

# FADD Deficiency Mimicking ALPS-FAS: An Expanding Phenotype.

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## Research Article

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# Abstract

Autoimmune lymphoproliferative syndrome (ALPS) is caused due to defects in the Fas-mediated apoptotic pathway. This disease is characterised by chronic non-malignant lymphoproliferation, autoimmune cytopenias and accumulation of double-negative T cells. *FAS* is the most commonly affected gene observed in patients with ALPS. There is a paucity of data in other ALPS associated genes. Mutations in the *FADD* gene is extremely rare, and to date, only five patients with a homozygous mutation in exon 2 and one patient with a compound heterozygous mutation are reported. The clinical spectrum of *FADD* includes neurological dysfunction, recurrent bacterial and viral infections and liver dysfunction. Here we report two patients with novel *FADD* mutation with clinical phenotype like ALPS-FAS. This article provides an expanding phenotype of *FADD* deficiency where patients can solely present with lymphoproliferation and autoimmunity without any features of febrile episodes or neurodevelopmental delay. We identified a novel homozygous *FADD* mutation by targeted Next-generation sequencing (NGS). We performed a comprehensive immune evaluation along with biomarker estimation, mTOR activity on DNTs and apoptosis assay. We describe two siblings born to third-degree consanguineous marriage with homozygous *FADD* mutation. The index patient P1 presented with lymphoproliferation, autoimmune manifestations in the form of Evans phenotype, lymphocytosis and elevated DNTs, whereas P2 only had mild lymphoproliferation with no autoimmune manifestations. The mutation in our patients lies in exon 2 of the *FADD* gene, encoding the death domain. The death domain (DD) of *FADD* protein interacts directly with the death domains of Fas, and mutation at this site disrupts binding to Fas and abolishes apoptosis. *FADD* deficiency should also be considered in patients presenting with lymphoproliferation and autoimmunity since they can mimic clinical features of ALPS-FAS.

## Introduction :

ALPS is an immune dysregulatory disorder caused due to defects in lymphocyte apoptosis. This defect leads to lymphoproliferative disease with generalised lymphadenopathy, splenomegaly, hepatomegaly, autoimmunity with increased risk of lymphomas [1]. Germline and somatic mutations in *FAS* are reported in nearly two-thirds of the ALPS patients. Mutations in other ALPS related genes, namely *FASLG*, *CASP8*, *CASP10* and *FADD*, are rarely described. To date, only six patients are reported with *FADD* deficiency [2] (Table S1). These patients usually present with recurrent bacterial and viral infections, encephalopathy and liver dysfunction and have a poor prognosis compared to ALPS-FAS. Here we report two females of a family with a novel *FADD* mutation, with clinical manifestations and immunophenotype mimicking ALPS-FAS.

## Methods :

### Patients and Ethical Approval.

3 ml of blood samples were collected in sodium-EDTA, plain and heparin vacutainer for all the family members after informed consent. The study was approved by the institutional ethics committee (IEC) of

## Flow cytometry

Immunophenotyping was performed on peripheral blood. Different panels were designed to characterise T/B and DNT subsets. Lymphocyte subset analysis was performed as described earlier[3]. B cell subpopulations were identified using CD19- APC-Cy-7(BD); CD27-PE (BC); IgM-PerCP-Cy-5.5 (BioLegend); IgD -FITC (BioLegend); CD21-BV510 (BD); CD38-PE-Cy7 (BD); CD24 PECF594 (BD); CD95 BV421 (BD); CD10 APC 700 (BC). DNTs were characterized using panel of markers like :CD3 BV510 (BD); CD4 APC750 (BC);CD8 APC750 (BC); TCRab PE (BD); B220 (CD45R)-APC (eBiosciences) ;KLRG1-Alexa Flour 488 (eBiosciences), CD57- Pacific Blue (BC), CD45RA PerCP Cy-5.5 (BD), CD38 APC700 (BD), CD27 PC7 (BC) , CD28 ECD (BC) , to identify the distinct differentiating pattern observed in patients with ALPS. For mTOR activity, pAkt (Ser473)-PE (BD) and pS6 (Ser235/235)-V450 (BD) were used. 200 microlitre of peripheral blood were washed with 3ml of phosphate buffer saline (PBS) twice, incubated with pre-titred antibody cocktail for 20 min at room temperature, lysed using Opti-Lyse solution (Beckman Coulter), centrifuged, and washed with PBS. The samples were acquired on Navios Ex/ Dxflex (Beckman Coulter) and the analysis was performed on Kaluza v 2.1. Phosphorylated proteins were detected as described earlier [4], and basal level of phosphorylation were analysed on untreated cells.

**Biomarker evaluation:** ELISA for Vitamin B 12 levels was done using Bioassay technology kit and quantified by ELISA plate reader. sFASL, IL-10, IL-18 and sCD25 were quantified by flow cytometry using AIMPLEX (Aimplex Biosciences, Inc) as described previously[4].

## Apoptosis Assay

An in-vitro apoptosis assay was performed as described earlier [5]. Flow cytometry was used to enumerate, and annexin V was used to identify these apoptotic cells along with a viability dye (7AAD). Apoptotic cells are positive for Annexin V but negative for viability dye [5].

## Results :

### Clinical and immunological phenotype

A 21-month-old female (P1), second by birth, born of third-degree consanguineous marriage presented with abdominal distension since 6 months of age. She had multiple hospital admissions in the past with abdominal distention, axillary and cervical lymphadenopathy, recurrent fevers and purpuric rashes.

On examination, she had pallor and failure to thrive with weight and height lower than the 3rd percentile. She had multiple bilateral cervical, axillary and inguinal lymphadenopathy, and the lymph nodes were firm, and non-tender. She also had hepatomegaly and splenomegaly of 4 and 3 cm, respectively, below the costal margin (Figure 1). Her father had a history of ecchymosis, thrombocytopenia and mild

hepatomegaly. He was diagnosed as a case of Immune thrombocytopenia (ITP) and was managed with multiple steroids during acute flare and is currently asymptomatic on dapsone.

Her laboratory and immunological workup confirmed non-malignant lymphoproliferation and autoimmune manifestations. She consistently had peripheral blood leukocytosis with predominantly atypical lymphocytes. Her Direct coombs test was strongly positive. Her bone marrow biopsy was normocellular and had no evidence of storage cells or blasts. Her right axillary lymph node biopsy showed widening of the interfollicular area with increased plasma cells and the absence of any atypical cells. Her CT scan of the brain was normal. Her immunological workup was done with ALPS as one of the differentials.

Her lymphocyte subset analysis was done initially at 21 months; when she was started on steroids in view of Evan's phenotype, it was near normal with marginally elevated B cells. Her DNTs were elevated (11%), and immunoglobulin levels were within normal ranges. A provisional diagnosis of ALPS was made. The patient responded to low dose prednisolone and Mycophenolate mofetil (MMF), which was gradually tapered. The patient had stopped MMF as she started feeling better but revisited the pediatric department with a history of head trauma at 36 months of age. Her lymphocyte counts were again elevated (29000 counts/mm<sup>3</sup>). The immunophenotyping of DNTs and B cell was also done. Her DNTs were 23% and nearly 85% of DNTs expressed B220 marker. The Fas- controlled DNTs (FC-DNTs) characterised using CD45RA and CD38 was nearly 85%. B cell subsets showed elevated CD21<sup>low</sup> B cells (11%), plasmablasts (13%), and borderline high transitional B cells. ALPS specific biomarker evaluation revealed elevated levels of soluble Fas-ligand (648pg/ml), IL-10 (458 pg/ml), Vitamin B12(>2000pg/L) and soluble CD25 (271700 units/ml), whereas IL-18 (321 pg/ml) was within normal range. Hyperactivity of mTORC1 and mTORC2 activity analysed by pS6(Ser235/236) and pAkt (Ser473) respectively were also elevated on DNTs. FAS mediated apoptosis was defective. CMV was also detected in the serum of P1 (using Neuro 9) (Table S2).

Her targeted gene sequencing by NGS was done, which identified a rare homozygous variant (c. 350G>A; p.Arg117His) in exon 2, which encodes for the death domain of *FADD*. The variant has a minor allele frequency of 0.0004%. *In-silico* prediction of the variant was damaging by SIFT and Polyphen-2, with a CADD (Phred) score of 32. Sanger confirmation suggested that the parents were heterozygous carriers for the same mutation, whereas the older sibling (P2) carried the same homozygous variant. On examination, she had cervical lymphadenopathy of 2cm without any autoimmune manifestations. Her lymphocyte subset analysis was within normal ranges with near-normal immunoglobulin levels except for IgM, which was low. Her DNTs were 19% and nearly 37% of DNTs expressed B220 marker, FC-DNTs were 80% and ALPS specific biomarker showed elevated sFASL (399pg/ml), soluble CD25 (113509 units/ml) and normal IL-10 levels (19pg/ml) (Table S3). Hyperactive mTOR activity was also observed. Defective Fas-mediated apoptosis was noted. She is currently off steroids.

Since the father had a history of ITP, we did a comprehensive ALPS workup for heterozygous parents. The DNTs of the heterozygous parents were not elevated, B220 expression on DNTs was also less than 10%,

the biomarkers were within normal ranges, hyperactive mTOR was not noted in either of them, and the apoptosis assay was also normal. However, FC DNTs population was nearly 25%. (Table S4)

## Discussion :

Fas-associated death domain-containing protein (FADD) is an adaptor protein that is responsible for relaying apoptotic signals initiated by Fas [14]. FADD has 2 functional domains: the death domain (DD) and the death effector domain (DED) [15]. The death domain (DD) of FADD protein interacts directly with the death domains of Fas and Tumor necrosis factor receptor type 1 associated death domain (TRADD), whereas DED comprises of binding site for procaspase-8 and 10. Apart from playing critical role in extrinsic apoptotic pathway, FADD also plays major role in cellular processes such as innate immunity, cell proliferation, autophagy and inflammation. Biallelic mutations in *FADD* are rarely described and only 6 patients are reported till date. The main clinical and biological features of previously reported *FADD* patients were neurological abnormalities (encephalopathy, seizures, cerebral atrophy), cardiac abnormalities, variable degree of lymphadenopathy or splenomegaly, liver dysfunction and functional hyposplenism along with hallmark immunological features of ALPS (elevated DNTs and serum biomarkers) [6–8]. We describe two patients with *FADD* deficiency who presented with lymphoproliferation and autoimmunity.

P1 solely presented with generalised adenopathy and autoimmunity. P2, on the other hand, only had cervical lymphadenopathy. Autoimmunity in the form of Evans syndrome was noted in P1, whereas the previously reported patients showed no evidence of autoimmune phenomenon except one with intermittent anti-erythrocyte antibodies [6]. Incidence of Evans syndrome is commonly associated with ALPS, and nearly 47% of patients with Evans syndrome have diagnosis consistent with ALPS [9] [10]. Since, *FADD* deficient patients have increased susceptibility to viral infections, viral workup was done. CMV was detected in serum of P1. Evidences indicates that CMV infection and autoimmune diseases can mutually affect each other. CMV is also associated with autoimmune diseases like Type 1 Diabetes (T1D), systemic lupus erthematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS) and has acquired ability to produce viral products homologs to cytokines, chemokines, and their receptors which can alter immune response and clearance of virus. CMV encodes IL-10 homolog (known as cmvIL-10), which can modulate immune response, induce replication and persistence of the virus, along with differentiation of autoreactive B cells. Although P1 and P2 harboured similar homozygous mutation, the clinical severity of disease was profound in P1. Since CMV can induce or perpetuate autoimmunity, the autoimmune phenomenon in P1 can be attributed to CMV [11]. IL-10 is an anti-inflammatory cytokine which helps in prevention of inflammatory and autoimmune pathologies. Studies on mouse models suggests that elevated levels of IL-10 contributes to development of autoimmunity. IL-10 indirectly enhances Th2 development by antagonising Th1 cell development. The Th2- oriented lymphocyte profile generated by IL-10 promotes B-cell production of antibodies, including autoantibodies [16], and hence influences B cell homeostasis and therefore the autoimmune manifestations seen in P1 might be associated by high levels of IL-10 in the serum.

Howell Jolly bodies which is hallmark of lack of splenic function were observed in previously reported patients. In contrast, they were not observed in our patients. Patients with ALPS-FAS might have mild B cell immunodeficiency characterised by low B memory, class switch memory along with low IgM, similar findings were observed in P1 and P2. The defects in B cell arise due to altered structure or function of the marginal zones. The accumulation or expansion of transitional B cells may represent a spillover from the bone marrow, disturbed selection/differentiation during transition from immature to mature naïve B cells or disturbed entrance into the splenic environment [17]. CD21<sup>low</sup> B cells which are known to be expanded in autoimmune conditions were expanded in P1, indicating anergic B cell with defective signalling.

Comprehensive DNTs profiling was performed in both our patients. DNTs are considered to be major hallmark for ALPS and they exhibit features of terminally differentiating T cells reexpressing CD45RA(TEMRA), but they also express naïve cell markers like CD27 and CD28 [12]. Recently published study claims that there are Fas controlled (FC) DNTs characterised by CD38<sup>+</sup> and CD45RA<sup>+</sup> expression which are expanded in patients with ALPS-FAS [13]. The immunophenotype of DNTs in P1 and P2 was strikingly similar to ALPS-FAS patients. Hyperactive mTOR signalling is considered to be the regulator of lymphoproliferation and the unique differentiation in ALPS-FAS, and also in maintenance of these DNTs. We analysed the basal levels of pAkt and pS6 in the *FADD* family. Interestingly, we found that basal levels of pAkt and pS6 was elevated significantly in P1 and P2 on DNTs whereas the heterozygous parents had levels similar to healthy control. The clinical and immunological similarity observed in our patients can be attributed to the site of the mutation. The R117 site in FADD is evolutionary conserved positively charged residue, located in alpha helix 2 region. It is critical for protein interaction and constitute a major binding site to interact with death domain of Fas receptor [19][20]. The mutation at this site disrupts binding to Fas and also abolishes apoptosis which was also observed in both our patients (Figure 2). C105, as delineated in the original report, is located in the alpha helix 1 of death domain which is located at interface of Fas-FADD complex. The protein folding stability of the C105W mutant protein was low which resulted in lower stability of Fas-FADD complex and impaired apoptosis [7].

P1 was started on management protocol for ALPS associated cytopenia. There was regression of lymphadenopathy on prednisolone 2 mg/kg/day. It was gradually tapered and MMF was started at 1200 mg/m<sup>2</sup>. The response to this immunosuppression was transient as the lymphocyte counts increased and thrombocytopenia recurred. Though hematopoietic stem cell transplantation is done previously in *FADD* deficiency, it might be considered if there is worsening of autoimmunity in our patient despite aggressive immunosuppression. P2 remains asymptomatic.

We report two siblings with novel mutation in *FADD* presenting with autoimmune manifestations and lymphoproliferation as seen in ALPS-FAS due to defective FADD-FAS interaction.

## Abbreviations

ALPS: Autoimmune lymphoproliferative syndrome

FADD: Fas-associated death domain

FASLG: Fas-ligand

CASP8: Caspase 8

CASP10: Caspase 10

HCMV: Human Cytomegalovirus

NGS: Next-generation sequencing

AIHA: Autoimmune haemolytic anaemia

ITP: Immune thrombocytopenia

DCT: Direct Coombs test

CT: Computed tomography

DNT: Double-negative T cells

IL-10: Interleukin -10

IL-18: Interleukin -18

MMF: Mycophenolate mofetil

ITP: Immune thrombocytopenia

## Declarations

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## **Contributions :**

(Priyanka Setia :PS, Umair Bargir :UB, Chandrakala Shanmukhaiah :CS, Neha Jodhawat: NJ, Priyanka Kambli:PK, Maya Gupta : MG, Aparna Dalvi:AD, Shweta Shinde :SSh, Nayana Nambiar :NN, Sneha Sawant :SSa, Shraddha Shelar : SSe, Pallavi Gaikwad : PG, Amruta Dhawale :ADh, Madhu Mohanty : MMo, Reetika Malik Yadav: RMY, Manisha Madkaikar :MM)

PS performed the experiments, analysed the data. PS and UB drafted the manuscript. PS, NJ, UB, MG, SSh, AD, NN, SSa, were involved in routine diagnosis and performed the flow cytometric analysis. PS,PK, PG, ADh were involved in molecular work. SSe did immunoglobulin levels and helped in DNA extraction for the patients family. UB and RMY helped in collecting clinical details for entire family. MMo did the viral workup for the entire patients family. CS was involved in management of the patient, MM conceptualised and approved the final draft.

**Ethical approval** : Institutional Ethics committee (IEC)-National institute of Immunohaematology (ICMR) Mumbai ,has approved the study.

**Consent to participate** : Written informed consent from patients guardians was obtained.

**Consent for publication** : Guardians have signed the informed consent regarding publishing their childrens data.

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## Figures



**Figure 1**

Massive hepatosplenomegaly noted in P1 at 2 years of age.

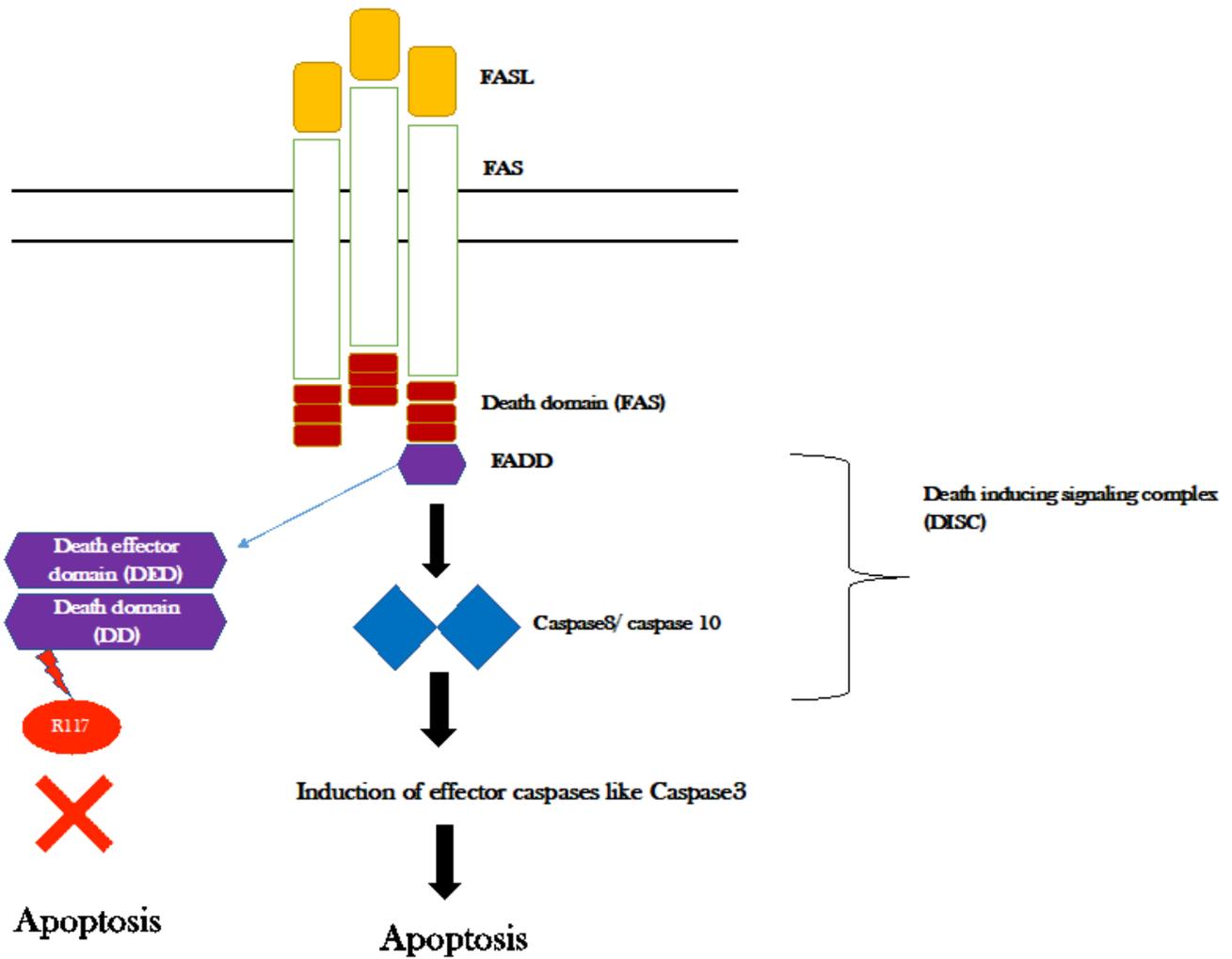


Figure 2

Proposed mechanism of R117 mutation in FAS mediated apoptotic signalling.

## Supplementary Files

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