

REVIEW

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Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome: from molecular genetics to clinical features

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Abstract: Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare but fatal autosomal recessive multisystem disorder caused by mutations in the *VPS33B* or *VIPAR* gene. The classical presentation of ARC includes congenital joint contractures, renal tubular dysfunction, and cholestasis. Additional features include ichthyosis, central nervous system malformation, platelet anomalies, and severe failure to thrive. Diagnosis of ARC syndrome relies on clinical features, organ biopsy, and mutational analysis. However, no specific treatment currently exists for this syndrome.

Conclusion: This is an overview of the latest knowledge regarding the genetic features and clinical manifestations of ARC syndrome. Greater awareness and understanding of this syndrome should allow more timely intervention with potential for improving long-term outcome.

Keywords: ARC syndrome, Arthrogryposis, Cholestasis, Renal dysfunction, *VPS33B*, *VIPAR*

“What is known - what is new” (Authors’ summary)

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome (MIM 208085), caused by mutations in the *VPS33B* or *VIPAR* gene, is a rare autosomal recessive multisystem disorder involving the liver, kidney, skin, and central nervous and musculoskeletal systems. In general, case reports of patients with ARC syndrome are not uncommon in Saudi Arabia and Pakistan, along with several sporadic cases all around the world. To help clinicians raise awareness of general clinical picture of ARC syndrome, we comprehensively characterize its major clinical presentation, namely, arthrogryposis, renal dysfunction, cholestasis, and other associated features.

Though a Leiden Open-Source Variation Database (LOVD) for ARC has been established by collating all relevant published variants observed in *VPS33B* and *VIPAR*, further analysis is still in urgent need to highlight variants that have been classified as “pathogenic” worldwide, and ultimately facilitate accurately counseling and improved disease management. Thus, we compile a total of 49

pathogenic *VPS33B* mutations and 14 pathogenic *VIPAR* mutations listed in the ARC-LOVD database to date.

All in all, this article focuses on the latest knowledge regarding both clinical and genetic features of ARC syndrome and discusses appropriate diagnosis and available treatment option currently, which gives clinicians an insight in children at risk of dying from this severe disease. Moreover, it still stands in need of future attempts at gene therapy for improvements in managing or even curing ARC syndrome.

Introduction

Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome (MIM 208085) is a rare autosomal recessive disorder, which was first recognized in the offspring of a consanguineous marriage in 1973 [1]. As a fatal multisystem disorder, an affected child would present a series of clinical features in musculoskeletal systems, kidney, liver, and central nervous at birth. The characteristic features of ARC syndrome include arthrogryposis, renal tubular acidosis, and neonatal cholestatic jaundice (see Figure 1) [2]. These features are sometimes accompanied by additional presentations, including ichthyosis (~50%), platelet anomalies (~25%), agenesis of the corpus callosum (>20%), congenital cardiovascular anomalies (~10%), deafness,

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Figure 1 An infant with ARC syndrome showing arthrogryposis and ichthyotic skin. (Reproduction permission of John Wiley and Sons License, Number: 3438240519407).

recurrent infection, and internal bleeding owing to coagulation dysfunction (see Table 1). The laboratory investigations and biopsy findings of liver or kidney could contribute to further evaluation and confirmation of ARC syndrome. Still, it may be very likely that mild or atypical symptoms at birth and during the first few weeks would lead to ignorance, misdiagnose and delayed treatment of this life-threatening disorder. Consequently, the prognosis of ARC syndrome is so poor that the majority of patients fail to survive beyond the first year of life [3,4].

The locus of this disorder has been mapped to chromosome 5q26.1, and germline mutations have been identified in vacuolar protein sorting 33 homolog B (*VPS33B*; MIM 608552) and *VPS33B*-interacting protein, apical-basolateral polarity regulator (*VIPAR*; MIM 613401) [3,5,6]. *VPS33B* encodes a 617-amino-acid protein that is a homolog of yeast Vps33p, a class C vacuolar protein sorting (vps) protein. Vps33p, along with other class C vps proteins, comprise the two multiprotein complexes, homotypic protein sorting (HOPS) and class C core vacuole/endosome tethering (CORVET), to play an essential

Table 1 Clinical characteristics of patients with ARC syndrome

Classification	Clinical characteristics
Classical clinical feature	Arthrogryposis
	Renal tubular dysfunction
	Neonatal cholestatic jaundice
Additional clinical feature	Ichthyosis
	Platelet abnormality
	Agenesis of the corpus callosum
	Congenital cardiovascular anomalies
	Deafness
	Recurrent sepsis
	Hypothyroidism
	Nephrogenic diabetes insipidus

role in intracellular vesicular trafficking pathways [7]. *VPS33B* is a member of the Sec1/Munc18 family proteins, which interact with soluble NSF attachment protein receptors (SNAREs). SNAREs are involved in a variety of processes—including vesicular exocytosis, synaptic transmission, and general secretion—by facilitating vesicle targeting and fusion [8]. Once mutations develop in the human *VPS33B* gene, the interaction between the expressed mutant protein and the SNARE protein at the late endosomal stage may be impeded and lead to abnormal localization or accumulation of plasma proteins in polarized cells, providing partial insights into the nature of the molecular pathophysiology of ARC syndrome.

VPS33B mutations are detectable in approximately 75% of patients with a clinical diagnosis of ARC syndrome [9]. Apart from locus heterogeneity or failure to detect mutation by direct sequencing analysis, another causative gene of the ARC syndrome, *VIPAR* (also called C14ORF133), was subsequently identified by combining functional and genetic approaches [6]. *VIPAR* consists of a golgin A5 domain and shares significant homology with the C-terminal region of Vps16, which exhibits pleiotropic effects in polarity and apical membrane protein restriction through the formation of *VPS33B-VIPAR* complexes [10]. The role of *VPS33B-VIPAR* complexes are suggested to involve the RAB11A-dependent apical recycling pathway and transcriptional regulation of adherent proteins such as E-cadherin, which ensures normal cellular structure with apical basolateral polarity [6]. It is noteworthy that further research has confirmed the role of epidermal growth factor (EGF) stimulation in the interactions between SPE-39—the *Caenorhabditis elegans* ortholog of *VIPAR*—and Vps33B by tyrosine phosphorylation and ubiquitination of SPE-39 [11-13]. Alternatively, the apical membrane protein was observed to be misrecruited to basolateral membranes and into the late endosomes and lysosomes in knockdown/

knockout studies of *VPS33B* or *VIPAR* [14]. Subsequently, abnormal organelle biogenesis may hinder the generation and maintenance of tissue structures, such as bile ducts and renal tubules, ultimately resulting in cholestasis and abnormal urine. These proteins are found at various locations throughout the body, including the skeletal muscles, kidneys, liver, skin, heart, lungs, and brain, which explains the multisystemic symptoms that are characteristic of the ARC clinical phenotype [5,6,15].

Clinical presentation of ARC syndrome

Arthrogryposis

Arthrogryposis is a primary symptom of ARC syndrome and presents with a spectrum of manifestations, including muscle atrophy, radial deviation of the wrist, dislocation of both hip joints, flexion contracture of the knee joints, and calcaneovalgus [2]. Musculoskeletal abnormalities observed during the first few weeks of life are not generally evident—or perhaps they are simply absent or atypical in certain instances of *VPS33B* mutations, such as 971delA/K324fs [16,17]. The pathogenesis characteristic of ARC syndrome is primarily degeneration of anterior motor neurons, whereas the severity of arthrogryposis may be traced to placental insufficiency during pregnancy with oligohydramnios in the mother and growth restriction of the fetus. In addition, osteopenia and pathological fractures in ARC syndrome are related to impaired reabsorption linked to renal tubular and secondary hyperparathyroidism. Nevertheless, fractures and osteopenia are due to decreased or absent fetal movements in other kind of congenital arthrogryposis such as Bruck syndrome [18]. In case of osteopenia and fractures with arthrogryposis at birth, it is also suggested that ARC syndrome should be included in the differential diagnosis. Especial attention should be paid to the patients associated with other clinical features, such as renal tubular dysfunction, and cholestasis.

Renal tubular dysfunction

Renal tubular dysfunction manifests in the form of Fanconi syndrome, with symptoms including renal tubular acidosis, nephrogenic diabetes insipidus, glucosuria, aminoaciduria, and phosphaturia [19,20]. During episodes of intercurrent illness, renal tubular acidosis may be notably exacerbated, which is symptomatic of renal tubular calcification and degeneration. Renal ultrasonography may be suggestive of nephrocalcinosis or a small dysplastic kidney, accompanied by inflammatory reaction of the renal interstitium and focus, sclerosis of some glomeruli, and tubular distortion and degeneration, per the results of renal biopsy [3,16].

Neonatal cholestatic jaundice

The third primary feature of ARC syndrome is neonatal cholestatic jaundice, concurrent with hepatomegaly, which

is the most common characteristic of ARC syndrome. The presentation of neonatal cholestatic jaundice in ARC syndrome is distinct from the other clinical presentations of neonatal cholestatic jaundice; patients who have ARC syndrome and develop neonatal cholestatic jaundice typically present with no biliary obstruction, have consistently low γ -glutamyl transpeptidase (γ GT) levels, and have normal or slightly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, although they have jaundice and liver cell dysfunction [17]. Indeed, it is well accepted that low GGT cholestasis is a differential feature of ARC syndrome. It is even recommended that patients with low-GGT conjugated hyperbilirubinemia associated with ichthyosis, deafness, platelet dysfunction and central nervous system malformation should be related to *VPS33B* disease [17]. Furthermore, liver biopsies suggest signs of paucity of bile ducts, giant cell transformation, bile plug or lipofuscin deposition, and portal fibrosis in these cases, which could exclude biliary atresia specifically [3,21,22].

Other associated features of ARC syndrome

Additional clinical symptoms of ARC syndrome principally include ichthyosis, abnormal platelet count and function, secondary infection, and cardiovascular anomalies [3,9]. Most patients are affected with ichthyosis (a heterogeneous family of skin disorders) stemming from defects in the SNARE protein, which participates in secretion and function in epidermal cohesion and waterproofing of lamellar granules [23,24]. Despite the fact that abnormal lamellar granule secretion exist in both ARC syndrome and cerebral dysgenesis–neuropathy–ichthyosis–keratoderma (CEDNIK) syndrome, lamellar granule internal structure is normal in ARC syndrome while it is abnormal in CEDNIK syndrome. An additional cause of ichthyosis in ARC syndrome is the lack of absorption of free fatty acids, which are critical for epidermal differentiation [25]. Furthermore, skin biopsy may indicate the presence of mild hyperkeratosis without parakeratosis. Self-limiting intra-abdominal hemorrhage often occurs in patients with ARC, in the absence of abnormal platelet morphology; therefore, normal routine platelet analysis cannot assess the risk of bleeding in ARC syndrome [9]. Despite the increased number of β -granules, similar to Grey platelet syndrome, platelets from patients with ARC syndrome develop abnormal biosynthesis and function of α -granules, which are essential for platelet aggregation, thrombogenesis, inflammation, and tumorigenesis [26,27]. Studies have demonstrated that a *VPS33B*-*VPS16B* complex participates in α -granule formation, since this complex was tracked with transport vesicles destined toward the development of mature α -granules [28,29]. Moreover, patients with ARC syndrome primarily have recurrent episodes of secondary infection coupled with hyperpyrexia and chronic diarrhea, although their immunological profiles are found

Table 2 Pathogenic VPS33B mutations listed in the ARC-LOVD database

Database ID	Exon	DNA change	Status	Protein change	Ethnicity	Reference
VPS33B_00235	1-23	c.(?-354)_(*431 + d127_?)del	Het	p.(0?)	Hispanic	[14]
VPS33B_00232	44	c.240-577_290-156del	Het	p.(Leu81Serfs*5)	South American	[14]
VPS33B_00221	1	c.67C > T	Het	p.(Arg23*)	-	[14]
VPS33B_00001	1	c.89 T > C	Hom	p.(Leu30Pro)	Pakistani	[3]
VPS33B_00223	1i	c.97-2A > C	Hom	p.(?)	-	[14]
VPS33B_00002	2	c.151C > T	Het	p.(Arg51*)	French	[8]
VPS33B_00011	2i	c.177 + 1G > A	Hom	p.(?)	Italian	[3]
VPS33B_00231	2i	c.178-2A > C	Hom	p.(?)	Turkish	[14]
VPS33B_00224	2i	c.178-1G > C	Hom	p.(?)	Pakistani	[14]
VPS33B_00233	3i	c.240-1G > C	Hom	p.(?)	-	[14]
VPS33B_00003	4	c.277C > T	Het	p.(Arg93*)	South American	[8]
VPS33B_00004	5	c.319C > T	Het	p.(Arg107*)	Scottish	[8]
VPS33B_00005	5	c.352C > T	Hom	p.(Gln118*)	Turkish	[7]
VPS33B_00023	5	c.350del	Hom	p.(Pro117Leufs*20)	Saudi Arabia	[3]
VPS33B_00024	6	c.369_370del	Het	p.(Cys123*)	South American	[8]
VPS33B_00013	6i	c.403 + 1G > T	Het	p.(?)	Scottish	[8]
VPS33B_00012	6i	c.403 + 1G > A	Het	p.(?)	Israel	[3]
VPS33B_00014	6i	c.403 + 2 T > A	Het	p.(?)	Korean	[7]
VPS33B_00025	7	c.436_445del	Het	p.(Leu146Metfs*5)	French	[8]
VPS33B_00015	7i	c.498 + 1G > A	Het	p.(?)	Swedish	[4]
VPS33B_00026	8	c.558_559del	Het	p.(Tyr187Trpfs*18)	Italian	[8]
VPS33B_00006	9	c.661C > T	Het	p.(Arg221*)	Korean	[21]
VPS33B_00016	9i	c.701-1G > C	Hom	p.(?)	Israel	[25]
VPS33B_00017	9i	c.700 + 1G > A	Het	p.(?)	Saudi Arabia	[15]
VPS33B_00225	10	c.711del	Het	p.(Phe237Leufs*2)	Pakistani	[14]
VPS33B_00007	10	c.728C > T	Het	p.(Ser243Phe)	Korean	[7]
VPS33B_00027	10	c.740_741del	Het	p.(Tyr247*)	Korean	[7]
VPS33B_00226	11i	c.853-3C > G	Hom	p.(?)	Turkish	[14]
VPS33B_00019	11i	c.853-2A > G	Het	p.(?)	Portuguese	[3]
VPS33B_00018	12i	c.940-1G > A	Het	p.(?)	French	[8]
VPS33B_00028	13	c.971del	Hom	p.(Lys324Argfs*11)	Pakistani	[17]
VPS33B_00227	13i	c.1030 + 5G > T	Hom	p.(?)	Saudi Arabia	[14]
VPS33B_00029	16	c.1208del	Het	p.(Leu403Cysfs*8)	Tahitian	[8]
VPS33B_00230	16i	c.1225 + 5G > C	Het	p.(?)	South American	[14]
VPS33B_00033	17	c.1235_1236delCCinsG	Hom	p.(Pro412Argfs*7)	Polish	[7]
VPS33B_00229	17	c.1261_1262del	Het	p.(Gln421Valfs*8)	South American	[14]
VPS33B_00008	18	c.1312C > T	Hom	p.(Arg438*)	Pakistani	[3]
VPS33B_00008	18	c.1312C > T	Het	p.(Arg438*)	Saudi Arabia	[15]
VPS33B_00008	18	c.1312C > T	Het	p.(Arg438*)	Pakistani	[14]
VPS33B_00219	18i	c.1406-2A > G	Hom	p.(?)	Saudi Arabia	[3]
VPS33B_00220	18i	c.1406-1G > C	Hom	p.(?)	Turkish	[8]
VPS33B_00228	20	c.1498G > T	Hom	p.(Glu500*)	Hispanic	[14]
VPS33B_00030	20	c.1509dupG	Het	p.(Lys504Glufs*23)	Korean	[7,21]
VPS33B_00009	20	c.1519C > T	Het/Hom	p.(Arg507*)	Portuguese	[3,18]

Table 2 Pathogenic VPS33B mutations listed in the ARC-LOVD database (Continued)

VPS33B_00218	20	c.1519C > T	Het	p.(Arg507*)	Korean	[21]
VPS33B_00031	20	c.1576_1577insT	Hom	p.(Glu526Valfs*13)	Polish	[7]
VPS33B_00010	21	c.1594C > T	Hom	p.(Arg532*)	Pakistani	[3]
VPS33B_00234	21i	c.1657 + 1G > A	Hom	p.(?)	Italian	[14]
VPS33B_00032	23	c.1803dupA	Het	p.(Val602Serfs*13)	Korean	[7]

Del, deletion; Fs, frameshift; i, intron; *, stop; Δ, whole exon deletion; Het, heterozygous; Hom, homozygous.
 p.(?), effect of the variant on the protein is unknown.
 p.(0?), no protein product is predicted.

to be within normal limits. It has been recently demonstrated that a profound defect in phagosome-lysosome fusion caused by Vps16B/Vps33B dysfunction may render patients with ARC syndrome increasingly sensitive to infections by nonpathogenic microbes [30]. Interestingly, bacterial endocarditis subject to recurrent infection has also been reported to originate from congenital cardiovascular anomalies, other than the structural abnormalities caused by defects in vesicular trafficking [3].

Genetic background

To gain an insight into worldwide genetic epidemiology and provide easy access to updated resources for researchers and clinicians, a Leiden Open-Source Variation Database (LOVD) for ARC (<https://grenada.lumc.nl/LOVD2/ARC>) was established in 2011 by collating all relevant published variants observed in *VPS33B* and *VIPAR* [31]. As for March 2014, this online locus-specific ARC database has compiled a total of 299 unique variants in *VPS33B* and 34 unique variants in *VIPAR*, of which sequence mutations are basically classified as “pathogenic,” “probably pathogenic,” “no

known pathogenicity,” “probably no pathogenicity,” and “effect unknown,” according to their projected effect on the protein and the clinical phenotype. To date, the database includes 49 published variants in *VPS33B* and 14 published variants in *VIPAR* worldwide that have been classified as “pathogenic.” Regarding *VPS33B*, most identified variants were substitutions (n = 34; 19 splice site, 13 nonsense, and two missense mutations), apart from deletions (n = 11), duplications (n = 2), insertions (n = 1), and indels (n = 1). It is noteworthy that three variants were prominent on account of their relative prevalence: c.403 + 2 T > A, c.1312C > T, and c.1519C > T (see Table 2). Most “pathogenic” variants in *VIPAR* are substitutions (n = 11; 8 nonsense, two missense, and one splice site mutation). Additionally, two deletions were present, of which two recurrent variants existed: c.658C > T and c.808C > T (see Table 3). This information is available in the ARC-LOVD database to inform clinicians and patient families on current prognoses, advances, and clinical course of ARC pathogenesis, ultimately contributing to accurately counseling and improved disease management.

Table 3 Pathogenic VIPAR mutations listed in ARC-LOVD database

Database ID	Exon	DNA change	status	Protein Change	Ethnicity	Reference
VIPAR_00001	1	c.2 T > G	Hom	p.(Met1Arg)	Turkish	[4]
VIPAR_00021	6	c.463_464del	Het	p.(Trp155Glufs*4)	Caucasian	[14]
VIPAR_00022	6	c.484C > T	Het	p.(Arg162*)	Caucasian	[14]
VIPAR_00002	7	c.535C > T	Hom	p.(Gln179*)	Turkish	[4]
VIPAR_00023	9	c.638 T > C	Het	p.(Leu213Pro)	-	[14]
VIPAR_00003	9	c.658C > T	Hom	p.(Arg220*)	Italian	[4]
VIPAR_00003	9	c.658C > T	Het	p.(Arg220*)	Turkish	[4]
VIPAR_00007	10	c.749_753del	Hom	p.(Thr250Argfs*17)	Croatian	[4]
VIPAR_00004	11	c.808C > T	Hom	p.(Arg270*)	Israel	[4,14]
VIPAR_00020	11i	c.837-1G > T	Hom	p.(?)	-	[14]
VIPAR_00005	12	c.871C > T	Het	p.(Gln291*)	Turkish	[4]
VIPAR_00019	13	c.1021 T > C	Hom	p.(Cys341Arg)	Pakistani	[14]
VIPAR_00006	17	c.1273C > T	Hom	p.(Gln425*)	Turkish	[4]

Del, deletion; Fs, frameshift; i, intron; *, stop; Δ, whole exon deletion; Het, heterozygous; Hom, homozygous.
 p.(?), effect of the variant on the protein is unknown.
 p.(0?), no protein product is predicted.

Diagnostic clues and workup

In general, case reports of patients with ARC syndrome are not uncommon in Saudi Arabia and Pakistan, where rates of consanguinity are high, whereas several sporadic case studies have been reported in Turkey, North Africa, Italy, Portugal, and Asia [5,31-34]. Despite these reports, the prevalence of ARC syndrome has not been accurately defined and is subject to potential underestimation because of lack of a broad clinical picture and of early recognition of this rare disease. It is worth mentioning that the relative incidence rate ratio of ARC was suggested to be 1/7 that of biliary atresia in 90 patients with neonatal cholestasis (95% CI 0.33 ~ 0.06) [21,22,35].

ARC syndrome is a life-threatening autosomal recessive multisystem disorder, and its early diagnosis is of vital importance for the development of an appropriate therapeutic regimen. Currently, clinical diagnosis of ARC syndrome consists of identifying the triad conditions of arthrogryposis, renal tubular acidosis, and neonatal cholestatic jaundice with low γ GT activity, combined with pathologic confirmation. However, the majority of patients are vulnerable to coagulation defects; in other words, kidney or liver biopsies result in a risk of fatal bleeding (>50%). Still, similar clinical and laboratory findings could be observed both in ARC syndrome and progressive familial intrahepatic cholestasis. Therefore, clinical presentations along with *VPS33B* and *VIPAR* sequencing analyses constitute an apparently safer diagnostic procedure. Currently, there are limitations in mutational analysis, such as the long duration required for analysis and the potential for false negatives, analysis of *VPS33B* protein expression in skin fibroblasts and platelet morphology in peripheral blood smears are two alternative techniques that have been proposed as valuable tools for diagnostic screening examinations [9,36].

Treatment options and prognosis

No specific treatment for ARC syndrome currently exists; rather, supportive care—including fluid infusion, anti-infection, supplement with ursodeoxycholic acid, fat-soluble vitamins, calcium glubionate, L-thyroxine and phosphate—is administered to patients for improving the quality of life. Nevertheless, some patients with joint contractures, congenital hip dislocation, and vertical talus are in need of immediate orthopedic intervention due to delayed diagnosis. Nevertheless, aggressive orthopedic management is still not recommended, since poor general status and low survival rates may affect the outcome of the surgery [37]. In cases of ARC syndrome that failed to respond to medical therapy, it is also advisable to consider liver transplant to ameliorate severe cholestasis and intractable pruritus. It is reported that an Iranian boy underwent a liver transplant have made a recovery. Specifically, the pruritus immediately improved

after the surgery, and his scaly skin was also normal in 6 months. Moreover, the patient stayed in good condition without any complications or rejection during more than 5 years' follow-up [38].

As a lethal multisystem disorder, prognosis of ARC syndrome is particularly poor. Most patients succumb within the first year of life after developing recurrent infection, severe hyponatremia, acidosis, or internal hemorrhaging, except for a few patients who have ARC syndrome but retain partial function of *VPS33B* [22].

Conclusion

No specific treatment currently exists for ARC syndrome. Comprehensive analysis of family history, classical clinical presentations, biopsy of the liver or kidney, and/or genetic mutational analysis may not only facilitate accurate diagnosis and the development of appropriately tailored treatment at an early stage but also provide genetic counseling and prenatal or preimplantation genetic diagnosis for the affected families. With the continued progress of molecular genetics and medical technologies, future attempts at gene therapy may yield improvements in managing or even curing ARC syndrome.

Consent

Written informed consent was obtained from the patient's guardian/parent/next of kin for the publication of this report and any accompanying images.

Abbreviations

ALT: alanine aminotransferase; AST: Aspartate aminotransferase; ARC: ARTHROGRYPOSIS-renal dysfunction-cholestasis; CEDNIK: Cerebral dysgenesis-neuropathy-ichthyosis-keratoderma; CORVET: Class C core vacuole/endosome tethering; EGF: Epidermal growth factor; γ GT: γ -Glutamyl transpeptidase; HOPS: Homotypic protein sorting; LOVD: Leiden open-source variation database; SNAREs: Soluble NSF attachment protein receptors; *VPS33B*: Vacuolar protein sorting 33 homolog B; *VIPAR*: *VPS33B*-interacting protein, apical-basolateral polarity regulator.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YZ participated in the design and draft of the manuscript. JZ was involved in designing and revising the manuscript critically for important intellectual content. Both authors read and approved the final manuscript.

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References

1. Lutz-Richner AR, Landolt RF: Familiäre Gallengansmissbildungen mit tubularer Neirensuffizienz. *Helv Paediatr Acta* 1973, **28**:1-12.
2. 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.

3. Gissen P, Tee L, Johnson CA, Genin E, Caliebe A, Chitayat D, Clericuzio C, Denecke J, Di Rocco M, Fischler B, FitzPatrick D, Garcia-Cazorla A, Guyot D, Jacquemont S, Koletzko S, Leheup B, Mandel H, Sanseverino MT, Houwen RH, McKiernan PJ, Kelly DA, Maher ER: **Clinical and molecular genetic features of ARC syndrome.** *Hum Genet* 2006, **120**(3):396–409.
4. Abdullah MA, Al-Hasnan Z, Okamoto E, Abomelha AM: **Arthrogyrosis, renal dysfunction and cholestasis syndrome.** *Saudi Med J* 2000, **21**(3):297–299.
5. Gissen P, Johnson CA, Morgan NV, Stapelbroek JM, Forshew T, Cooper WN, McKiernan PJ, Klomp LW, Morris AA, Wraith JE, McClean P, Lynch SA, Thompson RJ, Lo B, Quarrell OW, Di Rocco M, Trembath RC, Mandel H, Wali S, Karet FE, Knisely AS, Houwen RH, Kelly DA, Maher ER: **Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogyrosis-renal dysfunction-cholestasis (ARC) syndrome.** *Nat Genet* 2004, **36**(4):400–404.
6. Cullinane AR, Straatman-Iwanowska A, Zaucker A, Wakabayashi Y, Bruce CK, Luo G, Rahman F, Gurakan F, Utine E, Ozkan TB, Denecke J, Vukovic J, Di Rocco M, Mandel H, Cangul H, Matthews RP, Thomas SG, Rappoport JZ, Arias IM, Wolburg H, Knisely AS, Kelly DA, Muller F, Maher ER, Gissen P: **Mutations in VIPAR cause an arthrogyrosis, renal dysfunction and cholestasis syndrome phenotype with defects in epithelial polarization.** *Nat Genet* 2010, **42**(4):303–312.
7. Carim L, Sumoy L, Andreu N, Estivill X, Escarceller M: **Cloning, mapping and expression analysis of VPS33B, the human orthologue of rat Vps33b.** *Cytogenet Cell Genet* 2000, **89**(1–2):92–95.
8. Peterson MR, Emr SD: **The class C Vps complex functions at multiple stages of the vacuolar transport pathway.** *Traffic* 2001, **2**(7):476–486.
9. Cullinane AR, Straatman-Iwanowska A, Seo JK, Ko JS, Song KS, Gizewska M, Gruszfeld D, Gliwicz D, Tuysuz B, Erdemir G, Sougrat R, Wakabayashi Y, Hinds R, Barnicoat A, Mandel H, Chitayat D, Fischler B, Garcia-Cazorla A, Knisely AS, Kelly DA, Maher ER, Gissen P: **Molecular investigations to improve diagnostic accuracy in patients with ARC syndrome.** *Hum Mutat* 2009, **30**(2):E330–E337.
10. Gissen P, Johnson CA, Gentle D, Hurst LD, Doherty AJ, O’Kane CJ, Kelly DA, Maher ER: **Comparative evolutionary analysis of VPS33 homologues: genetic and functional insights.** *Hum Mol Genet* 2005, **14**(10):1261–1270.
11. Zhu GD, Salazar G, Zlatic SA, Fiza B, Doucette MM, Heilman CJ, Levey AI, Faundez V, L’Hernault SW: **SPE-39 family proteins interact with the HOPS complex and function in lysosomal delivery.** *Mol Biol Cell* 2009, **20**(4):1223–1240.
12. Tornieri K, Zlatic SA, Mullin AP, Werner E, Harrison R, L’Hernault SW, Faundez V: **Vps33b pathogenic mutations preferentially affect VIPAS39/SPE-39-positive endosomes.** *Hum Mol Genet* 2013, **22**(25):5215–5228.
13. Ishii A, Kamimori K, Hiyoshi M, Kido H, Ohta T, Konishi H: **Inhibitory effect of SPE-39 due to tyrosine phosphorylation and ubiquitination on the function of Vps33B in the EGF-stimulated cells.** *Febs Lett* 2012, **586**(16):2245–2250.
14. Zlatic SA, Tornieri K, L’Hernault SW, Faundez V: **Metazoan cell biology of the HOPS tethering complex.** *Cell Logist* 2011, **1**(3):111–117.
15. Matthews RP, Plumb-Rudewicz N, Lorent K, Gissen P, Johnson CA, Lemaigre F, Pack M: **Zebrafish vps33b, an ortholog of the gene responsible for human arthrogyrosis-renal dysfunction-cholestasis syndrome, regulates biliary development downstream of the oncut transcription factor hnf6.** *Development* 2005, **132**(23):5295–5306.
16. Arhan E, Yusufoglu AM, Sayli TR: **Arc syndrome without arthrogyrosis, with hip dislocation and renal glomerulocystic appearance: a case report.** *Eur J Pediatr* 2009, **168**(8):995–998.
17. Bull LN, Mahmoodi V, Baker AJ, Jones R, Strautnieks SS, Thompson RJ, Knisely AS: **VPS33B mutation with ichthyosis, cholestasis, and renal dysfunction but without arthrogyrosis: incomplete ARC syndrome phenotype.** *J Pediatr* 2006, **148**(2):269–271.
18. Sanseverino MT, de Souza CF, Gissen P, Sordi AO, Magalhaes JA, Schuler-Faccini L: **Increased nuchal translucency in arthrogyrosis, renal dysfunction and cholestasis (ARC) syndrome and discovery of a Portuguese specific mutation in the VPS33B gene.** *Ultrasound Obstet Gynecol* 2006, **28**(2):233–234.
19. Deal JE, Barratt TM, Dillon MJ: **Fanconi syndrome, ichthyosis, dysmorphism, jaundice and diarrhoea—a new syndrome.** *Pediatr Nephrol* 1990, **4**(4):308–313.
20. Malaki M, Mandana R, Ghaffari S: **ARC syndrome with complex renal problems: nephrocalcinosis, proximal and hyperkalemic distal RTA and nephrogenic diabetes insipidus.** *Saudi J Kidney Dis Transpl* 2012, **23**(4):804–809.
21. Jang JY, Kim KM, Kim GH, Yu E, Lee JJ, Park YS, Yoo HW: **Clinical characteristics and VPS33B mutations in patients with ARC syndrome.** *J Pediatr Gastroenterol Nutr* 2009, **48**(3):348–354.
22. Eastham KM, McKiernan PJ, Milford DV, Ramani P, Wyllie J, VanT HW, Lynch SA, Morris AA: **ARC syndrome: an expanding range of phenotypes.** *Arch Dis Child* 2001, **85**(5):415–420.
23. Choi HJ, Lee MW, Choi JH, Moon KC, Koh JK: **Ichthyosis associated with ARC syndrome: ARC syndrome is one of the differential diagnoses of ichthyosis.** *Pediatr Dermatol* 2005, **22**(6):539–542.
24. Franceschini P, Barberis L: **Arthrogyrosis, renal tubular dysfunction, cholestasis, ichthyosis syndrome (ARCI).** *Eur J Pediatr* 1997, **156**(1):78.
25. Hershkovitz D, Mandel H, Ishida-Yamamoto A, Chefetz I, Hino B, Luder A, Indelman M, Bergman R, Sprecher E: **Defective lamellar granule secretion in arthrogyrosis, renal dysfunction, and cholestasis syndrome caused by a mutation in VPS33B.** *Arch Dermatol* 2008, **144**(3):334–340.
26. Flaumenhaft R: **Alpha-granules: a story in the making.** *Blood* 2012, **120**(25):4908–4909.
27. Saadah OI, Bokhari BE, Alshaeri TM, Jastaniah W: **Haematological manifestations of arthrogyrosis-renal dysfunction-cholestasis (ARC) syndrome: a case report.** *Arab J Gastroenterol* 2013, **14**(1):26–28.
28. Lo B, Li L, Gissen P, Christensen H, McKiernan PJ, Ye C, Abdelhaleem M, Hayes JA, Williams MD, Chitayat D, Kahr WH: **Requirement of VPS33B, a member of the Sec1/Munc18 protein family, in megakaryocyte and platelet alpha-granule biogenesis.** *Blood* 2005, **106**(13):4159–4166.
29. Urban D, Li L, Christensen H, Pluthero FG, Chen SZ, Puhacz M, Garg PM, Lanka KK, Cummings JJ, Kramer H, Wasmuth JD, Parkinson J, Kahr WH: **The VPS33B-binding protein VPS16B is required in megakaryocyte and platelet alpha-granule biogenesis.** *Blood* 2012, **120**(25):5032–5040.
30. Akbar MA, Tracy C, Kahr WH, Kramer H: **The full-of-bacteria gene is required for phagosome maturation during immune defense in Drosophila.** *J Cell Biol* 2011, **192**(3):383–390.
31. Smith H, Galmes R, Gogolina E, Straatman-Iwanowska A, Reay K, Banushi B, Bruce CK, Cullinane AR, Romero R, Chang R, Ackermann O, Baumann C, Cangul H, Cakmak CF, Aygun C, Coward R, Dionisi-Vici C, Sibbles B, Inward C, Kim CA, Klumperman J, Knisely AS, Watson SP, Gissen P: **Associations among genotype, clinical phenotype, and intracellular localization of trafficking proteins in ARC syndrome.** *Hum Mutat* 2012, **33**(12):1656–1664.
32. Li LT, Zhao J, Chen R, Wang JS: **Two novel VPS33B mutations in a patient with arthrogyrosis, renal dysfunction and cholestasis syndrome in mainland China.** *World J Gastroenterol* 2014, **20**(1):326–329.
33. Kim KM, Kim GH, Park YS, Yoo HW: **Aberant splicing by a mutation, c.403 + 2 T > A, in Korean patients with arthrogyrosis-renal-dysfunction-cholestasis syndrome.** *Pediatr Int* 2011, **53**(4):609–610.
34. Tekin N, Durmus-Aydogdu S, Dinleyici EC, Bor O, Bildirici K, Aksit A: **Clinical and pathological aspects of ARC (arthrogryrosis, renal dysfunction and cholestasis) syndrome in two siblings.** *Turk J Pediatr* 2005, **47**(1):67–70.
35. Abu-Sa’Da O, Barbar M, Al-Harbi N, Taha D: **Arthrogyrosis, renal tubular acidosis and cholestasis (ARC) syndrome: two new cases and review.** *Clin Dysmorphol* 2005, **14**(4):191–196.
36. Kim SM, Chang HK, Song JW, Koh H, Han SJ: **Agranular platelets as a cardinal feature of ARC syndrome.** *J Pediatr Hematol Oncol* 2010, **32**(4):253–258.
37. Jang WY, Cho TJ, Bae JY, Jung HW, Ko JS, Park MS, Yoo WJ, Chung CY, Seo JK, Choi IH: **Orthopaedic manifestations of arthrogyrosis-renal dysfunction-cholestasis syndrome.** *J Pediatr Orthop* 2011, **31**(1):107–112.
38. Dehghani SM, Bahador A, Nikeghbalian S, Salahi H, Geramizadeh B, Malekpour A, Malek-Hosseini SA: **Liver transplant in a case of arthrogyrosis-renal tubular dysfunction-cholestasis syndrome with severe intractable pruritus.** *Exp Clin Transplant* 2013, **11**(3):290–292.

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