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CASE REPORT

# A Novel Homozygous ARPC1B Nonsense Variant in a Saudi Infant With Immunodeficiency Type 71: Expanding the Clinical and Molecular Spectrum

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**Abstract:** Autosomal recessive immunodeficiency type 71 (IMD71) is a rare primary immunodeficiency caused by biallelic pathogenic variants in the ARPC1B gene, part of the actin-related protein 2/3 complex. Patients typically present with recurrent infections, immune dysregulation, eczema, and congenital thrombocytopenia. We report the first Saudi infant with a novel homozygous nonsense variant in ARPC1B (NM_005720.4: c.180G>A; p.Trp60*), identified by exome sequencing. The variant introduces a premature stop codon, likely triggering nonsense-mediated decay and loss of WD40 domain function. It is absent from population databases and classified as likely pathogenic per ACMG/AMP guidelines. The patient exhibited recurrent infections, seborrheic dermatitis, congenital thrombocytopenia, craniofacial dysmorphism, and spine MRI showed spina bifida occulta, a feature not previously linked to ARPC1B deficiency. This case expands both the genetic and phenotypic spectrum of IMD71, highlighting the importance of early genomic testing for diagnosis, management, and genetic counseling, particularly in consanguineous populations.

**Keywords:** ARPC1B, Immunodeficiency type 71, Nonsense variant, Saudi infant, Whole-exome sequencing, Thrombocytopenia.

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## 1 Introduction

The actin-related protein 2/3 complex subunit 1B (ARPC1B) gene is part of the Arp2/3 complex, which is found exclusively in hematopoietic cells. It plays a vital role in the branching of actin filaments and the remodeling of the cytoskeleton in immune cells. By regulating actin polymerization, ARPC1B is essential for various processes, including the formation of immune synapses, T-cell activation, cell migration, and platelet development. Loss-of-function variants in ARPC1B gene (OMIM* 604223) have been identified as the cause of autosomal recessive immunodeficiency 71 (ARID71; OMIM# 617718), an autosomal recessive immunogenic disorder characterized by recurrent infections, immune dysregulation, and low thrombocytopenia1,2

Since its initial description in 2017, ARPC1B deficiency has been recognized as an extremely rare inborn error of immunity, with fewer cases reported worldwide3,4. The clinical manifestations vary but typically include failure to thrive, recurrent bacterial and viral infections, severe eczema, food allergies, asthma, vasculitis, and colitis5,6. Laboratory findings often show eosinophilia, elevated serum IgE and IgA, lymphocytosis, and microthrombocytopenia5. These features reflect the wide-ranging impact of ARPC1B dysfunction on immune regulation and hematopoietic cell function. Importantly, genotype–phenotype correlations remain only partially understood, with reported variants ranging from missense and synonymous splicing variants to frameshift and nonsense variants7.

Here, we describe the first reported case of a Saudi

infant harboring a novel homozygous nonsense pathogenic variant in the ARPC1B gene (c.180G>A, p.Trp60*), resulting in ARID71 identified through whole-exome sequencing. This variant has not been previously reported in the literature. Notably, she also exhibited spina bifida occulta, a phenotype not previously described in association with ARPC1B-related disorders. This suggests a broader developmental role for the ARPC1B gene beyond the hematopoietic system, thereby expanding the phenotypic spectrum of IMD71.

## 2 Case Presentation

Patient Selection The patient was referred to our specialized tertiary hospital as a case of recurrent infections and failure to thrive. Clinical information of the proband, including perinatal history, family background, and previous hospitalizations, was obtained through declarative interviews and review of medical records. Imaging studies and laboratory findings were retrieved from the hospital's electronic health record system. Informed consent was obtained from the proband's legal guardian. Molecular Genetic Analysis Genomic DNA was extracted from the proband's peripheral blood using standard methods. Exome sequencing (ES) was performed at an external accredited laboratory on the Illumina NovaSeq 6000 platform. Data were analyzed with standard bioinformatics tools. Reads were aligned to the human reference genome (GRCh37/hg19), and variants were identified and annotated using ANNOVAR8.

The pathogenicity of rare variants was assessed using multiple in silico prediction tools and was predicted to be deleterious by MutationTaster9 (score 1) and DANN10 (score 0.99). The variants were interpreted and classified according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines11. The proband, a 4-month-old Saudi girl born to consanguineous parents (figure 1), was referred for genetic evaluation due to recurrent infections and failure to thrive. The prenatal history included a maternal urinary tract infection in the third trimester, which was treated with antibiotics. She was delivered full term by cesarean section due to previous cesarean sections with a birth weight of 3.0 kg (21st percentile, -0.81 SD).

At 20 days of life, she was admitted to the neonatal intensive care unit (NICU) for 23 days with septicemia and severe diarrhea, initially attributed to cow's milk protein allergy. She was subsequently discharged on a hydrolyzed formula. She was admitted at 3 months old with sacral swelling and discharge, complicated by Salmonella infection producing extended-spectrum beta-lactamase (ESBL). An MRI of the spine showed features of spina bifida at the upper sacral level, with no associated meningoceles, lipomeningocele, myelocele, or mass lesions. No structural abnormalities were detected. At 4 months of age, she presented to the emergency department with cough and fever and was admitted with viral pneumonia caused by parainfluenza virus type 3. During hospitalization, she developed progressive respiratory distress, requiring transfer to the pediatric intensive care unit (PICU) and initiation of high-flow nasal cannula oxygen therapy. She was referred to the medical genetics team for assessment and evaluation. Upon physical examination, weight was 4 kg (below the 3rd centile, -2.96 SD), height was 52 cm (below the 3rd centile, -3.79), and head circumference was 40 cm (24th centile, -0.69 SD). Dysmorphic features included scaphocephaly with frontal bossing, patchy alopecia with seborrheic dermatitis, erythematous protruding ears, and a high-arched palate. Sacral exam revealed a sinus left lateral to the gluteal cleft with no discharge or swelling, no inflammation, no tenderness, and a diaper rash. The neurological examination was unremarkable. Laboratory investigations showed immunoglobulin levels of IgA at 3.52 g/L (high), IgG at 11.2 g/L (high), and IgM at 0.81 g/L. A peripheral blood smear revealed teardrop cells, microcytosis, giant platelets, and platelet clumping, findings that are consistent with congenital thrombocytopenia. Blood cultures were negative, but a groin swab grew multidrug-resistant Pseudomonas aeruginosa, and ear swabs cultured yeast and coagulase-negative Staphylococcus. Echocardiography showed mild left ventricular dilatation with borderline systolic function (ejection fraction of 60%), without structural abnormalities or vegetations. The patient received a single dose of intravenous immunoglobulin before discharge and was referred for continued follow-up with immunology, hematology, genetics, and general pediatric services.

Molecular Genetics findings: Solo exome sequencing identified a novel homozygous nonsense variant in the ARPC1B gene (NM_005720.4: c.180G>A; p.Trp60*), in exon 3 of the proband. This variant is also described as a stop-gained variant that introduces a premature termination codon at position 60 of the protein (tryptophan-to-stop codon change), which

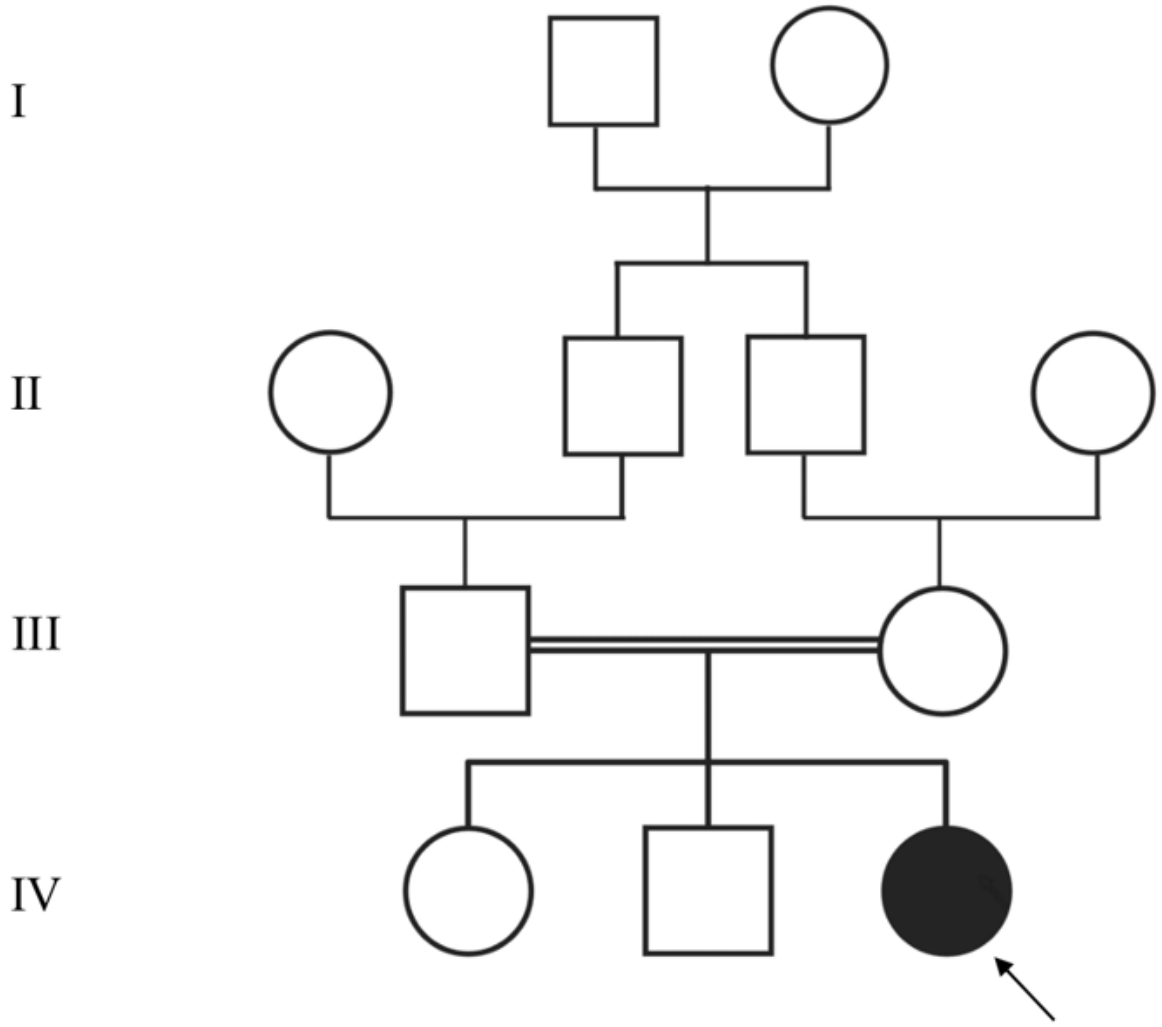


**Figure 1.** Pedigree of the consanguineous family carrying ARPC1B variant

is predicted to result in nonsense-mediated mRNA decay or the production of a severely truncated, nonfunctional ARPC1B protein. Loss-of-function variants in the ARPC1B gene are a recognized disease mechanism, supporting the pathogenic nature of this finding. According to the ACMG criteria9, this variant is classified as pathogenic, meeting criteria including PVS1 (null variant in a loss-of-function gene), PM2 (extremely low frequency in population databases like gnomAD, where it is absent), and PP4 (the patient's phenotype is highly specific for a single-gene disorder). Although ClinVar12 currently lists one submission for this variant as uncertain significance (variation ID: 3068072), the combined genetic and clinical evidence support its classification as pathogenic. The variant was confirmed by Sanger sequencing, and segregation analysis revealed that both parents were heterozygous carriers, consistent with autosomal recessive inheritance. Appropriate genetic counseling was provided to the family.

## 3 Discussion

This report, to the best of our knowledge, presents the first case of a Saudi infant with a novel homozygous nonsense pathogenic variant c.180G>A (p.Trp60*) in the ARPC1B gene, presenting with a severe immunodeficiency phenotype. ARPC1B deficiency (Immunodeficiency 71; IMD71) is a rare autosomal recessive disorder of the actin cytoskeleton that causes combined immunodeficiency, immune dysregulation, eczema, and thrombocytopenia.

The identified variant, p.(Trp60*), creates a premature stop codon in exon 3, leading to early truncation of the ARPC1B protein. This variant occurs before all six WD40-repeat domains (amino acids 45–264) (figure 2), which are essential for forming a $\beta$-propeller structure that mediates interactions with other Arp2/3 complex proteins and actin filaments. The

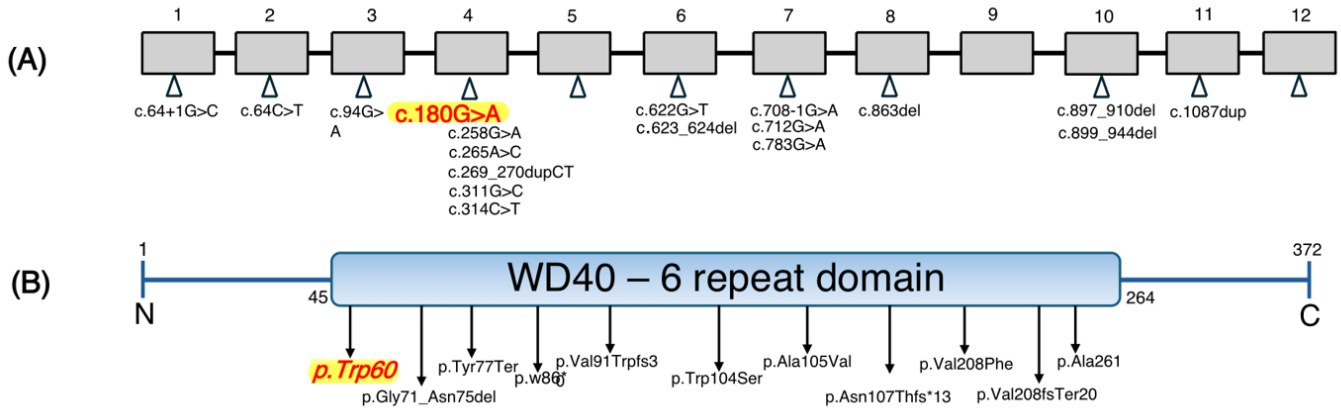


**Figure 2.** Schematic Illustration of the variants of the ARPC1B gene and its protein. A. Exon representation of APRC1B gene B. variants localization in WD40 domain of ARPC1B protein. (Variant identified in this study is shown in bold red)

absence of these domains likely impairs proper complex assembly, resulting in the complete loss of ARPC1B function. Similar truncating or splice-site pathogenic variants reported in previous studies have resulted in undetectable ARPC1B protein levels and defective actin polymerization13. Consequently, cytoskeletal organization in hematopoietic and immune cells is disrupted, which explains recurrent infections, eczema, and related phenotypes, such as thrombocytopenia. A recent molecular study of a founder ARPC1B mutation (c.899_944del) demonstrated that the resulting deficiency leads to complete loss of ARPC1B protein expression and is associated with markedly reduced class-switched memory B cells, CD4, CD8, and $\gamma$ $\delta$ T-lymphocyte populations, underscoring its pivotal role in both humoral and cellular immunity14.

Compared with other known pathogenic variants, the p.(Trp60*) variant is located further upstream and is among the earliest homozygous truncating variants identified. For instance, Kahr et al.3 reported a frameshift variant c.269_270dup p.(Val91Trpfs*30), and Kuijpers et al.1 described a complex deletion-insertion c.491_495delins p.(Phe164SerfsTer31). Both variants were shown to cause loss of ARPC1B protein and a severe clinical presentation. Other studies described splice-site or missense variants that also led to reduced protein expression and defective actin reorganization, but none occurred as early in the gene as p.Trp60*. Therefore, this variant is likely to produce a null effect, which explains the patient's severe, early-onset presentation. Clinically, our patient's findings of recurrent infections, eczema, and congenital thrombocytopenia are consistent with the known spectrum of ARPC1B deficiency. However, she also presented with spina bifida, a feature not previously described in any patient with ARPC1B mutations. To our knowledge, this is the first report connecting a neural tube defect (NTD) with ARPC1B deficiency. While this could be coincidental, there is a possible biological basis for this co-occurrence, suggesting that early disruption of ARPC1B might affect developmental processes beyond the immune and hematopoietic systems. Spina bifida occulta is one of the milder forms of NTDs, resulting from the failure of neural tube closure (NTC). The etiology underlying NTD is heterogeneous, involving both genetic and non-genetic factors. NTC is critically dependent on the precise regulation of the actin-myosin cytoskeleton, with disruption in key cytoskeletal proteins and associated signaling pathways leading to failed neuroepithelial folding and NTDs15. The ARPC1B protein is an essential component of the Arp2/3 complex, which plays a crucial role in cell movement and morphogenesis during embryonic development 16,17. Therefore, severe ARPC1B deficiency might have broader developmental consequences that have not yet been recognized.

## 4 Conclusion

In the present report, we describe a novel homozygous nonsense variant, p.(Trp60*), in the ARPC1B gene, predicted to result in nonsense-mediated decay and complete loss of ARPC1B function, causing a severe form of autosomal recessive immunodeficiency type 71 (IMD71) in a Saudi infant. This case broadens the known mutational and phenotypic spectrum of ARPC1B-related disorders. It suggests a potential

link to spina bifida occulta, indicating that ARPC1B may play a role in development beyond immune regulation. These findings highlight the importance of early genetic testing for accurate diagnosis, targeted treatment, and genetic counseling, particularly in consanguineous populations. Further research is needed to understand the molecular mechanisms of ARPC1B deficiency and its potential effects on development.

## Conflicts of Interest

The authors declare no competing interests.

## Ethical Approval

Ethical approval for this study was obtained from the Institutional Review Board of King Abdulaziz University Hospital (Reference No. 123-456). Informed consent was obtained from the parents of the infant.

## Acknowledgement

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