?	?	+

Patient 1: Schinzel [16]
Patient 2: van Gelderen [17]
Patient 3: Dumic et al. [5], case 1
Patient 4: Dumic et al. [5], case 2
Patient 5: Martino et al. [13]
Patient 6: Mégarbané et al. [14], case 1
Patient 7: Mégarbané et al. [14], case 2
Patient 8: patient in this study

as well as hormone analyses were normal. No abnormalities were found on abdominal sonography and echocardiography. At the age of 3 years, the patient developed seizures, which were adequately controlled by antiepileptic medication. In addition, cranial magnetic resonance (MR) imaging was performed, showing normal brain morphology. Laryngotracheoscopy and digital pharyngography were performed because of swallowing problems and velum paresis was detected. At the age of 2 years 10 months, bilateral orchidopexy and herniotomia were performed. At the age of 3 years 11 months, radiological analyses revealed butterfly vertebra at TH 8 and a severe kyphoscoliosis.

At the age of 10 years 1 month (Fig. 1), he presented as a cooperative, mentally retarded boy with short stature and distinct dysmorphic features. These findings included microdolichocephaly, high forehead, total alopecia, absent eyebrows and eyelashes, photophobia, hypertelorism, slightly upslanting palpebral fissures, nystagmus, strabismus convergens, hypolacrimation, long nose, short and flat philtrum, thin upper and lower lip, low-set, broad ears, ichthyosis, hyperkeratotic area at the back, ectrodactyly of the right hand, long fingers, zygodactyly of the second and third toes, contractures of knees and hips, and pes equinus. Height (105 cm), weight (13 kg), and head circumference (49 cm) were below the normal range (< p 3).

Laboratory results

Chromosome analysis and subtelomere fluorescence in situ hybridization (FISH) yielded normal results. Molecular genetic analysis was performed because mutations of the *TP73L* gene have been reported to be causative for several syndromes with ectodermal dysplasia characterised by skeletal involvement (EDSs), including ectrodactyly–ectodermal dysplasia–cleft lip/palate syndrome (EEC; OMIM %129900, #604292), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT; OMIM #103285), limb mammary syndrome (LMS; OMIM #603543), as well as Rapp-Hodgkin syndrome (anhidrotic ectodermal dysplasia with cleft lip/palate; OMIM #129400) and ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC; OMIM #106260). Sixteen fragments of exon 1 to 15 of the *TP73L* gene were amplified by PCR and sequenced as described previously by Celli 1999 [3]. No causative mutation was observed in any of the exon or exon-intron boundaries.

To investigate the patient's genomic DNA for submicroscopic deletions or duplications we used a whole genome tiling path BAC array consisting of 36,000 BAC clones. Array-CGH analysis was performed as described previously [11]. Patient's and reference DNA were labelled using Bioprime CGH labelling kit (Invitrogen) and hybridized on the array (Slide-Booster; Implen GmbH, Germany). Analysis and visualization were performed with BlueFuse software (Bluegenome, UK). Copy number changes were determined by a conservative log2ratio threshold (gain ≥0.3; loss ≤−0.3). Profile deviations consisting of three or more neighbouring BACs are considered as genomic aberrations.

We detected six genomic aberrations: deletions of genomic regions 2p11.2, 4p16.1, 8q21.2, 17q12, and 19p13.2 as well as a duplication of 7q11.1. However, all of these aberrations have been classified as genomic variants [4]. These variants are of no pathogenetic relevance and thus were not considered causative for the observed phenotype (Fig. 2).

Discussion

ACD syndrome was first described by Schinzel 1980 [16] and has a distinct phenotype including short stature, microcephaly, alopecia, ichthyosis follicularis, photophobia, contractures, skeletal anomalies, and some dysmorphic features (Table 1). As suggested by Schinzel [16], this combination of traits represents a well-defined and recognizable clinical syndrome within the large group of ectodermal dysplasias with major skeletal involvement as described by Priolo and Lagana in 2001 [15]. In addition, ACD syndrome shares a unique combination of features with the ichthyosis follicularis atrichia and photophobia syndrome (IFAP; OMIM %308205). The cardinal features of IFAP are congenital alopecia, ichthyosis follicularis, and photophibia. Patients with IFAP may also present with mental retardation, short stature, and microcephaly, but they do not have

Table 2 Main manifestations of alopecia–contractures–dwarfism mental retardation (ACD) syndrome and ichthyosis follicularis atrichia and photophobia (IFAP) syndrome

Trait	ACD syndrome	IFAP syndrome
Mental retardation	+	+
Alopecia	+	+
Microcephaly	+	+
Short stature	+	+
Ichthyosis	+	+
Hyperkeratosis	+	+
Ocular findings	+	+
Photophobia	+	+
Absent eyebrows	+	+
Absent eyelashes	+	+
Teeth findings	+	+
Brain abnormalities	+	+
Seizures	+	+
Multiple contractures	+	−
Skeletal abnormalities	+	−
Kyphosis/scoliosis	+	+
Limb anomalies	+	−

contractures or skeletal anomalies. Therefore, the patient described by Martino in 1992 [13] with IFAP syndrome who had vertebral anomalies (clefting of dorsal vertebral bodies and platyspondyly) may have been misdiagnosed and actually has ACD syndrome. This may also be true for the two brothers, one with ectrodactyly, reported by Mégarbané in 2004 [14]. It is noteworthy that all patients with ACD syndrome described so far had ichthyosis follicularis, except for the patient described by van Gelderen in 1979 [17] and the patient described by us, who has ichthyosis vulgaris. The broad overlap of clinical features in both syndromes suggests that ACD and IFAP syndromes may be part of a common developmental pathway (Table 2). Furthermore, autosomal–recessive or X-linked recessive inheritance has been proposed for ACD syndrome [5]. X-linked recessive inheritance was proposed for IFAP syndrome as well [1, 5, 6, 7, 10, 12], but the observation of Cambiaghi in 2002 [2], who described two female patients with IFAP syndrome, makes autosomal–recessive inheritance more likely. It remains to be determined whether these findings in ACD and IFAP patients represent different genetic entities (as suggested by Happle in 2004 [8]), different phenotypes of the same genotype, or the expression of a contiguous gene defect.

Cytogenetic analyses performed in the seven published cases with ACD syndrome and in the present patient were normal as well as subtelomere FISH in the present patient. High resolution array-CGH analysis, which had not been performed in the previous case reports, revealed six variations in the present patient of no pathogenetic relevance. Thus, ACD syndrome might be caused by mutations below the detection limit of the tiling path BAC array, or it might be caused by a combination of aberrations, each of which alone is not relevant, but together they may be causative for the distinct phenotype observed. Although the underlying basis of ACD syndrome is unknown, the clinical combination of specific findings, including total alopecia, ichthyosis, mental retardation, and skeletal anomalies are suggestive of this syndrome. Children who are suspected to have this condition should undergo a certain social pediatric protocol including EEG diagnostics, ophthalmological investigation, psychological testing, management of dermatologic and orthopedic problems, and genetic counseling.

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