

Accepted Manuscript

Novel *VIPAS39* Mutation in a Syndromic Patient with Arthrogyrosis, Renal Tubular Dysfunction and Intrahepatic Cholestasis

Majid Aflatounian, Holly Smith, Fatemeh Farahani, Azam Tofighi Naeem, Anna Straatman-Iwanowska, Samaneh Zoghi, Urvi Khatri, Parisa Tajdini, Gholam Hossein Fallahi, Paul Gissen, Nima Rezaei, MD, PhD

PII: S1769-7212(16)30005-2

DOI: [10.1016/j.ejmg.2016.01.005](https://doi.org/10.1016/j.ejmg.2016.01.005)

Reference: EJMG 3133

To appear in: *European Journal of Medical Genetics*

Received Date: 28 June 2015

Revised Date: 19 January 2016

Accepted Date: 21 January 2016

Please cite this article as: M. Aflatounian, H. Smith, F. Farahani, A.T. Naeem, A. Straatman-Iwanowska, S. Zoghi, U. Khatri, P. Tajdini, G.H. Fallahi, P. Gissen, N. Rezaei, Novel *VIPAS39* Mutation in a Syndromic Patient with Arthrogyrosis, Renal Tubular Dysfunction and Intrahepatic Cholestasis, *European Journal of Medical Genetics* (2016), doi: 10.1016/j.ejmg.2016.01.005.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Novel VIPAS39 Mutation in a Syndromic Patient with Arthrogryposis, Renal Tubular Dysfunction and Intrahepatic Cholestasis

Majid Aflatounian¹, Holly Smith², Fatemeh Farahani¹, Azam Tofighi Naeem¹, Anna Straatman-Iwanowska², Samaneh Zoghi⁴, Urvi Khatri², Parisa Tajdini¹, Gholam Hossein Fallahi¹, Paul Gissen², Nima Rezaei^{3,4,5}

¹ *Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

² *UCL Institute of Child Health and MRC Laboratory for Molecular Cell Biology, Great Ormond Street Hospital for Children, London, UK*

³ *Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

⁴ *Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

⁵ *Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

Corresponding author: Nima Rezaei, MD, PhD

Mailing address: Children's Medical Center Hospital, Dr. Qarib St, Keshavarz Blvd, Tehran 14194, Iran

Tel: +9821-6692-9234, Fax: +9821-6692-9235

E-mail: rezaei_nima@tums.ac.ir

Running Head: ARC syndrome

Abstract

ARC syndrome is a rare autosomal recessive disease, characterized by arthrogyriposis, renal tubular dysfunction and cholestasis. Herein a 2.5 month old infant with dysmorphic features, including small anterior fontanel, low set ears, beaked nose and high arched palate is presented who was referred because of icterus. He also suffered from some additional anomalies, including unilateral choanal atresia, club foot, and bilateral developmental dislocation of hip, while further studies showed renal tubular acidosis and hearing impairment in addition to cholestasis. Genetic studies showed a homozygous mutation in the *VIPAS39* gene. Making the definite diagnosis of the syndrome is important, while increased risk of mutation in other siblings highlights the importance of prenatal diagnosis.

Key words: Syndrome, mutation, prenatal diagnosis, cholestasis

Introduction

ARC syndrome is a rare disease, characterized by arthrogyriposis, renal tubular dysfunction, and intrahepatic cholestasis (1). However, there is clinical variability in this syndrome. There are some reports showing musculoskeletal manifestations of arthrogyriposis multiplex, or association of vertical talus, pes calcaneovalgus, hip dislocation, pathologic fractures, and rigid kyphosis in affected patients (2). Renal manifestations also varies from isolated renal tubular acidosis to severe fanconi syndrome with nephrogenic diabetes insipidus, interstitial nephritis and nephrocalcinosis (3,4). Hepatic involvement in ARC syndrome includes intrahepatic biliary ducts paucity, lipofuscin deposition, giant cell hepatitis, fibrosis and cirrhosis (4). Meanwhile normal hepatic histology could also be seen (5). Unfortunately, the syndrome has no curative therapy (6), and most patients die because of recurrent febrile illness and pneumonia before first birthday (4,7). ARC syndrome can be caused by homozygous or compound heterozygous mutations in VPS33B or VIPAS39 genes (8). Herein, a case with clinical manifestations compatible with ARC syndrome is reported, in which the definite diagnosis was made by genetic study.

Case report

A 2.5-month old male infant, born from consanguineous Iranian parents, was admitted to the Children's Medical Center Hospital, the Pediatrics Center of Excellence in Tehran, Iran because of icterus from 3 weeks of age. This infant was the first child of family, born at gestational age of 35 weeks by cesarean section because of breech presentation. In prenatal evaluation, oligohydramnios had been detected. He had a birth weight of 2,700 gram; and was under levothyroxin therapy because of hypothyroidism. He has a dysmorphic features, including small anterior fontanel, low set ears, beaked nose and high arched palate. Additional anomalies were

unilateral choanal atresia, club foot, and bilateral developmental dislocation of hip (DDH). Because of his icterus and hepatomegaly, liver investigations were performed, which revealed hyperbilirubinemia, mild increased transaminases, greatly increased alkaline phosphatase and normal gamma glutamyl transpeptidase (AST=156, ALT=174, ALP=4467, GGT=46, Bil total=7.1, Bil direct=3.9, total protein=5.3, albumin=3.2). Hepatic histology showed hepatocyte disarray with scattered giant cell transformation intra and extra hepatocytic bile stasis in porta; no evidence of necrosis was seen. Portal spaces showed mild inflammation with mild fibrous expansion and decreased number of bile ducts. During the course of the admission, the patient developed polyuria, metabolic acidosis, glucosuria, phosphaturia, and aminoaciduria, which are the characteristics of renal tubular acidosis. Abdominal sonography showed increased echogenicity of kidneys. As of suspicious to ARC syndrome, ABR (Auditory Brainstem Response) test was performed which was abnormal. Genomic DNA of the patient was screened for mutations in VPS33B and VIPAS39 genes using Sanger sequencing and identified a homozygous missense c.1130G>C point mutation (SCV000258931) in VIPAS39 which cause arginine to proline amino acid change (Arg377Pro). Both parents were found to be heterozygous carriers of this mutation (Figure 1).

Discussion

ARC syndrome is a rare disease that usually manifests by arthrogyriposis, renal tubular dysfunction and cholestasis. Herein clinical feature of a patient is presented that was similar to previous case reports; so, genetic study was done which confirmed the diagnosis. This is the first report of the c.1130G>C mutation in VIPAS39, which encodes VIPAR. Our patient has a severe ARC phenotype which suggests that arginine at position 377 is important to VIPAR function (9).

Additional feature in our patient was unilateral choanal atresia. There is an increased prevalence of autosomal recessive disorders in consanguineous populations. As siblings have one in four chance of inheriting the same disorder, the importance of prenatal diagnosis cannot be overemphasized. Therefore as mutation is confirmed in this family, prenatal test could be done on chorionic villus sample or amniotic fluid. This practice is important, especially in the Middle East region, where there are high rate of consanguinity and increased frequency of autosomal recessive disorders (10).

Acknowledgement

This study was supported in part by grants from Tehran University of Medical Sciences and Health Services (89-04-80-11945) and the MRC Laboratory for Molecular Cell Biology.

References

- 1- Horslen, S.P., et al., 1994. Liver histology in the arthrogryposis multiplex congenita, renal dysfunction, and cholestasis (ARC) syndrome: report of three new cases and review. *J. Med. Genet.* 31, 62-64.
- 2- Jang, W.Y., et al., 2011. Orthopaedic manifestations of arthrogryposis-renal dysfunction-cholestasis syndrome. *J. Pediatr. Orthop.* 31, 107-12.
- 3- Malaki, M., et al., 2012. ARC syndrome with complex renal problems: Nephrocalcinosis, proximal and hyperkalemic distal RTA and nephrogenic diabetes insipidus. *Saudi. J. kidney. Dis. Transpl.* 23, 804-809.
- 4- Eastham, K.M., et al., 2001. ARC syndrome: an expanding range of phenotypes. *Arch. Dis. Child.* 85, 415-420.
- 5- Howells, R., Ramaswami, U., 2002. ARC syndrome: an expanding range of phenotypes. *Arch. Dis. Child.* 87, 171.

- 6- Jang, J.Y., et al., 2009. Clinical characteristics and VPS33B mutations in patients with ARC syndrome. *J. Pediatr. Gastroenterol. Nutr.* 48, 348-54.
- 7- Kim, S.M., et al., 2010. Agranular platelets as a cardinal feature of ARC syndrome. *J. Pediatr. Hematol. Oncol.* 32, 253-8.
- 8- Sanseverino, M.T.V., et al., 2006. Increased nuchal translucency in arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome and discovery of a Portuguese specific mutation in the VPS33B gene. *Ultrasound. Obstet. Gynecol.* 28, 233–234.
- 9- Smith, H., et al., 2012. Associations among genotype, clinical phenotype, and intracellular localization of trafficking proteins in ARC syndrome. *Hum. Mutat.* 33, 1656-64.
- 10- Rezaei, N., et al., 2006. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. *Am. J. Reprod. Immunol.* 56, 145-51.

