Bare Lymphocytic Syndrome Type I Due to TAP2 Mutation in an 18-Year-Old Male- A case report

Abstract:

Bare lymphocyte syndrome type I (BLS I) is a rare autosomal recessive primary immunodeficiency caused by defective major histocompatibility complex class I expression due to abnormalities in antigen-processing pathways. We report an 18-year-old male with recurrent respiratory infections, bilateral bronchiectasis, vasculitic skin ulcers, severe malnutrition, and neurological manifestations, including previous varicella zoster encephalopathy. Whole exome sequencing identified a homozygous *TAP2* splice-site mutation (c.1272+1del), confirming BLS I. The patient was managed with antimicrobial therapy, nutritional rehabilitation, and supportive care. This case highlights the importance of considering underlying primary immunodeficiency disorders in patients presenting with recurrent respiratory infections and multisystem inflammatory manifestations.

Keywords: Bare lymphocyte syndrome type I; TAP2 mutation; bronchiectasis; primary immunodeficiency; MHC class I deficiency.

Introduction

Bare lymphocyte syndrome type I (BLS I) is a rare autosomal recessive primary immunodeficiency characterized by defective expression of major histocompatibility complex (MHC) class I molecules on the cell surface due to abnormalities in antigen-processing pathways. Mutations involving transporter associated with antigen processing genes, particularly *TAP1* and *TAP2*, impair peptide transport into the endoplasmic reticulum, resulting in reduced MHC class I expression and defective CD8+ T-cell mediated immunity. [1,2]

Patients commonly present with recurrent sinopulmonary infections, chronic respiratory symptoms, bronchiectasis, skin ulcers, and growth failure, usually during childhood or adolescence.[3] Chronic pulmonary involvement secondary to recurrent bacterial infections remains one of the major causes of morbidity. Neurological manifestations and vasculitic complications are uncommon and have been infrequently reported.[4]

Because of its rarity and overlapping clinical features with autoimmune and other immunodeficiency disorders, diagnosis is often delayed until molecular genetic testing is performed.[5] We report an 18-year-old male with recurrent respiratory infections, bronchiectasis, vasculitis, and neurological manifestations who was diagnosed with BLS I secondary to a homozygous *TAP2* splice-site mutation identified on whole exome sequencing.

Case Presentation

An 18-year-old male born to consanguineous parents presented to the Emergency Department with a 1-week history of productive cough and progressive breathlessness. He was a known case of recurrent respiratory tract infections with multisystem involvement suggestive of an underlying immunodeficiency disorder. His respiratory symptoms included acute onset cough with mucopurulent sputum without hemoptysis, chest pain, or wheezing. Breathlessness was classified as grade II on the Modified Medical Research Council (mMRC) dyspnea scale.

The patient had a significant past medical history of recurrent respiratory infections since childhood and previous hospitalization for varicella zoster encephalopathy in 2018, which had been confirmed by cerebrospinal fluid analysis and treated successfully. He also experienced recurrent transient neurological episodes characterized by transient weakness involving the right upper and lower limbs associated with impaired awareness. In addition, he developed bilateral lower limb ulcers secondary to mixed medium and small vessel vasculitis. Progressive severe malnutrition was noted, with a body mass index of 12.6 kg/m². The chronological progression of the patient's clinical manifestations and diagnostic evaluation is summarized in Figure 1.

On examination, the patient appeared cachectic and undernourished. Respiratory system examination revealed bilateral coarse crackles predominantly over the lower lung fields. Healed ulcerative lesions were present over both lower limbs. No focal neurological deficits were observed during the present admission.

Laboratory investigations demonstrated iron deficiency anemia. Clinical and radiological evaluation supported the diagnosis of acute infective exacerbation of bilateral bronchiectasis. The discharge summary documenting bronchiectasis, neurological manifestations, vasculitis, and associated comorbidities is provided as Supplementary Figure S1.

Considering the recurrent respiratory infections, neurological manifestations, and vasculitic features, a primary immunodeficiency disorder was suspected. Whole exome and mitochondrial genome sequencing identified a homozygous splice-site mutation in intron 7 of the *TAP2* gene (c.1272+1del; ENST00000374897.4), which was classified as likely pathogenic and associated with major histocompatibility complex class I deficiency inherited in an autosomal recessive pattern. No clinically significant mitochondrial variants or pathogenic copy number variations were detected. The genetic sequencing report is provided as Supplementary Figure S2.

High-resolution human leukocyte antigen typing was additionally performed for transplant evaluation and demonstrated partial parental donor compatibility, showing a 6/12 match with the mother and a 7/12 match with the father. The HLA typing report is provided as Supplementary Figure S3.

Based on the recurrent respiratory infections, bronchiectasis, neurological manifestations, vasculitic complications, and molecular confirmation of a pathogenic *TAP2* mutation, a diagnosis of Bare Lymphocyte Syndrome Type I was established. The patient was managed conservatively with antimicrobial therapy, nutritional rehabilitation, respiratory supportive care, and multidisciplinary immunological follow-up. His respiratory symptoms improved during hospitalization, and he was discharged in stable condition with advice for continued follow-up and future hematopoietic stem cell transplantation evaluation.

Discussion

Bare lymphocyte syndrome type I (BLS I) is a rare primary immunodeficiency caused by defective major histocompatibility complex (MHC) class I expression due to abnormalities in antigen-processing pathways.[1,2] Impaired MHC class I surface expression results in defective CD8+ T-cell mediated immunity, predisposing affected individuals to recurrent respiratory infections, chronic inflammation, and bronchiectasis.[3,6] In the present case, whole exome sequencing confirmed a homozygous *TAP2* splice-site mutation (c.1272+1del), correlating with the patient's recurrent bronchopulmonary infections, severe malnutrition, and vasculitic manifestations.

Respiratory involvement is among the most frequently reported manifestations of BLS I. Zimmer et al. [3] described recurrent sinopulmonary infections, chronic cough,

bronchiectasis, and growth failure in patients with *TAP2* deficiency, findings similar to those observed in our patient. de la Salle et al. [7] also reported severe MHC class I deficiency secondary to *TAP2*mutation associated with recurrent infections. Defective cytotoxic T-cell and natural killer cell responses contribute significantly to susceptibility to chronic infections in these patients.[6]

Neurological and vasculitic manifestations are less commonly reported in BLS I. [4,8] Our patient demonstrated recurrent transient neurological episodes and a previous history of varicella zoster encephalopathy, suggesting immune dysregulation and vulnerability to opportunistic infections. Bilateral lower limb vasculitic ulcers further indicated chronic inflammatory involvement. Autoimmune and inflammatory manifestations have increasingly been recognized in monogenic immunodeficiency disorders and may contribute to delayed diagnosis. [8,9]

Altered MHC class I expression has also been linked to impaired immune surveillance and dysregulated inflammatory responses. [10-13] These mechanisms may partly explain the persistent inflammatory manifestations observed in severe MHC class I deficiency.

Management of BLS I remains largely supportive.[5] Early diagnosis and prompt treatment of respiratory infections are essential to prevent progressive bronchiectasis lung damage. Nutritional rehabilitation, antimicrobial therapy, and multidisciplinary follow-up are important components of care. Hematopoietic stem cell transplantation may be considered in severe cases, although outcomes remain variable.[5] Cutaneous inflammatory lesions may additionally require long-term dermatological monitoring and supportive management.[14]

Conclusion

This case highlights the clinical complexity and diagnostic challenges associated with Bare Lymphocyte Syndrome Type I secondary to *TAP2* mutation. Recurrent respiratory infections with bronchiectasis, combined with neurological manifestations, vasculitis, and severe malnutrition, should raise suspicion for an underlying primary immunodeficiency disorder. Early molecular diagnosis through genetic testing is crucial for timely diagnosis, targeted counselling, and appropriate long-term management. Increased awareness of this rare condition may facilitate earlier recognition and help prevent irreversible pulmonary complications.

Conflict of interest: None

References:

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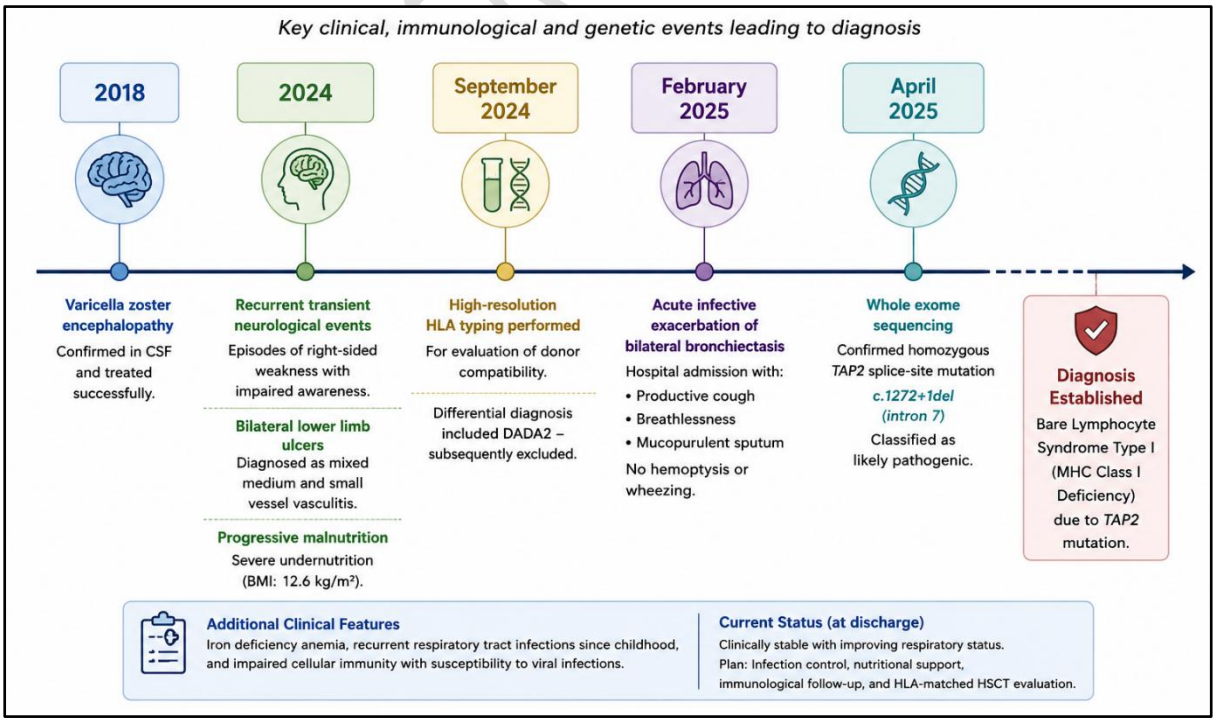
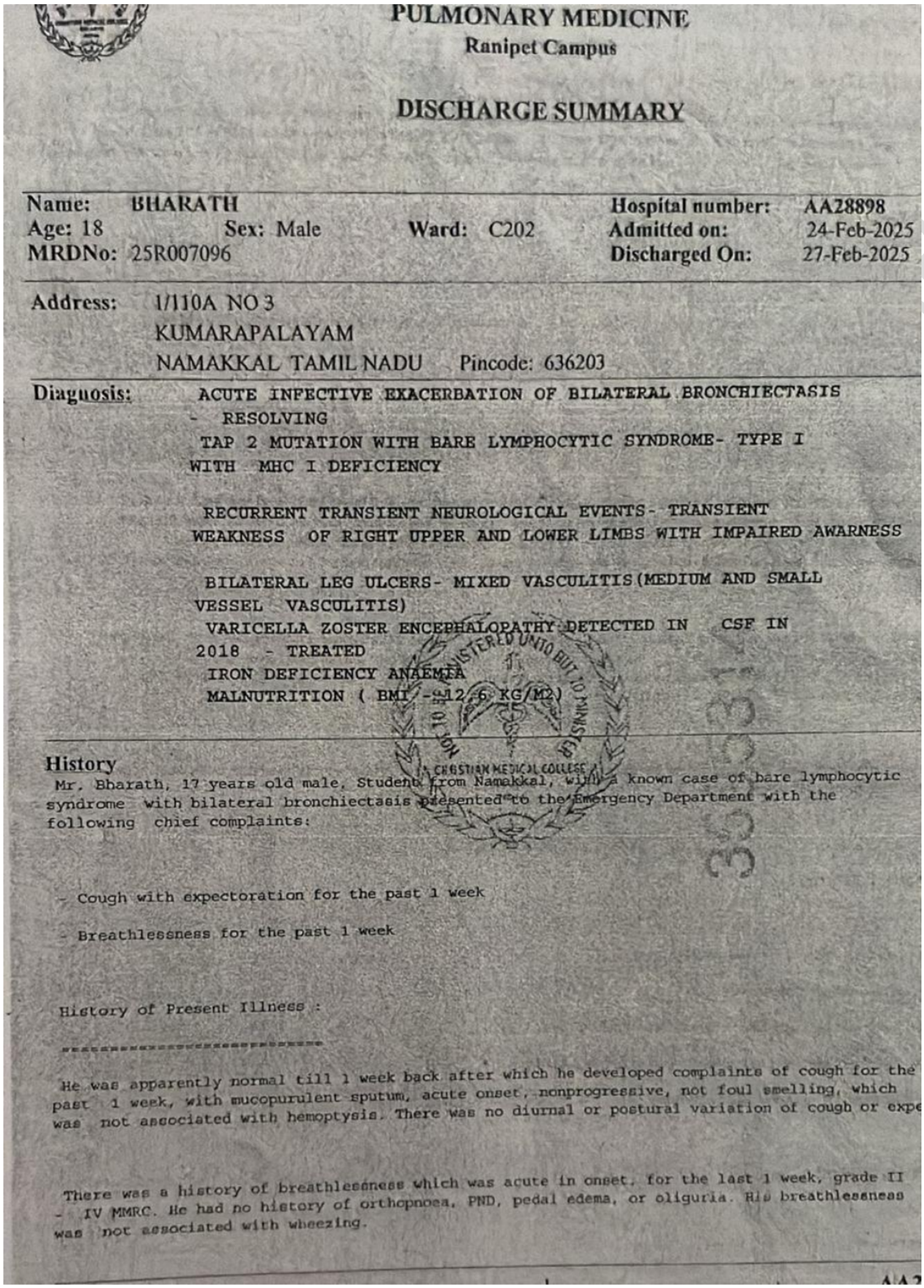
Figure 1. Clinical timeline of disease progression and diagnostic evaluation in a patient with TAP2-associated Bare Lymphocyte Syndrome Type I.



Supplementary Figure S1. Hospital discharge summary documenting bilateral bronchiectasis, neurological manifestations, vasculitis, and associated clinical findings.



PULMONARY MEDICINE
Ranipet Campus

DISCHARGE SUMMARY

Name: BHARATH
Age: 18 Sex: Male
MRDNo: 25R007096
Ward: C202
Hospital number: AA28898
Admitted on: 24-Feb-2025
Discharged On: 27-Feb-2025

Address: 1/110A NO 3
KUMARAPALAYAM
NAMAKKAL TAMIL NADU Pincode: 636203

Diagnosis:
ACUTE INFECTIVE EXACERBATION OF BILATERAL BRONCHIECTASIS - RESOLVING
TAP 2 MUTATION WITH BARE LYMPHOCYTIC SYNDROME- TYPE I WITH MHC I DEFICIENCY
RECURRENT TRANSIENT NEUROLOGICAL EVENTS- TRANSIENT WEAKNESS OF RIGHT UPPER AND LOWER LIMBS WITH IMPAIRED AWARNESS
BILATERAL LEG ULCERS- MIXED VASCULITIS(MEDIUM AND SMALL VESSEL VASCULITIS)
VARICELLA ZOSTER ENCEPHALOPATHY DETECTED IN CSF IN 2018 - TREATED
IRON DEFICIENCY ANAEMIA
MALNUTRITION (BMI -12.6 KG/M2)

History
Mr. Bharath, 17 years old male, Student from Namakkal, with a known case of bare lymphocytic syndrome with bilateral bronchiectasis presented to the Emergency Department with the following chief complaints:

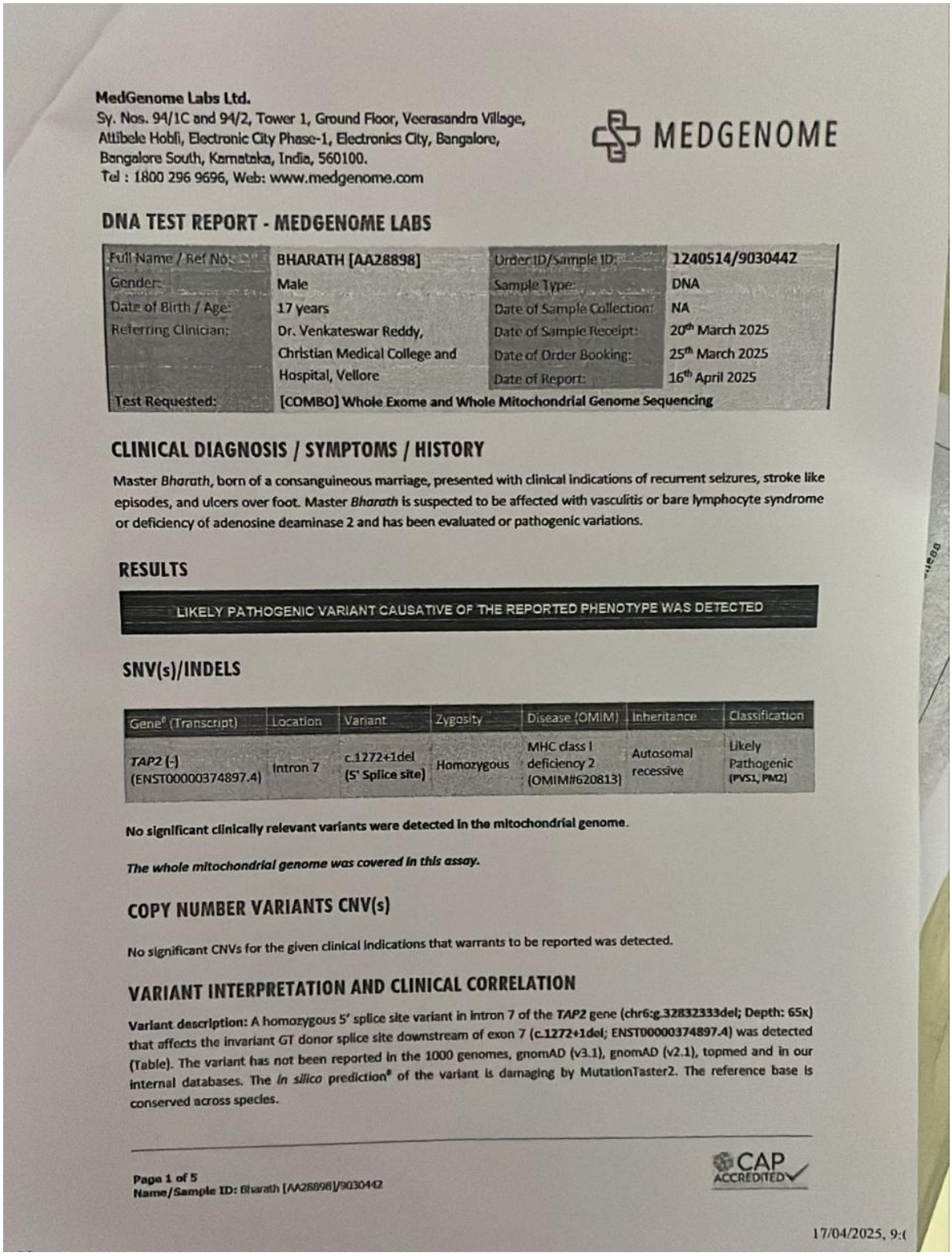
- Cough with expectoration for the past 1 week
- Breathlessness for the past 1 week

History of Present Illness :

He was apparently normal till 1 week back after which he developed complaints of cough for the past 1 week, with mucopurulent sputum, acute onset, nonprogressive, not foul smelling, which was not associated with hemoptysis. There was no diurnal or postural variation of cough or expe

There was a history of breathlessness which was acute in onset, for the last 1 week, grade II - IV MMRC. He had no history of orthopnoea, PND, pedal edema, or oliguria. His breathlessness was not associated with wheezing.

Supplementary Figure S2. Whole exome sequencing report demonstrating a homozygous *TAP2* splice-site mutation (c.1272+1del) associated with major histocompatibility complex class I deficiency.



MedGenome Labs Ltd.
Sy. Nos. 94/1C and 94/2, Tower 1, Ground Floor, Veerasandra Village,
Attibele Hobli, Electronic City Phase-1, Electronics City, Bangalore,
Bangalore South, Karnataka, India, 560100.
Tel : 1800 296 9696, Web: www.medgenome.com

MEDGENOME

DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	BHARATH [AA28898]	Order ID/Sample ID:	1240514/9030442
Gender:	Male	Sample Type:	DNA
Date of Birth / Age:	17 years	Date of Sample Collection:	NA
Referring Clinician:	Dr. Venkateswar Reddy,	Date of Sample Receipt:	20th March 2025
	Christian Medical College and	Date of Order Booking:	25th March 2025
	Hospital, Vellore	Date of Report:	16th April 2025
Test Requested:	[COMBO] Whole Exome and Whole Mitochondrial Genome Sequencing		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Master *Bharath*, born of a consanguineous marriage, presented with clinical indications of recurrent seizures, stroke like episodes, and ulcers over foot. Master *Bharath* is suspected to be affected with vasculitis or bare lymphocyte syndrome or deficiency of adenosine deaminase 2 and has been evaluated or pathogenic variations.

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene[#] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
TAP2 (-) (ENST00000374897.4)	Intron 7	c.1272+1del (5' Splice site)	Homozygous	MHC class I deficiency 2 (OMIM#620813)	Autosomal recessive	Likely Pathogenic (PVS1, PM2)

No significant clinically relevant variants were detected in the mitochondrial genome.

The whole mitochondrial genome was covered in this assay.

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A homozygous 5' splice site variant in intron 7 of the *TAP2* gene (chr6:g.32832333del; Depth: 65x) that affects the invariant GT donor splice site downstream of exon 7 (c.1272+1del; ENST00000374897.4) was detected (Table). The variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1), topmed and in our internal databases. The *in silico* prediction[#] of the variant is damaging by MutationTaster2. The reference base is conserved across species.

Page 1 of 5
Name/Sample ID: Bharath [AA28898]/9030442

CAP ACCREDITED

17/04/2025, 9:(

Supplementary Figure S3. High-resolution HLA typing report demonstrating parental donor compatibility assessment for potential hematopoietic stem cell transplantation evaluation.

DEPARTMENT OF TRANSFUSION MEDICINE AND IMMUNOHAEMATOLOGY

HLA LABORATORY

HLA TYPING REPORT

PATIENT NAME	BHARATH	FIRM	HEMATOLOGY
HOSPITAL NO	AA28898	METHOD	ILLUMINA NEXT –GENERATION SEQUENCING
REFERENCE NO	3119/24	SAMPLE	WHOLE BLOOD EDTA
AGE/SEX	17 YRS /MALE	SAMPLE COLLECTED ON	24.09.2024
CLINICAL DIAGNOSIS	RECURRENT TRANSIENT NEUROLOGICAL EVENTS DD: DADA2	TEST DONE ON	30-09-2024

PATIENT TYPING

LOCUS	HLA- A*	HLA –B*	HLA –C*	HLA –DPB1*	HLA -DQB1*	HLA -DRB1*
	A*11:01:01	B*57:01:01	C*06:02:01	DPB1*04:01:01	DQB1*03:03:02	DRB1*07:01:01
	A*11:01:01	B*57:01:01	C*06:02:01	DPB1*04:01:01	DQB1*03:03:02	DRB1*07:01:01
REMARKS	HLA-DPB1*04:01:01 +HLA-DPB1*939:01 IS EQUALLY POSSIBLE.					

DONOR 1 SAMPLE COLLECTED ON: 14-02-2025 TEST DONE ON: 20-02-2025

NAME	MAGESHWARI SENDHIL	AGE/SEX	35 YRS/ FEMALE
HOS:NO	---	RELATIONSHIP	MOTHER
REF:NO	524/25		

LOCUS	HLA- A*	HLA –B*	HLA –C*	HLA –DPB1*	HLA -DQB1*	HLA -DRB1*
	A*02:11:01	B*40:06:01	C*07:02:01	DPB1*04:01:01	DQB1*03:02:01	DRB1*04:01:01
	A*11:01:01	B*57:01:01	C*06:02:01	DPB1*04:02:01	DQB1*03:03:02	DRB1*07:01:01
REMARKS	HLA-DPB1*04:02:01 +HLA-DPB1*939:01 IS EQUALLY POSSIBLE. HLA-DPB1*105:01:02+HLA-DPB1*126:01:01 IS EQUALLY POSSIBLE.HLA-DPB1*1171:01+HLA-DPB1*126:01:01 IS EQUALLY POSSIBLE. .					
COMMENT	6/12 MATCHED AT HIGH RESOLUTION (HLA-A*, B*, C*, DRB1*, DQB1* and DPB1* LOCUS)					
NOTE						

DONOR 2 SAMPLE COLLECTED ON: 14-02-2025 TEST DONE ON: 20-02-2025

NAME	JEYSENTHIL S	AGE/SEX	45 YRS/ MALE
HOS:NO	-----	RELATIONSHIP	FATHER
REF:NO	525/25		

LOCUS	HLA- A*	HLA –B*	HLA –C*	HLA –DPB1*	HLA -DQB1*	HLA -DRB1*
	A*11:01:01	B*57:01:01	C*06:02:01	DPB1*04:01:01	DQB1*03:03:02	DRB1*07:01:01
	A*02:131:01	B*07:06:01	C*07:02:01	DPB1*04:01:01	DQB1*05:03:01	DRB1*14:04:01
REMARKS	HLA-DPB1*04:01:01 +HLA-DPB1*939:01 IS EQUALLY POSSIBLE.					
COMMENT	7/12 MATCHED AT HIGH RESOLUTION (HLA-A*, B*, C*, DRB1*, DQB1* and DPB1* LOCUS)					
NOTE						

REPORTED BY	DATE
DR.DOLLY DANIEL	24-02-2025

IMGT/HLA release : 3.54.0

Sequencing Coverage : Class I (A,B,C) –Whole gene
: Class II (DRB1) –Whole gene except intron 1
: Class II (DQB1) – Whole gene
: Class II (DPB1) –Exon 2 to Exon 4

STATUS OF THE REPORT –COMPLETED

Note: This report is electronically generated and does not require a manual signature.