



**HAL**  
open science

## **A case report of Folliculin interacting protein 1 deficiency**

Nidia Moreno-Corona, Alice Valagussa, Romane Thouenon, Alain Fischer,  
Sven Kracker

► **To cite this version:**

Nidia Moreno-Corona, Alice Valagussa, Romane Thouenon, Alain Fischer, Sven Kracker. A case report of Folliculin interacting protein 1 deficiency. *Journal of Clinical Immunology*, In press, 10.1007/s10875-023-01559-8 . hal-04173110

**HAL Id: hal-04173110**

**<https://hal.science/hal-04173110v1>**

Submitted on 28 Jul 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

## **A case report of Folliculin interacting protein 1 deficiency**

Nidia Moreno-Corona<sup>1,2</sup>, Alice Valagussa<sup>1,2</sup>, Romane Thouenon<sup>1,2</sup>, Alain Fischer<sup>3,4,5</sup>, Sven Kracker<sup>1,2</sup>

(1) Université Paris Cité, F-75015, Paris, France

(2) Laboratory of Human Lymphohematopoiesis, Imagine Institute, INSERM UMR 1163, F-75015, Paris, France

(3) Imagine Institute, INSERM UMR 1163, Paris, FRANCE

(4) Necker Hospital, Pediatric Hematology-Immunology and Rheumatology Unit, APHP Paris, France

(5) Collège de France, Paris, France.

**Corresponding author:** Dr. Sven Kracker

INSERM U1163, Imagine Institute, 24 Boulevard du Montparnasse, F-75015 Paris, France

e-mail: [sven.kracker@inserm.fr](mailto:sven.kracker@inserm.fr); tel.: +33-142-754-336

<http://orcid.org/0000-0003-4543-8236>

**To the editor,**

Folliculin interacting protein 1 (FNIP1) deficiency is an autosomal recessive inborn error of immunity caused by homozygous or compound heterozygous loss-of function (LOF) mutations in the *FNIP1* gene (1,2). FNIP1 deficiency presents predominantly as an antibody deficiency associated with syndromic features, such as hypertrophic cardiomyopathy. Two different case studies reported clinical and immunological phenotypes of 6 patients from 5

“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

families. Disease-causing *FNIP1* homozygous LOF mutations were described for 4 patients from 3 different consanguineous families (1,2). One patient carried compound heterozygous mutations inherited from the parents, and one patient carried a splice-site mutation in conjunction with an uniparental disomy (2). Clinical manifestations of *FNIP1* deficiency occurring within the first year of life include severe and/or recurrent upper and lower respiratory tract infections. Immunological abnormalities in the peripheral blood show strongly diminished (nearly absent) B cell numbers and severe reductions in all serum immunoglobulin isotypes (profound hypogamma/agammaglobulinemia) associated with severe or intermittent neutropenia (1,2). In addition to cardiomyopathy, central nervous system involvement was reported in 4 out of 6 patients (1,2). Microcephaly and motoric developmental delay was reported for 2 patients (1). In one patient, neurodevelopmental delay associated with magnetic resonance imaging abnormalities was reported (2). However, these manifestations were observed only in patients with consanguineous pedigrees, raising the possibility that they may be caused by other (as yet to be discovered) genetic factors.

### **Case report**

In our cohort of primary antibody-deficient patients, we identified a new *FNIP1*-deficient male patient, bringing the total number of reported *FNIP1*-deficient patients to 7 (Supplemental information Table 1). The patient, a child of non-consanguineous parents of European ancestry, presented with upper and lower respiratory tract infections from the first month of life. A primary immunodeficiency (PID) associated with severely decreased B lymphocyte counts and undetectable IgM (>0.05g/l), IgA (0.08g/l) and low IgG serum levels

“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

(0.52g/l) together with an intermittent neutropenia was diagnosed at the age of 11 months, and Ig replacement therapy was initiated. Cardiomyopathy was diagnosed at the age of 3 months, and the patient was treated until the age of 4 years with digoxin. He presented with a vascular enteropathy, and a deformation of the left foot (congenital convex pes valgus) was diagnosed at the age of 18 months. He also suffered from recurrent gingivitis and recurrent abscesses located at the anal margin. Both complications were possibly associated with chronic neutropenia, which was responsive to granulocyte-colony stimulating factor (G-CSF) treatment (Supplemental information figure 1). During his life, the patient suffered from several episodes of eczema (skin lesions) and presented delayed psycho-motor development (sitting at 11 months). A global intellectual developmental delay was later identified. Further investigation of the cardiomyopathy at the age of 18 years revealed a hypertrophic cardiomyopathy (left ventricle) associated with Wolff-Parkinson-White Syndrome. The patient died at 40 years of age due to heart failure associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The patient encountered SARS-CoV-2 during the first wave of infections in Europe; at this time SARS-CoV-2 vaccines were not available. During this time, a genetic analysis was undertaken to identify a possible monogenic defect. Trio-whole exome sequencing identified a nonsense variant (NM\_133372.3; c.3334C>T; g.130982871; GRCh37) in the *FNIP1* gene, which was heterozygous in the mother and appeared homozygous in the patient. The nonsense variant is located in exon 17 and is predicted to result in a premature stop codon Q1112\*. This variant was not reported in the public data bases (gnomAD v3.1.2, ESP6500SI-V2, 1000 Genomes) and is exclusive to the family in our internal database polyweb (containing 21709

“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

Exomes and 7697 Genomes, June 2023). Comparison of the read depth in the trio-whole exome sequencing data across the genomic locus surrounding the *FNIP1* gene identified a *de novo* copy number variant affecting the paternal allele. This large hemizygous deletion (approximate location 5: 130720000 - 131190000; GRCh37) affected the genes *CDC42SE2*, *RAPGEF6*, *FNIP1* and *MEIKIN* (Supplemental information figure 2). The hemizyosity of the c.3334C>T variant was confirmed by Sanger sequencing on genomic DNA and on cDNA from the patient (Figure 1a). Immunoblotting demonstrated the absence of FNIP1 protein in patient-derived T cell blasts (consistent with previous reports) and patient-derived EBV-immortalized B (B-EBV) cells (Figure 1b). Of note, the absence of the FNIP1 protein did not appear to affect FNIP2 protein abundance in these cells (Figure 1b). As previously described for FNIP1-deficient patients (1,2), peripheral B cells were barely detectable and a mild increase in CD3 T lymphocytes was observed at 30 years of age (Table 1).

FNIP1 and its close homologue FNIP2 were identified as folliculin (FLCN) interacting proteins (3,4). The FLCN-FNIP1 complex has been shown to interact with adenosine monophosphate (AMP)-activated protein kinase (AMPK), a key enzyme that negatively regulates mTOR activity. This interaction implicates the complex as an important regulator for cellular energy consumption (5). The strong phenotype of FNIP1-deficient patients underlines the essential role of FNIP1 in B lymphocyte development and cardiomyocyte function. It also suggests a non-redundant function of FNIP1 in neutrophils.

In summary, our case report of an additional FNIP1-deficient patient reinforces the clinical and immunological presentations of FNIP1-deficiency: a PID presenting with peripheral B cell deficiency, severe hypogammaglobulinemia/agammaglobulinemia, intermittent neutropenia

“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

responsive to G-CSF treatment, in conjunction with hypertrophic cardiomyopathy of the ventricle associated with Wolff-Parkinson-White Syndrome and psycho-motor as well as intellectual developmental delay.

### **Acknowledgements**

The authors would like to thank the patients and their families for contributing to the study.

We thank the Necker Imagine *Centre de Ressources Biologiques* for generating EBV-transformed lymphoblastoid cell lines, the bioinformatic platform from the Imagine Institute for their help in analysing the whole exome sequencing data, the clinical research team at the Imagine Institute for their support and the members of the human lymphohematopoiesis laboratory for helpful discussions.

### **Funding**

The work was funded by the French state (via the Agence Nationale de la Recherche’s “Investissements d’avenir” program (ANR-10-IAHU-01), and grants ANR-19-CE17-0012-01 and ANR-19-CE17-0012-02 (ANR-AID)). SK is a Centre National de la Recherche Scientifique staff researcher.

### **Conflict of Interest/Competing interests**

The authors declare no relevant competing interests.

### **Availability of data and material**

Not applicable

### **Authors contributions**

“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

NMC, AV and RT performed and analyzed experiments. AF provided patient care, clinical information and samples from patients and controls. SK supervised research. SK and NMC wrote the manuscript, and all the co-authors revised, edited and approved the manuscript.

### **Ethics approval**

Genetic studies and data collection procedures were approved by the local institutional review board (*Comité de Protection des Personnes Ile de France II*, Paris, France; reference: 2015-01-05; 2015-01-05 MS2) and the French Advisory Committee on Data Processing in Medical Research (*Comité Consultatif sur le Traitement de l’Information en matière de Recherche dans le domaine de la Santé*, Paris, France; reference: 15.297bis).

### **Consent to Participate**

Informed consent was obtained from all individual participants included in the study.

### **Consent for publication**

Not applicable

### **References**

1. Nihues T, Özgür TT, Bickes M, Waldmann R, Schöning J, Bräsen J, et al. Mutations of the gene *FNIP1* associated with a syndromic autosomal recessive immunodeficiency with cardiomyopathy and pre-excitation syndrome. *Eur J Immunol*. 2020 Jul;50(7):1078–80.
2. Saettini F, Poli C, Vengoechea J, Bonanomi S, Orellana JC, Fazio G, et al. Absent B cells, agammaglobulinemia, and hypertrophic cardiomyopathy in folliculin-interacting protein 1 deficiency. *Blood*. 2021 Jan 28;137(4):493–9.
3. Baba M, Hong SB, Sharma N, Warren MB, Nickerson ML, Iwamatsu A, et al. Folliculin encoded by the *BHD* gene interacts with a binding protein, FNIP1, and AMPK, and is involved in AMPK and mTOR signaling. *Proc Natl Acad Sci*. 2006 Oct 17;103(42):15552–7.
4. Hasumi H, Baba M, Hong SB, Hasumi Y, Huang Y, Yao M, et al. Identification and characterization of a novel folliculin-interacting protein FNIP2. *Gene*. 2008 May;415(1–2):60–7.
5. Baba M, Keller JR, Sun HW, Resch W, Kuchen S, Suh HC, et al. The folliculin-FNIP1 pathway deleted in human Birt-Hogg-Dube´ syndrome is required for murine B-cell

“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

development. 2012;120(6):8.



“This version of the article has been accepted for publication, after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s10875-023-01559-8>. Use of this Accepted Version is subject to the publisher’s Accepted Manuscript terms of use <https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms>”.

**Figure legend**

**Figure 1: FNIP1 deficiency. a)** Pedigree and Sanger sequencing profiles from genomic DNA (gDNA) and cDNA. **b)** Immunoblots against FNIP1, FNIP2 and GAPDH as loading control were performed with cell lysates from B-EBV cells and T cell blast from patient and controls.