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CASE REPORT

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Arthrogryposis, renal dysfunction, cholestasis syndrome with a novel mutation in two siblings

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Key Clinical Message

This current case series adds to the spectrum of Arthrogryposis renal dysfunction cholestasis (ARC)-associated variants. Increased awareness and early genetic testing for ARC are suggested in cases with failure to thrive, renal tubular dysfunction, and rickets, even when the degree of cholestasis is mild. Prompt identification and intervention may improve the quality of life.

KEYWORDS

arthrogryposis, cholestasis, genetics, pediatrics

1 | INTRODUCTION

Arthrogryposis renal dysfunction cholestasis (ARC) syndrome is a rare autosomal recessive condition caused by mutations in the VPS33B and VIPAR genes. Several mutations have previously been described and associated with either a severe or mild phenotype, with the severity correlating with fatality. Given the spectrum of phenotypes, milder presentations can be elusive and more difficult to diagnose. Our case illustrates a mild presentation of ARC syndrome with cholestasis that improved over time in the setting of a novel, pathogenic variant (c.1609 del, p. Asp538Metfs*17).

1.1 | Case history and examination

1.1.1 | Patient 1

A 4-month-old female with intrauterine growth restriction, arthrogryposis multiplex congenita (arthrogryposis multiplex congenita refers to multiple joint contractures at birth), and sensorineural hearing loss was referred to a pediatric gastroenterology clinic for poor growth and feeding problems. She was born at 40 weeks of gestation to a healthy, nonconsanguineous, biracial Hispanic–Asian couple. Mother had alpha thalassemia trait and hemoglobin E trait, and paternal half brother had lipoprotein

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deficiency. Patient's birth weight was 2.72 kg. She had postnatal growth failure with a weight of 4.23 kg (0.03% tile, *Z* score −3.40) and a length of 52.8 cm (<0.01% tile, *Z* score −4.07) at 4 months of age. On examination, she had mild jaundice, microcephaly (small head), ocular hypotelorism (increased distance between two eyes), micrognathia (small lower jaw), highly arched palate, bilateral hearing loss, bilateral transverse palmar creases, dry skin without ichthyosis (excess dry scaling of skin), enlarged liver, mild hypotonia (muscle weakness), and bilateral rocker bottom feet (congenital anomaly of the foot characterized by a prominent heel and a convexly rounded sole) as shown (Figure 1A–C).

Patient 2: Patient was born at 39 weeks of gestation to the same biological parents as sibling 1. Her birth weight was 2.72 kg. Subsequently, she was also found to have growth failure, with a weight of 2.70 kg (<0.01% tile, *Z* score −3.90) and a length of 46.7 cm (<0.01% tile, *Z* score −4.31) at 1.5 months of age. On examination, she had microcephaly (small head), bilateral hearing loss, bilateral transverse palmar creases, dry skin without ichthyosis, mild hypotonia, and bilateral rocker bottom feet as shown (Figure 1D,E).

1.2 | Investigations, differential diagnosis and treatment

1.2.1 | Patient 1

Labs upon presentation showed fasting hypoglycemia and cholestatic hepatitis (Table 1). She was also found to have severe vitamin D deficiency rickets based upon her labs and wrist X-rays. Abdominal ultrasound (US) showed hepatosplenomegaly as well as bilateral increased renal echogenicity surrounding the medullary pyramids. MRI brain revealed a thin corpus callosum with an overall decreased volume of cerebral white matter. MRI spine was normal. Renal tubular dysfunction was identified on labs that showed acidosis, proteinuria, and glucosuria. She had a normal coagulation profile and negative infectious hepatitis panel. The constellation of physical exam and

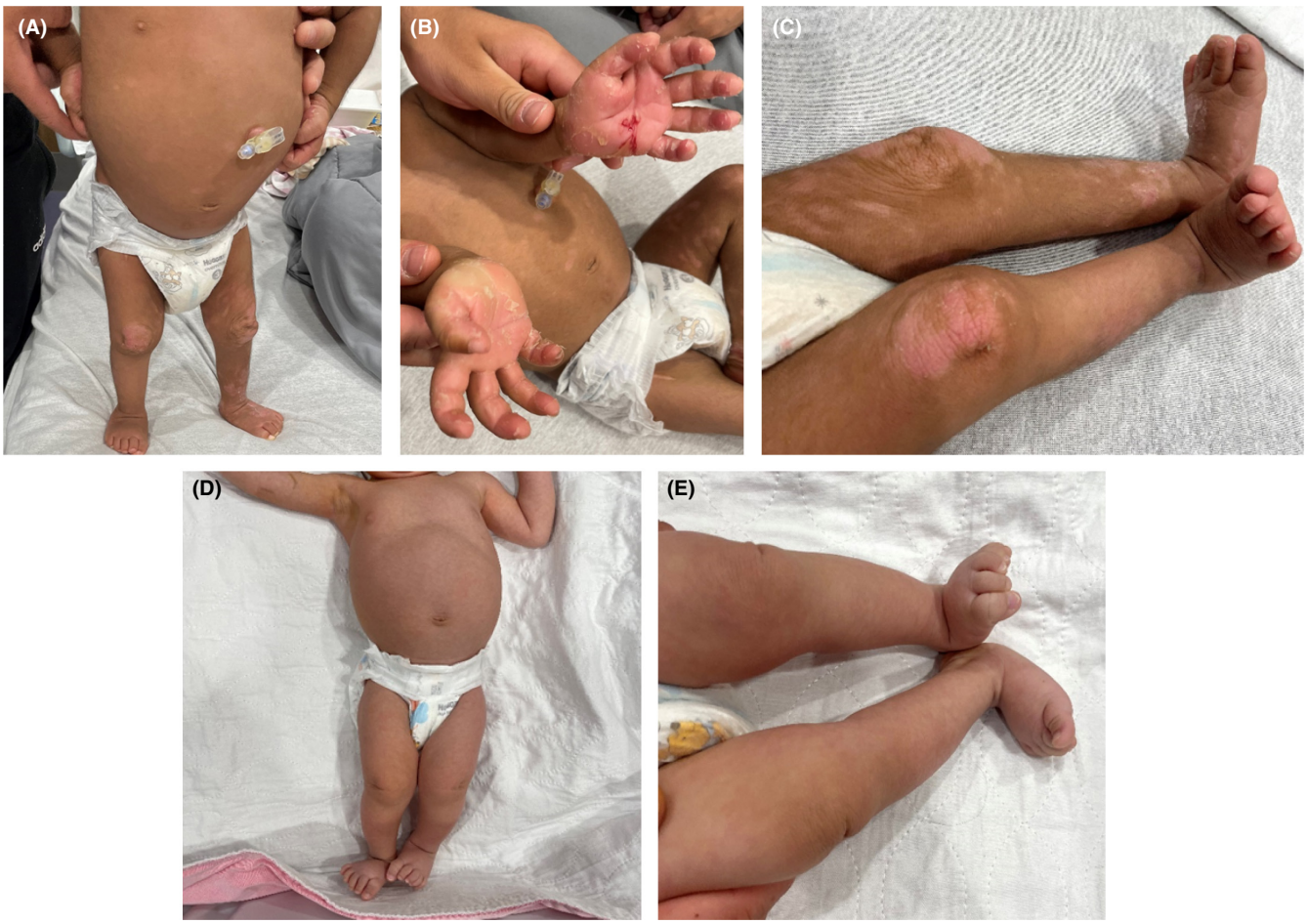

FIGURE 1 (A–C) Patient 1 with muscular atrophy, abdominal distention, ichthyosis, scarring, and rocker bottom feet. (D, E) Patient 2 with muscular atrophy, abdominal distention, and rocker bottom feet.

TABLE 1 Pertinent laboratory investigations obtained in our patients.

	Patient 1			Patient 2		
Lab values	**Diagnosis (4-month age)**	**1 year later**	**2.5 years later (present)**	**2-month age**	**8-month age (present)**	**Normal range**
Sodium (mEq/L)	134	139	139	135	136	131–145 mEq/L
Potassium (mEq/L)	4.8	4.3	4.0	5.4	4.3	4.1–5.3 mEq/L
Chloride (mEq/L)	110	107	106	106	103	98–118 mEq/L
CO2 (mEq/L)	15	21	22	19	21	22–32 mEq/L
Creatinine (mg/dL)	<0.20	0.20	0.22	0.22	0.20	0.20–0.40 mg/dL
Glucose (mg/dL)	52	81	66	58	51	60–100 mg/dL
Calcium(mg/dL)	8.2	10	9.9	9.5	10.4	9.0–10.9 mg/dL
Phosphorus (mg/dL)	2.5	4.7	3.0	—	4.5	3.4–5.9 mg/dL
25-Hydroxy vitamin D (ng/mL)	7.4	44	25.6	—	30	30.0–100.0 ng/mL
Alkaline phosphatase (IU/L)	2434	889	998	2325	1051	60–321 IU/L
Parathyroid hormone (pg/mL)	91	30	—	—	—	18–80 pg/mL
Aspartate aminotransferase AST (IU/L)	108	154	59	25	144	18–63 IU/L
Alanine aminotransferase ALT (IU/L)	130	281	58	16	183	10–32 IU/L
Albumin (g/dL)	3.9	3.9	4.0	3.7	4.0	2.7–4.8 g/dL
Gamma glutamyl transferase GGT (IU/L)	44	20	24	25	18	>3 months: 5–35 IU/L; 1–15 year: 6–19 IU/L
Bilirubin, total (mg/dL)	2.5	0.8	0.8	1.1	0.4	0.6–1.4 mg/dL
Bilirubin, direct (mg/dL)	1.2	0.5	—	—	0.2	0.0–0.3 mg/dL
Cholyglycine bile acids total (μmol/L)	—	169	168	—	120	<10 μmol/L
Vitamin A (retinol) mg/L	—	0.16	<0.06	—	—	0.20–0.50 mg/L
Vitamin E (alpha tocopherol) mg/L	—	3.3	2.6	—	—	3.5–8.0 mg/L
Glucose on urinalysis	3+	—	—	—	2+	Nil
Protein on urinalysis (mg/dL)	100	—	—	—	100	<10 mg/dL
Total carnitine (μmol/L)	—	—	35	—	35	38–73 μmol/L
Free carnitine (μmol/L)	—	—	30	—	21	29–61 μmol/L
Hemoglobin (g/dL)	11.6	10.6	11.9	9.9	11.6	11–16.3 g/dL
Platelets (10^9/L)	361	273	422	555	457	168–382 × 10^9/L
White blood cells (10^9/L)	7.3	6.5	5.9	14.5	8.0	4.4–16.00 × 10^9/L

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

laboratory findings pointed toward a syndromic disorder rather than a single isolated condition.

Several differential diagnoses were considered including Zellweger syndrome characterized by clinical features of growth restriction, craniofacial abnormalities (such as microcephaly, hypotelorism, micrognathia, and highly arched palate), sensorineural hearing loss, liver dysfunction, hypotonia, and neurological abnormalities; Trisomy 18 characterized by intrauterine growth restriction, multiple congenital anomalies (including rocker bottom feet, microcephaly, ocular hypotelorism, micrognathia), and visceral malformations (such as hepatosplenomegaly); Smith–Lemli–Opitz syndrome: disorder characterized by growth restriction, dysmorphic facial

features (including micrognathia), cleft palate, syndactyly, and rocker bottom feet. However, these disorders do not have arthrogryposis, cholestasis, and renal tubular dysfunction all in one. ARC syndrome was therefore highest on the differential given the fact that it encompassed the spectrum of physical exam findings (microcephaly, micrognathia, rocker bottom feet, sensorineural deafness) with classic features of arthrogryposis multiplex congenita, as well as lab derangements with characteristic cholestasis and renal tubular dysfunction.

A commercial genetic cholestasis panel was therefore ordered, which then identified variants in the VPS33B gene: c.1225 + 5G > C and c.1609del p. Asp538Metfs*17.

The genetic mutations are described using the Human Genome Variation Society (HGVS) nomenclature, which is a standardized way of representing genetic variations. In c.1225 + 5G > C: "c." stands for coding DNA reference sequence. "1225" refers to the position within the coding sequence of the gene. "+5" indicates that the mutation occurs 5 nucleotides downstream of position 1225. "G > C" means that in the reference sequence, there is a G (guanine) at this position, but it is changed to a C (cytosine) due to the mutation. This mutation affects the splice site, which is the region where the intron is removed during the process of mRNA splicing. It suggests a change in the normal splicing pattern of the gene, which can lead to aberrant mRNA transcripts and potentially dysfunctional or truncated protein products.

In c.1609del p. Asp538Metfs*17: "c." refers to the coding DNA reference sequence. "1609" indicates the position within the coding sequence of the gene. "del" signifies a deletion mutation. "p. Asp538Metfs*17" is the predicted consequence of this mutation at the protein level (p). Asp538Met "denotes the change of the amino acid at position 538 from aspartic acid (Asp) to methionine (Met).fs17" suggests a frameshift mutation leading to a premature stop codon 17 amino acids downstream from the site of mutation. This mutation results in a frameshift, altering the reading frame of the gene's coding sequence. As a consequence, it leads to the generation of a truncated protein that is likely nonfunctional due to the premature stop codon.

The c.1225 + 5 G > C has been previously described in association with a milder presentation of the ARC syndrome. However, c.1609del is a novel pathogenic variant, that has not been described in the literature or reported in a large population database. Both mutations have the potential to disrupt the normal function of the gene and create dysfunctional proteins, and lead to variable phenotypes.

Treatment of ARC syndrome is mainly symptomatic and targeted toward preventing significant liver and renal injury. There is no gene therapy currently available to cure the disease. Our patient's vitamin D deficiency improved over time with supplementation and repeat labs showed normal vitamin D, calcium, and phosphorus. Her acidosis improved with sodium citrate supplementation (4 mL/kg/day). She was started on ursodiol (15 mg/kg/day) for cholestasis and her total and direct bilirubin levels also normalized. She required frequent follow-up with the gastroenterology clinic for her growth and nutritional support. Given the inability to meet nutritional needs with just oral feeds, she later required a gastrostomy tube placement for supplemental feeds.

1.2.2 | Patient 2

Patient's mother had undergone amniocentesis during pregnancy that confirmed biallelic pathogenic variants in VPS33B: c.1225 + 5G > C and c.1609del p. Asp538Metfs*17, which were also seen in her sibling (patient 1) confirming a diagnosis of ARC syndrome, as in patient 1. She did not have any additional mutations. Initial laboratory tests, including bilirubin and thyroid profile, were within the normal range. Overtime, she also developed hepatitis and experienced fasting hypoglycemia, similar to her older sibling (Table 1). Abdominal US revealed a congenital gallbladder anomaly (multiseptated gallbladder), without any associated hepatosplenomegaly or renal defects. MRI brain was normal. Renal tubular dysfunction was identified on labs that showed acidosis, proteinuria, and glucosuria. She had a normal coagulation profile.

Treatment: She was started on fat-soluble DEKA vitamins early on, and fortunately, did not develop vitamin D deficient rickets, as seen in her sibling. She also required close follow-up with the gastroenterology for her nutritional needs. However, given her failure to thrive, and evidence from her sister with a similar mutation that she may not meet her caloric needs with oral feeds alone, she also required a gastrostomy tube placement. She is also on sodium citrate supplementation (4 mL/kg/day) for her renal tubular acidosis.

1.3 | Outcome and follow-up

1.3.1 | Patient 1

Since diagnosis, her course has been dominated by chronic malnutrition requiring gastrostomy tube feeds to meet caloric needs, hypothyroidism (requiring levothyroxine), and complications from arthrogryposis multiplex congenita. She underwent hip surgery for her hip dysplasia. She continues to have chronic fluctuating hepatitis (ALT fluctuates between 100 and 400) with stable hepatomegaly.

TABLE 2 Clinical features in a patient with classic ARC syndrome and our patients with a milder phenotype.

Organ system affected	Manifestations of ARC syndrome reported in literature	Manifestations of ARC in our patients with a novel mutation	
		Patient 1	Patient 2
Musculoskeletal	Arthrogryposis multiplex congenita: (multiple joint contractures, rocker bottom feet) Hip dislocation Muscular atrophy	Mild arthrogryposis multiplex congenita (mild joint contractures, rocker bottom feet) Hip dysplasia Muscle atrophy Vitamin D deficiency rickets (resolved)	Mild arthrogryposis multiplex congenita (mild joint contractures, rocker bottom feet) No hip dysplasia Muscular atrophy
Gastrointestinal	Failure to thrive Cholestasis (severe) High serum bile acids Malabsorption Hepatitis Normal/low GGT Abdominal distention US abdomen findings: Hepatomegaly	Failure to thrive Mild cholestasis (direct bilirubin normalized overtime) High serum bile acids Malabsorption Hepatitis (improved) Normal/mildly elevated GGT Abdominal distention US abdomen: Hepatosplenomegaly. Splenomegaly resolved overtime	Failure to thrive No cholestasis Hepatitis Abdominal distention US abdomen: Multiseptated gallbladder, no hepatosplenomegaly
Renal	Renal tubular dysfunction/Fanconi syndrome: acidosis, glucosuria, aminoaciduria, phosphaturia Nephrogenic diabetes insipidus US abdomen findings: renal hyperechogenity, nephrocalcinosis, dysplastic kidney	Renal tubular dysfunction: acidosis, glucosuria, proteinuria US abdomen findings: bilateral renal hyperechogenity with obscured corticomedullary differentiation	Renal tubular dysfunction: acidosis, glucosuria, proteinuria US abdomen: normal kidneys
Central nervous system	Developmental delay Sensorineural deafness MRI brain findings: thin and hypoplastic corpus callosum, white matter hypoplasia and delayed myelination, increased signal in basal ganglia, abnormal ventricles	Developmental delay Sensorineural deafness MRI brain: thin corpus callosum with diminished cerebral white matter	Developmental delay Sensorineural deafness MRI brain: Normal contrast-enhanced brain imaging
Skin	Pruritis Ichthyosis	Pruritus Atopic dermatitis Ichthyosis (developed around 2-years age)	Pruritis
Endocrine	Hypothyroidism Short stature	Hypothyroidism Fasting hypoglycemia Short stature	Normal thyroid profile Fasting hypoglycemia Short stature
Hematology	Platelet function disorder: History of easy bleeding/bruising Agranular large platelets Prolonged platelet aggregation	No history of easy bruising or bleeding	History of easy bruising, suspected to have platelet function disorder
Immunology	Sepsis/fever/recurrent infection	None	None
Cardiology	Persistent foramen ovale Secundum atrial septal defect	Normal echocardiogram	Normal echocardiogram
Dysmorphology	Low set ears Transverse palmar crease Microcephaly Micrognathia	Microcephaly Micrognathia Transverse palmar crease	Microcephaly Transverse palmar crease

Abbreviations: ARC, arthrogryposis renal dysfunction cholestasis; GGT, gamma glutamyl transferase; US, ultra sound.

She has elevated serum bile acids leading to pruritus for which she is being treated with ursodiol (15 mg/kg/day) and odevixibat (400 μg/day). She is also on DEKA vitamins. Despite these complications, the child is a happy toddler approaching 3 years of age, and otherwise stable.

1.3.2 | Patient 2

Similar to her sibling, she also has chronic fluctuating hepatitis and elevated serum bile acids leading to pruritus for, which she is being treated with ursodiol (15 mg/kg/day) and odevixibat (300 μg/day). At 11 months of age, while her clinical features are somewhat less severe compared to her sibling, the presence of similar mutations suggests that she is likely to follow a comparable course of the condition. She is continuing to require frequent follow-up with genetics, gastroenterology, and nephrology clinics for clinical and laboratory monitoring.

2 | DISCUSSION

Arthrogryposis renal dysfunction cholestasis syndrome is a rare multisystem disorder involving the liver, kidney, musculoskeletal, skin, and central nervous systems with early mortality and a poor prognosis seen in severe forms. ARC is characterized by autosomal recessive mutations in the VPS33B (vacuolar protein sorting 33 homolog B) and VIPAR (VPS33B-interacting protein, apical basolateral polarity regulator) genes which are involved in the intracellular protein sorting and vesicular trafficking pathways.[1] These are expressed in several organs and mutations lead to disruption of cell polarization that is crucial to cellular development and function.

There are various described phenotypes associated with ARC syndrome with the three core features being arthrogryposis, renal dysfunction, and cholestasis. Different genetic mutations are associated with different phenotypic variations. The prognosis of ARC syndrome is poor, especially in cases with severe mutations. Most patients usually die within the first year of life after developing acidosis, recurrent infection, or internal bleeding.[2,3]

Our patients' genetic testing identified pathogenic variants in VPS33B (c.1225 + 5G > C) and (c.1609del p. Asp538Metfs*17), with the latter not described in the literature or reported in a large population database previously. The phenotype of our patients is unique in that on presentation there was no ichthyosis or sepsis-like illness that is typically life limiting before 1 year of age. Table 2 illustrates the differentiating factors of a classic ARC patient as compared to our patients (Figure 1) with a milder phenotype. Hepatitis and hepatomegaly with giant cell transformation, biliary plugs, and portal fibrosis can be seen to varying degrees in this disorder in part due to disruption in trafficking of bile components. While severe cholestasis is one of the core findings in ARC syndrome, patient 1 only had mild elevation in total and direct bilirubin that resolved overtime. Patient 2 also followed a similar course which may be explained by milder phenotype associated with this unique mutation.[1,2,4] Both patients continue to have intermittently elevated serum bile acids and pruritus that is currently treated with the selective inhibitor of the ileal bile acid transporter (odevixibat). These features along with fasting hypoglycemia and rickets are clinical features less described in the literature in the setting of a novel mutation (c.1609del, p. Asp538Metfs*17). Overall, the prognosis for rare forms of ARC syndrome can be variable, ranging from severe cases with significant morbidity and mortality to milder presentations with better long-term outcomes. There is no literature regarding the life expectancy of patients with milder phenotypes but cases of survival in the adolescent age group have been described.[5,6]

AUTHOR CONTRIBUTIONS

Rahiya Rehman: Data curation; formal analysis; investigation; writing – original draft; writing – review and editing. **Leslia Gonzalez:** Data curation. **Kelsey Kolbe:** Data curation. **William Brucker:** Conceptualization; writing – review and editing. **Mohammed Khurram Faizan:** Conceptualization; writing – review and editing. **Carolina Cerezo:** Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this case series is available from the corresponding author upon request.

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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REFERENCES

1. Zhou Y, Zhang J. Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome: from molecular genetics to clinical features. *Ital J Pediatr*. 2014;40:77.

2. Del Brío Castillo R, Squires JE, McKiernan PJ. A novel mutation in VPS33B gene causing a milder ARC syndrome phenotype with prolonged survival. *JIMD Rep*. 2019;47(1):4-8.
3. Agawu A, Sheppard S, Lin HC. A novel VPS33B mutation causing a mild phenotype of arthrogryposis, renal dysfunction, and cholestasis syndrome. *J Pediatr Gastroenterol Nutr*. 2019;69(2):e55-e56.
4. Agakidou E, Agakidis C, Kambouris M, et al. A novel mutation of VPS33B gene associated with incomplete arthrogryposis-renal dysfunction-cholestasis phenotype. *Case Rep Genet*. 2020;2020:8872294.
5. Li LT, Zhao J, Chen R, Wang JS. Two novel VPS33B mutations in a patient with arthrogryposis, renal dysfunction and cholestasis syndrome in mainland China. *World J Gastroenterol*. 2014;20(1):326-329.
6. Taha D, Khider A, Cullinane AR, Gissen P. A novel VPS33B mutation in an ARC syndrome patient presenting with osteopenia and fractures at birth. *Am J Med Genet A*. 2007;143A(23):2835-2837.

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