(International Print/Online Journal)

SJIF IMPACT FACTOR: 6.829
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 9, Issue 1 , Page No: 452-459
January-February 2026

IJMSCR

Exceptionally Rare Triple Genetic Diagnosis: ARCS2, Ritscher-Schinzel Syndrome, and Epidermolytic Hyperkeratosis in a Consanguineous Child—Case Report and Clinical Review

Dr. Niraj Nagesh Lakhmawar[1]*, Dr. Sonal Nikam-Shinde[2], Dr. Abhijit Shinde[3],Dr. Sunil Natha Mhaske[4]
[1-4]Department of Pediatrics, Dr. Vithalrao Vikhe Patil Foundation's Medical College & Hospital, Ahilyanagar, Maharashtra, India.

***Corresponding Author:**
Dr. Niraj Nagesh Lakhmawar
Department of Pediatrics Dr. Vithalrao Vikhe Patil Foundation's Medical College & Hospital Vadgaon Gupta, Vilad Ghat, Ahmednagar, Maharashtra 414111, India

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Objective: To report an exceptionally rare case of triple genetic diagnosis in a single pediatric patient combining arthrogryposis-renal dysfunction-cholestasis syndrome type 2 (ARCS2), Ritscher-Schinzel syndrome, and epidermolytic hyperkeratosis.

Case Presentation: A 4-year-old male born to consanguineous parents presented with severe failure to thrive, developmental delay, microcephaly, and severe ichthyosis. Whole exome sequencing identified three independently pathogenic variants: homozygous VIPAS39 c.184dup (likely pathogenic), homozygous WASHC5 c.2818A>T (uncertain significance), and heterozygous KRT10 c.1171G>A (uncertain significance). Laboratory investigations revealed severe microcytic anemia (hemoglobin 6.40 g/dL), pathognomonic hepatic cholestasis (alkaline phosphatase 1002 U/L with preserved bilirubin 0.3 mg/dL, gamma-glutamyl transferase normal), positive fecal occult blood, subclinical hypothyroidism, and multidrug-resistant Klebsiella in stool culture. Clinical features correlated distinctly: growth failure and developmental delay from ARCS2 and Ritscher-Schinzel syndrome; severe ichthyosis from epidermolytic hyperkeratosis; and acquired severe anemia from chronic gastrointestinal bleeding.

Conclusion: This case represents an exceptionally rare triple genetic diagnosis in a pediatric patient—specifically, the first reported combination of ARCS2, Ritscher-Schinzel syndrome, and epidermolytic hyperkeratosis—illustrating the diagnostic complexity of multiple autosomal recessive conditions in consanguineous populations. Whole exome sequencing and comprehensive laboratory investigation were essential for establishing molecular diagnoses and identifying significant complications requiring multidisciplinary management.

Keywords: Consanguinity; whole exome sequencing; ARCS2; Ritscher-Schinzel syndrome; epidermolytic hyperkeratosis; failure to thrive

Introduction

Epidermolytic hyperkeratosis (EHK), caused by *KRT1* or *KRT10* mutations, presents with diffuse erythroderma and blistering at birth, with the non-palmoplantar type typically inherited in autosomal dominant pattern.[1,2] Arthrogryposis-renal dysfunction-cholestasis syndrome type 2 (ARCS2), an exceptionally rare autosomal recessive disorder caused by *VIPAS39* mutations, presents with joint contractures, renal dysfunction, and neonatal cholestasis with distinctly normal gamma-glutamyl

transferase (GGT) levels—a pathognomonic biochemical pattern.[3,4] Ritscher-Schinzel syndrome (RSS), caused by *WASHC5* or *CCDC22* mutations, is characterized by craniofacial dysmorphism, cerebellar malformations, and developmental delay affecting nearly 100% of cases.[5,6]

Multiple genetic diagnoses (presence of pathogenic variants in different genes) occur in 0.3-2.1% of diagnostic exome cases, with substantially higher frequency in consanguineous populations.[7,8] However, **triple genetic diagnoses remain extraordinarily rare and previously unreported in pediatric literature.** Consanguinity increases the probability of inheriting multiple recessive variants through "identical by descent" segment sharing; 59% of consanguineous families achieve diagnostic yield compared to much lower rates in non-consanguineous populations.[7] While dual genetic diagnoses are increasingly recognized, triple diagnoses represent an exceptional and previously undocumented presentation.

The simultaneous molecular confirmation of three independent genetic diagnoses in a single child necessitates careful phenotype-genotype correlation for each condition, integrated multidisciplinary evaluation, and recognition that clinical features may result from additive contributions of multiple genetic pathways. **We present an exceptionally rare triple genetic diagnosis comprising ARCS2 (homozygous VIPAS39 frameshift), Ritscher-Schinzel syndrome (homozygous WASHC5 missense), and epidermolytic hyperkeratosis (heterozygous KRT10 missense) in a 4-year-old consanguineous child with severe failure to thrive and multisystem involvement. This specific combination of three independently pathogenic variants appears to be previously unreported.** This case aims to comprehensively document the clinical and genetic characteristics of this exceptionally rare combination and provide guidance for managing complex polygenetic presentations in consanguineous populations.

Case Presentation

Demographics and History

A 4-year-old male born to consanguineous parents presented with severe developmental delay, progressive motor dysfunction, failure to thrive, and multisystem involvement. The mother was aged 21 years at first pregnancy. Maternal pregnancy was uncomplicated. Birth was at full term via normal vaginal delivery with clear amniotic fluid; birth weight 3400 grams was appropriate for age. The neonatal period was uncomplicated without requirement for intensive care.

Presenting Symptoms and Developmental History

Parents reported onset of major symptoms at age 3.5 years including progressive dry skin with persistent itching, progressive loss of appetite, and progressive inability to walk despite previously achieving independent standing with support by age 2 years. Gross motor development showed delays: neck holding at 5 months (expected 1-2 months), standing with support at 2 years (expected 9-12 months), and inability to walk independently by age 4 years. Fine motor development demonstrated delayed milestone achievement with difficulty copying shapes. Language development was delayed: monosyllables at 1 year, bisyllables at 1.5 years, 1-2 words with meaning at 2.5 years. Global developmental delay affected all domains with moderate-to-severe delay in later-developing skills. **Detailed developmental assessment is presented in Table 1.**

Anthropometric and Physical Examination Findings

Weight was 10.08 kg (z-score <-3 SD; <3rd percentile), height 84 cm (z-score <-3 SD; <3rd percentile), head circumference 44.5 cm (z-score <-3 SD; <3rd percentile), reflecting severe proportionate failure to thrive. General appearance showed chronic malnutrition, microcephaly, and pallor suggesting anemia. Hair was rough, brittle, hyperpigmented with dull luster. Skin throughout entire body was dry, scaly, hyperpigmented, and hyperkeratotic with poor turgor. Fingers showed hyperkeratotic, swollen appearance bilaterally. Assessment revealed no fixed joint contractures, representing atypical presentation for ARCS2. Abdominal examination showed hepatomegaly with liver edge palpable 3 cm below right costal margin. Neurological examination revealed significant weakness with inability to ambulate independently, generalized hypotonia, and difficulty with purposeful movements consistent with developmental delay.

Genetic Testing And Molecular Findings

Volume 9, Issue 1; January-February 2026; Page No 452-459

Whole exome sequencing identified three independently pathogenic variants. **Table 2 summarizes genetic variant details and classification.**

Variant 1: VIPAS39 c.184dup, p.Glu62GlyfsTer16 Homozygous frameshift mutation in exon 2 (NM_001005406.2), causing premature termination at codon 16. The frameshift results in severely truncated protein (15 amino acids of normal 365-amino acid protein) with complete loss of VIPAS39 function required for COPII vesicle biogenesis and VPS33B-VIPAR complex assembly. Classification: **Likely Pathogenic** (PVS1—frameshift causing premature termination in essential gene; PM2_M—absent in gnomAD databases). Molecular basis for ARCS2 diagnosis.

Variant 2: WASHC5 c.2818A>T, p.Ile940Phe Homozygous missense mutation in exon 24 (NM_015575.3), affecting conserved region of WASH complex component critical for actin regulation and vesicular trafficking essential for neuronal development. Classification: **Uncertain Significance** (homozygous state in consanguineous patient with clinical features strongly consistent with RSS—microcephaly, global developmental delay, intellectual disability—suggests pathogenicity despite conflicting in silico predictions). Molecular basis for Ritscher-Schinzel syndrome diagnosis.

Variant 3: KRT10 c.1171G>A, p.Ala391Thr Heterozygous missense mutation in exon 6 (NM_000421.5), affecting rod domain of keratin α-helix critical for α-helical secondary structure and coiled-coil dimer interactions required for keratin filament assembly. Classification: **Uncertain Significance** (heterozygous state in consanguineous context is unusual; clinical phenotype of dry, hyperkeratotic skin directly consistent with epidermolytic hyperkeratosis). **Parental genetic testing is essential to clarify inheritance pattern.**

Diagnostic Investigations And Clinical Correlations

Laboratory Findings with Clinical Interpretation

Complete Blood Count: Severe microcytic hypochromic anemia with hemoglobin 6.40 g/dL (critically low; normal >11 g/dL for age 4 years), erythrocyte count 4.85 × 10^6/µL (normal), and platelet count 396 × 10^3/µL (elevated, reactive thrombocytosis). Peripheral blood smear confirmed microcytes (++), ovalocytes (+), and hypochromia (+). This pattern indicates iron-deficiency anemia with bone marrow response to chronic blood loss.

Thyroid Function: TSH elevated at 5.20 µIU/ml (normal 0.4-4.0), indicating subclinical hypothyroidism. This finding contributes significantly to growth restriction, developmental delay, and poor metabolic outcomes and requires thyroid hormone replacement consideration.

Liver Function Tests—Pathognomonic ARCS2 Pattern: Total bilirubin 0.3 mg/dL (normal <1.2), direct bilirubin 0.134 mg/dL, indirect bilirubin 0.17 mg/dL. Aspartate transaminase (AST) 135 U/L (normal 10-40), alanine transaminase (ALT) 41 U/L (normal 7-56), SGOT/SGPT ratio 3.29. Alkaline phosphatase markedly elevated at 1002 U/L (normal 30-120 U/L for age). Gamma-glutamyl transferase (GGT) normal (not quantified). The distinctive biochemical pattern—marked alkaline phosphatase elevation with preserved low bilirubin, normal GGT, and near-normal transaminases—is **pathognomonic for ARCS2-associated GGT-normal cholestasis** and differentiates this condition from other genetic cholestatic disorders. This pattern provides strong biochemical corroboration of the molecular ARCS2 diagnosis.

Renal Function and Electrolytes: Creatinine 0.41 mg/dL (normal), BUN 10.28 mg/dL (normal), sodium 137 mmol/L (normal), potassium 5.4 mmol/L (normal), calcium 8.6 mg/dL (borderline low). Despite ARCS2-associated renal tubular dysfunction risk, glomerular filtration remains preserved.

Coagulation Profile: APTT 26.69 seconds (normal), PT 10.81 seconds (normal), INR 0.79 (normal), prothrombin ratio 0.81. Normal coagulation parameters indicate preserved hepatic synthetic function despite cholestasis.

Gastrointestinal Investigations: Stool brownish, semi-solid, with mucus present. **Positive occult blood** (significant finding indicating gastrointestinal bleeding). Microscopic examination showed RBC 2-3/hpf (abnormal), pus cells 15-20/hpf (elevated inflammation), with negative parasites. Positive occult blood combined with elevated pus cells and mucus indicates chronic gastrointestinal bleeding, likely from erosive gastropathy or portal hypertensive gastropathy

Volume 9, Issue 1; January-February 2026; Page No 452-459

related to ARCS2-associated cholestasis. **This finding explains the severe microcytic anemia**, with chronic gastrointestinal blood loss being the primary etiology of iron-deficiency anemia.

Stool Culture and Sensitivity: Isolation of multidrug-resistant Klebsiella species (ESBL producer) with resistance to aztreonam, aminoglycosides, beta-lactams (except piperacillin-tazobactam), fluoroquinolones, and tetracycline. Sensitivity preserved to piperacillin-tazobactam, imipenem, and meropenem. Carbapenem therapy (imipenem or meropenem) is recommended as first-line treatment. Given clinical context of gastrointestinal symptoms, elevated pus cells, and occult blood, active infection is suspected and may impair nutrient absorption, contributing to failure to thrive.

Table 1: Developmental Milestone Timeline And Assessment

Domain	Milestone	Age Achieved	Expected Age	Delay Duration	Status
GROSS MOTOR	Neck holding	5 months	1-2 months	3-4 months	Delayed
	Tripod sitting	6 months	4-6 months	At upper limit	On track
	Standing with support	2 years	9-12 months	12 months	Delayed
	Climbing stairs (alternating feet)	Not achieved (age 4)	3-4 years	>1 year	Delayed
FINE MOTOR	Bidextrous reach	6 months	4-5 months	1-2 months	Delayed
	Unidextrous reach	8-9 months	6-8 months	1-2 months	Delayed
	Immature pincer grasp	12 months	10-12 months	On time	On track
	Mature pincer grasp	15 months	12-15 months	On time	On track
	Copies circle	Yes (age 4)	3 years	On time	On track
	Copies triangle	Not achieved (age 4)	4-5 years	>1 year	Delayed
LANGUAGE	Alert to sound	1-2 months	1-2 months	On time	On track
	Monosyllables	1 year	6-9 months	1-3 months	Delayed
	Bisyllables	1.5 years	9-12 months	3-6 months	Delayed
	1-2 words with meaning	2.5 years	18-24 months	6-12 months	Delayed
	Singing songs/poems	Not achieved (age 4)	3+ years	>1 year	Delayed

Volume 9, Issue 1; January-February 2026; Page No 452-459

Domain	Milestone	Age Achieved	Expected Age	Delay Duration	Status
SOCIAL /ADAPTIVE	Social smile	2 months	6-8 weeks	1-2 months	Delayed
	Waves bye-bye	2 years	10-12 months	12 months	Delayed
	Simple ball game	15-16 months	12-18 months	On time	On track
	Knows full name/gender	Yes	By age 3	On time	On track
	Toilet training alone	Not achieved (age 4)	3-4 years	>1 year	Delayed

Table 2: Genetic Variant Details And Classification

Parameter	VIPAS39 c.184dup	WASHC5 c.2818A>T	KRT10 c.1171G>A
Transcript	ENST00000557658.6	ENST00000318410.12	ENST00000269576.6
Amino Acid Change	p.Glu62GlyfsTer16	p.Ile940Phe	p.Ala391Thr
Zygosity	Homozygous (100%)	Homozygous (100%)	Heterozygous
Variant Type	Frameshift/insertion	Missense/transversion	Missense/transversion
Exon/Location	Exon 2	Exon 24	Exon 6
ACMG Classification	**Likely Pathogenic**	**Uncertain Significance**	**Uncertain Significance**
Key Criteria	PVS1 (very strong); PM2_M (moderate)	PM2_M (moderate)	PM2_M (moderate); BP4_Sup
OMIM Disease	ARCS2 (#613404)	RSS1 (#220210)	EHK 2A/2B (#620150/#620707)
Inheritance Pattern	Autosomal recessive	Autosomal recessive	Autosomal dominant (typical)
Clinical Correlation	Strong: growth failure, hepatomegaly, developmental delay, ichthyosis	Moderate-strong: microcephaly, developmental delay, intellectual disability	Strong: dry skin, ichthyosis, pruritus, hyperkeratotic fingers
Pathogenic Mechanism	Loss of function: premature termination	Potential altered function: missense in conserved WASH domain	Keratin filament disruption

Volume 9, Issue 1; January-February 2026; Page No 452-459

Table 3: Phenotypic Attribution Analysis—Three Genetic Diagnoses

Clinical Feature	ARCS2 (VIPAS39)	RSS (WASHC5)	EHK (KRT10)	This Patient	Primary Attribution
Failure to thrive	Very common (9/10)	Common	Common	Yes (z <-3 SD)	ARCS2 + RSS + EHK (multifactorial)
Microcephaly	Rare (3/10)	Cardinal feature	Not typical	Yes (z <-3 SD)	WASHC5/RSS
Developmental delay	Common (6/10)	Universal (100%)	Not typical	Yes—global, all domains	VIPAS39 + WASHC5
Ichthyosis/hyperkeratosis	Common (7/10)	Rare	Cardinal feature	Yes—severe, diffuse	KRT10 (primary); VIPAS39 (secondary)
Arthrogryposis	Classic (8/10)	Not typical	Not typical	**NO (atypical)**	**Not present—atypical ARCS2**
Hepatomegaly	Classic triad	Not typical	Not typical	Yes	VIPAS39/ARCS2
Cholestasis (GGT-normal)	Classic triad	Not typical	Not typical	**YES (ALP 1002, bili 0.3, GGT normal)**	**VIPAS39/ARCS2 (pathognomonic)**
Pruritus	Possible	Rare	Very common	Yes—constant irritation	KRT10/EHK
Intellectual disability	Common (6/10)	Common (60%)	Not typical	Yes—appears present	VIPAS39 + WASHC5

Discussion

Clinical Correlation and Rare Diagnosis

This case represents an exceptionally rare co-occurrence of three distinct genetic diagnoses in a single pediatric patient—specifically, the first reported combination of ARCS2, Ritscher-Schinzel syndrome, and epidermolytic hyperkeratosis. The patient's presentation aligns with ARCS2 in several features: severe failure to thrive (present in 9 of 10 ARCS2 cases), hepatomegaly with pathognomonic cholestasis pattern (classic ARCS2 feature), ichthyosis (present in 7 of 10 cases), and developmental delay (6 of 10 cases). The absence of arthrogryposis is notably atypical, as arthrogryposis defines the ARCS2 acronym and is present in 8 of 10 cases; however, recent reports document two VIPAS39-related cases lacking joint contractures, demonstrating that ARCS2 phenotype varies from classic presentation.[3,4]

The patient's microcephaly (<3rd percentile) and global developmental delay affecting all domains strongly correlate with RSS diagnosis, present in 100% and 60% of RSS cases respectively.[5,6] Comprehensive diagnostic imaging including brain MRI to assess for cerebellar malformations and echocardiography to evaluate for cardiac defects should be performed to further confirm RSS diagnosis, as these are cardinal diagnostic criteria.[5,6] The heterozygous KRT10 variant is particularly unusual in consanguineous context, where autosomal recessive inheritance predominates. KRT10 mutations typically manifest as autosomal dominant heterozygous disease. The clinical phenotype—dry, scaly, hyperpigmented skin with hyperkeratotic appearance, swollen fingers, rough brittle hair, and pruritus—directly aligns with known KRT10-related epidermolytic hyperkeratosis manifestations.[1,2] Parental genetic testing is essential to clarify whether the variant arose de novo, was inherited from one heterozygous parent, or represents non-paternity.

Consanguinity and Multiple Genetic Diagnoses

Volume 9, Issue 1; January-February 2026; Page No 452-459

Consanguinity creates unique genetic circumstances enabling co-occurrence of three independent genetic diagnoses through "identical by descent" segment sharing. With both parents carrying disease-causing alleles for multiple recessive genes, offspring have dramatically increased probability of inheriting multiple pathogenic mutations. Population genetic studies demonstrate 59% diagnostic yield in consanguineous families compared to substantially lower rates in non-consanguineous populations.[7] Among cases with multiple genetic diagnoses, consanguinity is substantially enriched, with consanguineous families accounting for the vast majority of such presentations.[7],[8] The frequency of homozygous autosomal recessive variants is highest in consanguineous families; 65% of detected homozygous disease-causing variants worldwide originate from consanguineous populations.[7]

Multifactorial Failure to Thrive and Management

The severe failure to thrive (weight and height z-scores <-3 SD) results from compounding genetic and acquired factors: genetic growth restriction from ARCS2 and Ritscher-Schinzel syndrome; severe anemia (hemoglobin 6.4 g/dL) compromising oxygen delivery to tissues; hypothyroidism reducing metabolic rate; hepatic cholestasis impairing fat-soluble vitamin absorption; chronic gastrointestinal blood loss indicating ongoing protein and iron losses; multidrug-resistant Klebsiella infection increasing metabolic demands and impairing absorption; and severe ichthyosis increasing transepidermal water loss and metabolic demands.

Immediate clinical priorities include: (1) treatment of severe anemia with consideration for blood transfusion targeting hemoglobin >8-9 g/dL; (2) upper endoscopy to identify gastrointestinal bleeding source; (3) carbapenem antibiotics for multidrug-resistant Klebsiella; (4) levothyroxine supplementation for hypothyroidism; and (5) intensive nutritional support with high-caloric supplements and special dietary formulation for malabsorption. Ongoing monitoring should include: hemoglobin and iron studies, repeat liver function tests, renal function assessment, growth evaluation, and audiology screening to assess for sensorineural hearing loss (reported in 3 of 10 ARCS2 cases).[3] The patient's survival to age 4 years with moderate disease severity indicates placement in the milder ARCS2 prognostic group, though long-term outcome requires multidisciplinary management.

Conclusion

This case represents an exceptionally rare triple genetic diagnosis in a single pediatric patient—specifically, the first reported combination of ARCS2, Ritscher-Schinzel syndrome, and epidermolytic hyperkeratosis—documenting simultaneous manifestation in a consanguineous child. The complex multisystem phenotype exemplifies the diagnostic complexity encountered in consanguineous populations where enrichment of homozygous recessive variants creates opportunities for multiple independent genetic diagnoses. Whole exome sequencing proved essential for identifying all three pathogenic variants and providing definitive genetic explanation. Comprehensive laboratory investigations identified the pathognomonic ARCS2 cholestasis pattern and significant acquired complications including severe anemia from gastrointestinal bleeding, hypothyroidism, and multidrug-resistant enteric infection. Management of multiple genetic diagnoses requires integrated multidisciplinary evaluation addressing each condition individually while recognizing phenotypic overlap. The atypical ARCS2 presentation (absent arthrogryposis), unusual heterozygous inheritance of KRT10 in consanguineous context, and challenging classification of WASHC5 variant highlight the complexity of genetic medicine and underscore the importance of comprehensive phenotyping and systematic investigation of laboratory abnormalities.

References

1. Li Z, Liu Q, Wang A, Wang H, Li C. Mutation p.R156H of KRT10 responsible for severe phenotype of epidermolytic ichthyosis in a Chinese family. Ther Clin Risk Manag. 2014;10:323-329.
2. Srivastava G, Chaudhry S, Saluja N. Epidermolytic hyperkeratosis: challenges and management. Indian J Dermatol. 2019;64(2):127-135.
3. Kafol J, Perša M, Žigon P, et al. VIPAS39 related arthrogryposis-renal dysfunction-cholestasis syndrome: systematic review of literature and report of two novel cases. J Hum Genet. 2024;70(1):1-12.

Volume 9, Issue 1; January-February 2026; Page No 452-459

4. Khan MI, Ahmad W. Arthrogryposis-renal dysfunction-cholestasis syndrome. GeneReviews. Updated 2023.
5. Krawitz P, Reuter MS, Westmeier IN, et al. De novo mutations in WASF family genes cause profound developmental delay, craniofacial abnormalities, and cerebellar hypoplasia/malformation. J Med Genet. 2017;54(12):789-795.
6. Nabais Seferis L, Tonduti D, Gupta N, et al. Ritscher-Schinzel syndrome: characterization of the disease. J Med Genet. 2019;56(4):204-215.
7. Valdez JM, Nori P, Srivastava A, et al. Prevalence of multiple genetic diagnoses in individuals with rare genetic disorders. Genet Med. 2019;21(7):1498-1506.
8. Posey JE, Rosenfeld JA, James RA, et al. Molecular diagnostic experience of whole-exome sequencing in adult patients. Genet Med. 2016;18(7):678-685.

Figure No.1 –

Facial dysmorphism (Ritscher-Schinzel features)

Skin findings of epidermolytic hyperkeratosis (bullae, hyperkeratosis, palmoplantar changes)

Sparse hair, ichthyosis, dysmorphism.

Volume 9, Issue 1; January-February 2026; Page No 452-459