CASE REPORT
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Description of a Novel Pathogenic Variant in the *ARPC1B* and a Severe Allergy in Two Infants

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ABSTRACT

Actinrelated protein 2/3 complex subunit 1B (ARPC1B) deficiency is an inborn errors of immunity (IEI) characterized by a combination of immunodeficiency and immune dysregulation and classified as an IEI with allergic manifestations. Here, we describe two patients with pathogenic variants in the *ARPC1B* gene. The first patient presented with eczema and bronchospasm at six months of age. The second patient presented with eczema and milk protein allergy at five months of age. The c.899_944 (p.Glu300Glyfs*7) pathogenic variant was previously described, whereas the c.863del (p.Pro288Leufs*9) variant was novel. ARPC1B deficiency should be considered because of the severe allergic manifestations at an early age.

Keywords: ARPC1B protein, human; Bronchial spasm; Eczema; Hypersensitivity; Primary immunodeficiency diseases

INTRODUCTION

The actin-related protein 2/3 (ARP2/3) complex is triggered by the WASP (Wiskott-Aldrich syndrome protein), WIP (WASP interacting protein) Cdc42 (Cell division control protein 42 homolog) axis. For cell migration, endocytosis, vesicle trafficking, and cytokinesis, the ARP2/3 complex increases actin polymerization and the formation of a new branched actin filament matrix.[1] There are 7 subunits in the ARP2/3 complex: ARP2 (actin-related protein 2), ARP3 (actin-related protein 3), ARPC2 (actin-related protein 2/3 complex subunit 2), ARPC3 (actin-related protein 2/3 complex subunit 3), ARPC4 (actin-related protein 2/3 complex subunit 4), and both isoforms of ARPC1A (actin-related protein 2/3 complex subunit 1A)/ARPC1B (actin-related protein 2/3 complex subunit 1B) and ARPC5A (actin-related protein 2/3 complex subunit 5A)/ARPC5B (actin-related protein 2/3 complex subunit 5B).[2] ARPC1A and ARPC1B have six WD40 domain repeats that are predicted to form a β-propeller fold. A canonical WD40 domain consists of 7 sheets or repeats, each containing 40-60 residues with a tryptophan (W) and aspartic acid (D) motif. The blades then fold into a propeller shape, exposing the top, bottom, and side surfaces. These surfaces are thought to be involved in molecular recognition and interaction. WD40 domains often form functional complexes or

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protein-protein interactions, acting as scaffolds to recruit other molecules.[3] ARPC1B is predominantly expressed in hematopoietic and immune cells.[4] ARPC1B deficiency was first reported in 2017.[2,5] All pathogenic variants affect the WD40 repeat motif.[6]

ARPC1B deficiency is classified as an inborn errors of immunity (IEI) and is characterized by combined immunodeficiency, immune dysregulation, and platelet dysfunction.[7] Due to thrombocytopenia and platelet dysfunction, most patients have an increased bleeding tendency. Recurrent respiratory, skin, and gastrointestinal infections, both bacterial and viral, are common. Eczema, food allergy, and asthma are common hypersensitivity features. Predominant autoimmune features include cutaneous vasculitis and inflammatory bowel disease. The disease is clinically similar to that caused by pathogenic loss-of-function variants in the *WAS* (Wiskott-Aldrich Syndrome) gene.[7] Here, we describe two patients from unrelated families with pathogenic variants in the ARPC1B gene, both of whom presented with severe allergic diseases. One patient had a novel mutation. Both cases add to the understanding of this recently described entity.

Patients' Characteristics

Case 1

The first case was a 7-year-old boy, the progeny of consanguineous parents. The child had no adverse reactions to the BCG (Bacillus Calmette Guérin) vaccine but suffered from severe eczema and recurrent bronchospasm events since he was six months and one year old, respectively. The patient exhibited specific IgE sensitivity against different allergens. At three years old, he experienced a unique bloody diarrhea event. Six months later, the patient presented with an abscess in the right thigh that was treated in the hospital. During admission, his condition worsened, and he experienced pneumonia and pleural effusion. He was admitted to the hospital again at six years of age because of fever and a rapidly increasing left periodontal abscess on the right side of the face and neck (Figure 1A). Computed tomography revealed inflammation in soft tissues (Figure 1B-C), while microbiologic examination detected the presence of *Klebsiella oxytoca* in the purulent discharge. He received intravenous treatment with ertapenem, fasciotomy of the neck, and vacuum-assisted closure therapy. We detected chronic malnutrition and enlarged cervical, axillary, and inguinal lymph nodes during hospitalization. Due to the severe recurrent infections, we suspected IEI. Laboratory tests showed anemia, lymphopenia, thrombocytopenia, increased IgA and IgE serum levels, and decreased CD3+CD4+ and CD3+CD8+ T cells (Table 1). In addition, we observed decreased serum levels of C3 and C4 and positive pANCA and cANCA results, which are alterations associated with autoimmunity. After two weeks, the patient was discharged and followed up as an outpatient; he developed macular erythema and continued with eczema (Figure 1E-F). He also developed a keloid scar at the neck incision of the surgical site (Figure 1G-H).

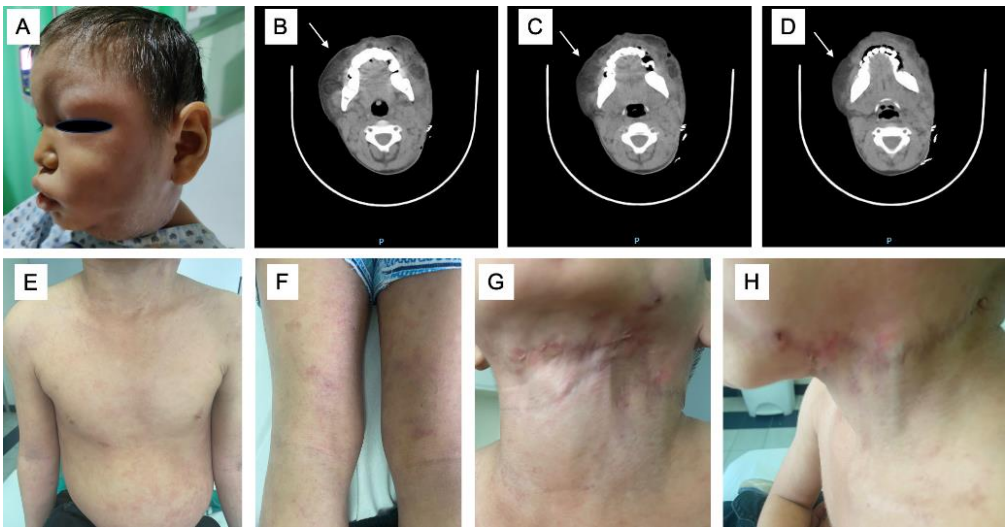

Figure 1. Clinical and radiological images of Patient 1. A) Right side facial and cervical cellulitis. B-D) Various slices of a CT scan of the head show swelling of the soft tissues. E) Eczema and macular erythema on the anterior thorax. F) Eczema on the posterior legs. G &H) The keloid scar on the neck.

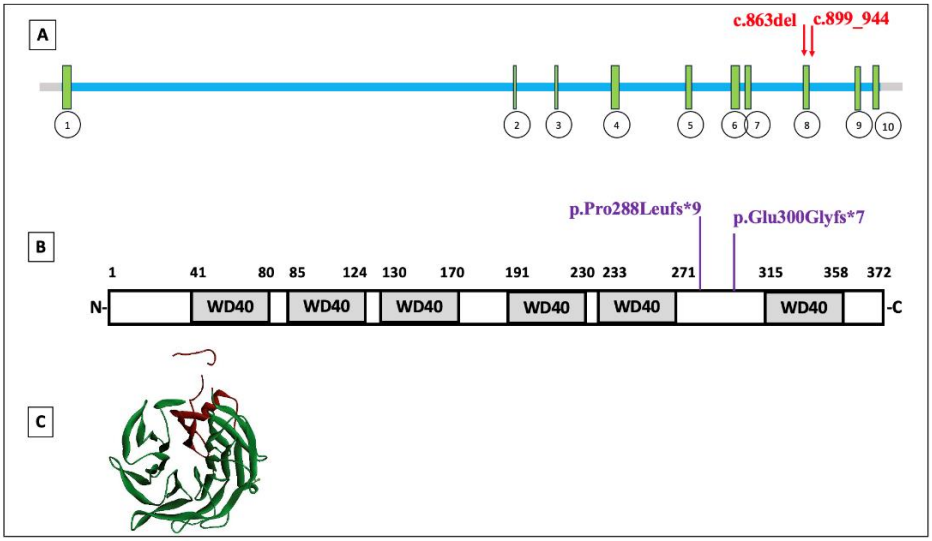

Figure 2. Genetic analysis in Patient 1 and Patient 2. A) Positions of the identified pathogenic variants (red arrows) relative to the actin-related protein 2/3 complex subunit 1B (ARPC1B) encoding exons (accession number: NM_005720.3). Exons 1-10 are represented in green color. Patient 1 is homozygous for c.899_944, patient 2 is homozygous for c.863del. B) ARPC1B has six WD40 repeat domains that form a propeller required for the function of the Arp (Actin-Related Protein) 2/3 complex. The amino acid change caused by the pathogenic variants results in a frameshift. This is predicted to result in a protein lacking the last WD40 domain. C) Crystalline structure of ARPC1B. The missing structure in the patient with the c.863del pathogenic variant is shown in red.

Table 1. Hematological and immunological laboratory test results and reference values for P1 and P2. Reference values are in parentheses.

PATIENT CODE	LABORATORY TEST
	Hematology Tests
P1	Hemoglobin 11.2 g/dL (11.8-14.6), MCV 75.5 fL (77-91), leucocytes 6.87 10^3/µL(5-10), neutrophils 2.19 10^3/µL (9-12), lymphocytes 3.24 10^3/µL (3-5), eosinophils 110^3/µL 1 (0-0.5) and platelets 94 10^3/µL (150-450), MPV 7.5 (9-12)
P2	Hemoglobin 9 g/dL (9.5-14 g/dL), MCV 78 fL (77-91), leukocytes 46.2 10^3/µL (6.4-13.0), lymphocytes 5.0 10^3/µL (3.4-9.0), platelets 2 10^3/µL (150-450), MPV 8.2
	Serology
P1	IgG 1,524 mg/dL (681-1648), IgA 804 mg/dL (87-474), IgM 40 mg/dL (48-312), IgE 3114 UI/ml (0-195),
P2	IgG 1226 mg/dL (174-814), IgA 230 mg/dL (8-84), IgM 157 mg/dL (33-108), IgE 2500 UI/ml (0-161)
P1	C3 83 mg/dl (90-207), C4 11 mg/dl (17-52)
P2	C3 140 mg/dl (64-167), C4 36 mg/dl (7-36)
	Immunophenotyping
P1	CD3 500 cells/µL (1200-2600), CD4 310 cells/µL (650-1500), CD8 160 cells/µL (370-1100), CD19 520 cells/µL (270-860), CD56/16 1920 cells/µL (100-480).
P2	CD3 2962 cells/µL (2500-5600), CD4 2243 cells/µL (800-3900), CD8 521 cells/µL (350-2,200), CD19 3790 cells/µL (529-1930), CD56/16 4024 cells/µL (180-920)
	Neutrophil reactive oxygen species production
P1	Dihydrorhodamine Oxidation index with PMA > 30 (Reference >30)
P2	Dihydrorhodamine Oxidation index with PMA >30 (Reference >30)

PMA: phorbol myristate acetate

We subjected P1 to the IEI gene panel test, a next-generation sequencing (NGS)-based examination, and detected a homozygous pathogenic variant in the *ARPC1B* gene, c.899_944 (p.Glu300Glyfs*7) (Figure 2). After genetic diagnosis, the patient received monthly intravenous immunoglobulin and prophylactic antimicrobials and was referred to a specialized hospital for hematopoietic stem cell transplantation (HSCT).

Case 2

The second case was a 2-year-old female, the progeny of consanguineous parents. She suffered from severe eczema (Figure 3A) and allergy to cow's milk proteins since she was five months old, with both allergic manifestations persisting to date. At four months old, the patient developed facial cellulitis and chronic external otitis secondary to *Pseudomonas aeruginosa* infection (Figure 3B). At 16 months old, she was admitted because of a fever and an abscess on the front side of the thorax (Figure 3C). Microbiological analysis revealed the presence of *Acinetobacter amalonaticus*. The patient's health improved after intravenous gammaglobulin (IVIG) and antibiotics treatment. In addition, she was diagnosed with erythematous and scaly dermatitis (Figure 3D), and biopsy findings revealed superficial perivascular spongiform and psoriasiform dermatitis. Due to the severe recurrent infections, we suspected IEI. Laboratory tests showed anemia, thrombocytopenia, and increased IgG, IgM, IgA, and IgE (Table 1). The IEI gene panel test detected a homozygous pathogenic variant in the *ARPC1B* gene, c.863del (p.Pro288Leufs*9) (Figure 2). After her condition improved, she was discharged and returned home. She is undergoing monthly IVIG treatment, receiving prophylactic antimicrobials, and is currently awaiting hematopoietic stem cell transplantation (HSCT).

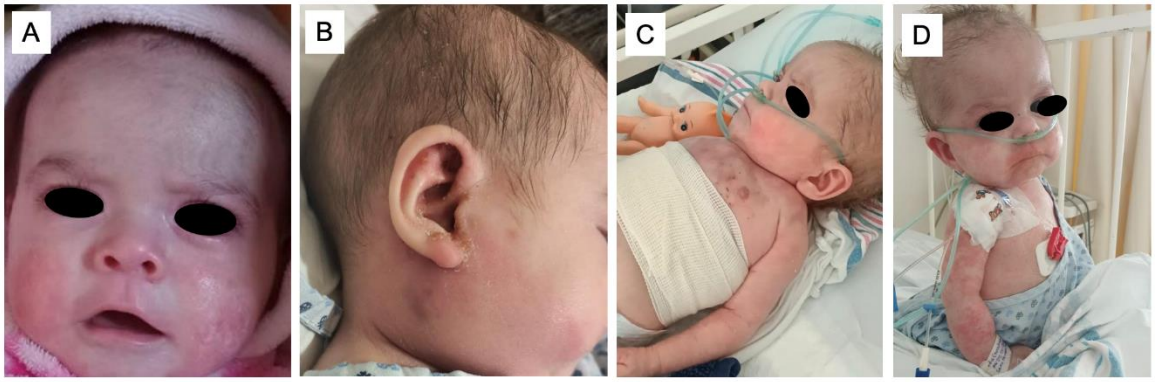

Figure 3. Dermatological manifestation in Patient 2. A) Severe eczema on the face. B) Facial cellulitis and chronic external otitis. C) Abscess on the front side of the thorax. D) Erythematous and scaly dermatitis and sparse hair

Allergies should prompt the consideration of an IEI secondary to a pathogenic variant in *ARPC1B*, *ZAP70*, *CARD11*, *MALT1*, *WAS*, *WIPF1*, *DOCK8*, and *CARMIL2*, among other genes, especially when allergies are severe and manifest at an early age.[2,5] For instance, P1 exhibited eczema and bronchospasms at six months, and P2 presented with eczema and allergy to milk proteins at five months. IEI is generally not suspected until a severe infection has occurred.[4] Associated allergic abnormalities in the 36 ARPC1B-deficient patients described to date include severe early-onset chronic eczema (88%); food, pollen, animal epithelium, and mite allergies (37%); hyper-IgE (97%); and hypereosinophilia (92%).[1,5,6,8] Other less common allergic manifestations include anaphylaxis and allergic asthma.[5]

NGS has revolutionized the diagnosis of IEI, facilitating the identification of patients, as reported here. To date, 19 different pathogenic variants of ARPC1B have been describe.[6] P1 carried the c.899_944 variant, which produces a frameshift coding effect starting at the Glu300 codon; the new reading frame ends with a stop codon at position 7. c.899_944 was previously reported in only three Mexican families.[6] two homozygous and one compound heterozygous; P1 is unrelated to any of these families.[6] These four families with the c.899_944 variant

are from geographically distant places in Mexico, including Veracruz, Monterrey, and Michoacan. The P2 variant, c.863del, has not been previously described; the variation produces a frameshift coding effect that starts at the Pro288 codon; the new reading frame ends with a stop codon at position 9, resulting in the absence of the sixth and final WD40 domain (Figure 2), which is known to play anessential role in many fundamental biological processes.

ARPC1B deficiency is a recently described IEI; very few patients have been reported.. The patients described here presented with severe allergic manifestations, but IEI was not suspected until infectious manifestations occurred. It is important to describe the clinical and genetic features of new cases to characterize this new disease.

STATEMENT OF ETHICS

Informed consent has been obtained from the two patients involved in the study. The study protocol has received approval from the Research Ethical Committees of the participating centers. Ethics Committee Approval Code is 030/2020.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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