SAR Journal of Medical Case Reports

Abbreviated Key Title: *SAR J Med Case Rep*
Home page: https://sarmedjournals.com

ISSN 2707-7780 (P)
ISSN 2709-6947 (O)

Case Report

New Gene Mutation in Lebanese Infant with Arthrogryposis–Renal Dysfunction–Cholestasis (ARC) Syndrome

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Article History: | Received: 28.07.2020 | Accepted: 18.08.2020 | Published: 30.08.2020 |

Abstract: ARC syndrome is a life-threatening autosomal recessive multisystem disorder, caused by mutations in the VPS33B or VIPAR genes and its early diagnosis is of vital importance for the development of an appropriate therapeutic regimen. The cardinal features of ARC syndrome are arthrogryposis, renal tubular acidosis, and neonatal cholestatic jaundice with normal gamma glutamyltranspeptidase (GGT) level. To date, the database includes 49 published variants in VPS33B and 14 published variants in VIPAR worldwide. Here we report a new variant in VPS33B gene mutation in a 50 days old Lebanese baby boy featuring cholestatic jaundice, multiple contractions of lower limbs including talipes equinovarus and laboratory findings of renal tubular acidosis.

Keywords: ARC syndrome (arthrogryposis, renal dysfunction, cholestasis), VPS33B, VIPAR, GGT (gamma glutamyltranspeptidase).

INTRODUCTION

ARC syndrome refers to an association between arthrogryposis, renal tubular dysfunction, and cholestasis. Eleven pedigrees have been reported since the association was first described in 1973. Autosomal recessive inheritance is suggested by the frequency of parental consanguinity and recurrence in siblings [1, 2]. ARC syndrome is a multisystem disorder it affects the musculoskeletal system, kidneys, liver, and central nervous system at birth. Additional presentations, includes ichthyosis (~50%), platelet anomalies (~25%), agenesis of the corpus callosum (>20%), congenital cardiovascular anomalies (~10%), deafness, recurrent infection, and internal bleeding owing to coagulation dysfunction. From laboratory findings perspective unlike other cholestatic diseases GGT is normal. In addition to clinical and laboratory findings; the diagnosis of ARC syndrome is made by molecular analysis when VPS33B mutation analysis is used instead of organ biopsy as a first line diagnostic test for ARC syndrome. Since 49 published variants in VPS33B and 14 published variants in VIPAR are present worldwide, in this article we report a new mutation p.l340fs in VPS33B gene in a 50 days old Lebanese baby boy featuring cholestatic jaundice with normal GGT and lower limbs contractions.

CASE PRESENTATION

A 50 days old Lebanese baby boy, born by normal vaginal delivery to a 32 years old mother (G2P2A0) of an A positive blood group, an A positive blood group father, with first degree consanguinity between parents. The mother TORCH status was unknown, GBS unknown. The baby was born with Apgar score 9-10, no neonatal resuscitation was needed, no previous ICN admission, birth weight 3200g and exclusively breastfeed. The baby was referred for history of jaundice at day 50 of life. History goes back since day 25 of life when mother sought medical consultation for jaundice so was advised to withhold breastfeeding and the baby was shifted to term formula. Clinically the jaundice kept increasing in severity reaching toes, and the baby

became hypotonic, lethargic, and failed to gain weight (Weight 3000g) with acholic stools. Laboratory findings showed direct hyperbilirubinemia (total bilirubin 12 and direct bilirubin 10), slightly elevated transaminase (SGOT 120, SGPT 236), normal GGT 13.36, normal alfa1 antitrypsin and remarkable elevation in alkaline phosphatase (1731 IU/L). TORCH serology was negative except for positive toxoplasma IgG. Ultrasound of abdomen and pelvis showed normal size and echo texture of the liver, distended gallbladder with no intra or extra hepatic biliary ductal dilatation. Biliary atresia was suspected, yet the exploratory cholangiography performed showed no atretic biliary tree. Based on the patient's set of symptoms including arthrogryposis, unlike other cholestatic disease cholestasis gamma GT was normal. In addition to clinical and laboratory findings the diagnosis of ARC syndrome was confirmed by high-throughput sequencing exam results of genes involved in cholestasis discovery of a new mutation in the VPS33B gene, yet in previously unreported locus p.l340Fs, data analysis, assuming progeny homozygote revealed the presence of a homozygous variation in the patient.

DISCUSSION

This is an overview of a newly identified mutation p.l340fs in VPS33B gene reported in a 50 days old Lebanese baby boy who was presented with cholestatic jaundice (with normal GGT) and lower limbs contractions which constitute the main clinical features of ARC syndrome. Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a multisystem disorder associated with consanguinity and is generally supposed to be a rare autosomal disorder involving the liver, kidneys, skin, and central nervous and musculoskeletal systems. The classical presentation of ARC syndrome includes arthrogryposis and neonatal cholestatic jaundice. Additional features include: ichthyosis, central nervous system malformation, platelet anomalies, severe failure to thrive, recurrent infections, and internal bleeding owing to coagulation dysfunction. ARC syndrome may present with mild or atypical symptoms at birth or during the first few weeks of life, which may lead to misdiagnosis, un-noticed insidious symptoms and result in delayed treatment of this life-threating disorder [1, 2]. The genetic lesion which is responsible for the phenotype of ARC syndrome has been mapped to the chromosome 5q26.1 at the locus of VPS33B or VIPAR gene [3, 4]. The VPS33B gene is classified as a member of the Sec- 1/Munch 18 family which is involved in vesicular trafficking among cell compartments in processes such as synaptic transmission, vesicular exocytosis, and general secretion, this family and the members of synaxtin family regulate the membrane fusion events. The VPS33B-VIPAR complex also participates in the development and maturation of platelet α-granules, which is required to form stable aggregates. VPS33B-VIPAR deficiency leads to abnormal morphology of epidermal lamellar bodies, which affects epidermal homeostasis and disrupts skin barrier function. These proteins are expressed throughout the body including: liver, skin, brain, kidneys and skeletal muscle which may explain the systemic symptoms observed in ARC syndrome [3]. To date, the database includes 50 published variants in VPS33B and 14 published variants in VIPAR worldwide that have been classified as "pathogenic". Most "pathogenic" variants in VPS33B were substitutions (nonsense and missense mutations), apart from deletions, duplications, insertions, and indels. Regarding VIPAR, most identified variants are substitutions; additionally, two deletions were present (Tables 1 and 2) [5].

Table-1: Pathogenic VPS33B mutations listed in ARC-LOVD database

Database ID	Exon	DNA change	Status	Protein change	Ethnicity
VPS33B_00235	1-23	c. (?_-354)_(*431 + d127_?)del	Het	p.(0?)	Hispanic
VPS33B_00232	△4	c.240-577_290-156del	Het	p.(Leu81Serfs*5)	South American
VPS33B_00221	1	c.67C > T	Het	p.(Arg23*)	-
VPS33B_00001	1	c.89 T > C	Hom	p.(Leu30Pro)	Pakistani
VPS33B_00223	1i	c.97-2A > C	Hom	p.(?)	-
VPS33B_00002	2	c.151C > T	Het	p.(Arg51*)	French
VPS33B_00011	2i	c.177 + 1G > A	Hom	p.(?)	Italian
VPS33B_00231	2i	c.178-2A > C	Hom	p.(?)	Turkish
VPS33B_00224	2i	c.178-1G > C	Hom	p.(?)	Pakistani
VPS33B_00233	3i	c.240-1G > C	Hom	p.(?)	-
VPS33B_00003	4	c.277C > T	Het	p.(Arg93*)	South American
VPS33B_00004	5	c.319C > T	Het	p.(Arg107*)	Scottish
VPS33B_00005	5	c.352C > T	Hom	p.(Gln118*)	Turkish
VPS33B_00023	5	c.350del	Hom	p.(Pro117Leufs*20)	Saudi Arabia

VPS33B_00024	6	c.369_370del	Het	p.(Cys123*)	South American
VPS33B_00013	6i	c.403 + 1G > T	Het	p.(?)	Scottish
VPS33B_00012	6i	c.403 + 1G > A	Het	p.(?)	Israel
VPS33B_00014	6i	c.403 + 2 T > A	Het	p.(?)	Korean
VPS33B_00025	7	c.436_445del	Het	p.(Leu146Metfs*5)	French
VPS33B_00015	7i	c.498 + 1G > A	Het	p.(?)	Swedish
VPS33B_00026	8	c.558_559del	Het	p.(Tyr187Trpfs*18)	Italian
VPS33B_00006	9	c.661C > T	Het	p.(Arg221*)	Korean
VPS33B_00016	9i	c.701-1G > C	Hom	p.(?)	Israel
VPS33B_00017	9i	c.700 + 1G > A	Het	p.(?)	Saudi Arabia
VPS33B_00225	10	c.711del	Het	p.(Phe237Leufs*2)	Pakistani
VPS33B_00007	10	c.728C > T	Het	p.(Ser243Phe)	Korean
VPS33B_00027	10	c.740_741del	Het	p.(Tyr247*)	Korean
VPS33B_00226	11i	c.853-3C > G	Hom	p.(?)	Turkish
VPS33B_00019	11i	c.853-2A > G	Het	p.(?)	Portuguese
VPS33B_00018	12i	c.940-1G > A	Het	p.(?)	French
VPS33B_00028	13	c.971del	Hom	p.(Lys324Argfs*11	Pakistani
VPS33B_00227	13i	c.1030 + 5G > T	Hom	p.(?)	Saudi Arabia
VPS33B_00029	16	c.1208del	Het	p.(Leu403Cysfs*8)	Tahitian
VPS33B_00230	16i	c.1225 + 5G > C	Het	p.(?)	South American
VPS33B_00033	17	c.1235_1236delCCinsG	Hom	p.(Pro412Argfs*7)	Polish
VPS33B_00229	17	c.1261_1262del	Het	p.(Gln421Valfs*8)	South American
VPS33B_00008	18	c.1312C > T	Hom	p.(Arg438*)	Pakistani
VPS33B_00008	18	c.1312C > T	Het	p.(Arg438*)	Saudi Arabia
VPS33B_00008	18	c.1312C > T	Het	p.(Arg438*)	Pakistani
VPS33B_00219	18i	c.1406-2A > G	Hom	p.(?)	Saudi Arabia
VPS33B_00220	18i	c.1406-1G > C	Hom	p.(?)	Turkish
VPS33B_00228	20	c.1498G > T	Hom	p.(Glu500*)	Hispanic
VPS33B_00030	20	c.1509dupG	Het	p.(Lys504Glufs*23)	Korean
VPS33B_00009	20	c.1519C > T	Het/Hom	p.(Arg507*)	Portuguese
VPS33B_00218	20	c.1519C > T	Het	p.(Arg507*)	Korean
VPS33B_00031	20	c.1576_1577insT	Hom	p.(Glu526Valfs*13)	Polish
VPS33B_00010	21	c.1594C > T	Hom	p.(Arg532*)	Pakistani
VPS33B_00234	21i	c.1657 + 1G > A	Hom	p.(?)	Italian
VPS33B_00032	23	c.1803dupA	Het	p.(Val602Serfs*13)	Korean

Table-2: Pathogenic VIPAR mutations listed in ARC-LOVD database

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

In addition to the mutations described in the above tables, genetic analysis in two sibling patients revealed a novel homozygous mutation in NM_018668.4 (VPS33B):c.1157A > C (p.His386Pro) published recently in march 2019.

CONCLUSION

More attention should be paid and earlier to newborns with arthrogryposis-renal dysfunction-cholestasis (ARC). We do recommend routine serum measurements and genetic studies early on, to identify asymptomatic cases of this insidious life-threatening disease, it's the only way to have a prompt diagnosis, provide timely support and improve the baby's chances for a better outcome and reduced complications.

REFERENCES

1. Gissen, P., Tee, L., Johnson, C. A., Genin, E., Caliebe, A., Chitayat, D., & FitzPatrick, D. (2006). Clinical and molecular genetic features of ARC syndrome. *Human genetics*, *120*(3), 396-409.
2. Wang, J. S., Zhao, J., & Li, L. T. (2014). ARC syndrome with high GGT cholestasis caused by VPS33B mutations. *World Journal of Gastroenterology: WJG*, *20*(16), 4830.
3. Gissen, P., Johnson, C. A., Morgan, N. V., Stapelbroek, J. M., Forshew, T., Cooper, W. N., ... & McClean, P. (2004). Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome. *Nature genetics*, *36*(4), 400-404.
4. Cullinane, A. R., Straatman-Iwanowska, A., Zaucker, A., Wakabayashi, Y., Bruce, C. K., Luo, G., & Denecke, J. (2010). Mutations in VIPAR cause an arthrogryposis, renal dysfunction and cholestasis syndrome phenotype with defects in epithelial polarization. *Nature genetics*, *42*(4), 303-312.
5. Zhou, Y., & Zhang, J. (2014). Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome: from molecular genetics to clinical features. *Italian journal of pediatrics*, *40*(1), 77.