

# Clinical and Immunologic Characterization of *NFKB1* Mutations

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ISAAI Annual Meeting 2021





TRANSLATIONAL AND CLINICAL IMMUNOLOGY | [VOLUME 146, ISSUE 4, P901-911,](#)

OCTOBER 01, 2020

# Characterization of the clinical and immunologic phenotype and management of 157 individuals with 56 distinct heterozygous *NFKB1* mutations

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Published: April 09, 2020 • DOI: <https://doi.org/10.1016/j.jaci.2019.11.051> •



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# Disclosures

No conflicts of interest to disclose.

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# Major Questions

If I have a patient with a *NFKB1* mutation, what can I expect to see clinically?

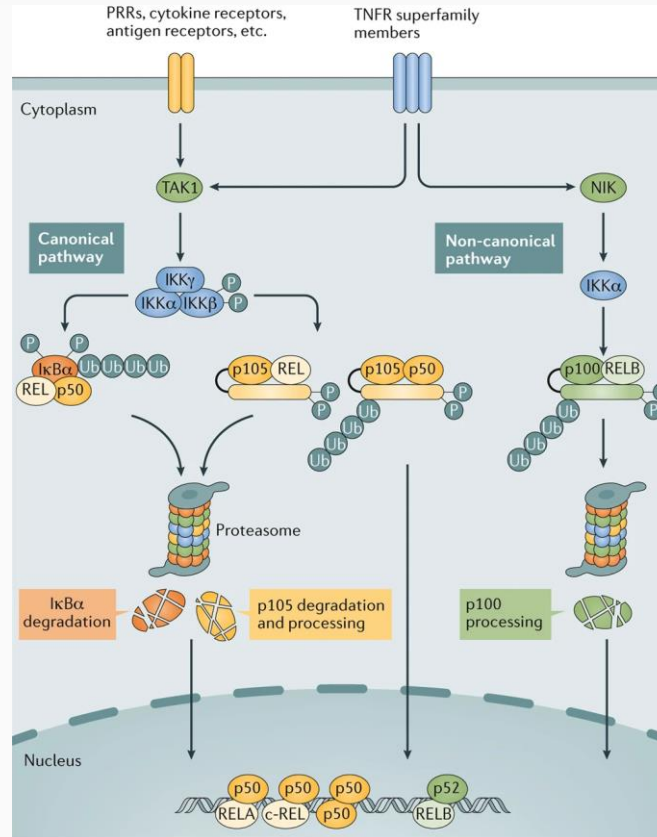
How should I treat my patients with *NFKB1* mutations?



# Background



**Canonical**  
Proliferation  
Apoptosis  
Inflammation

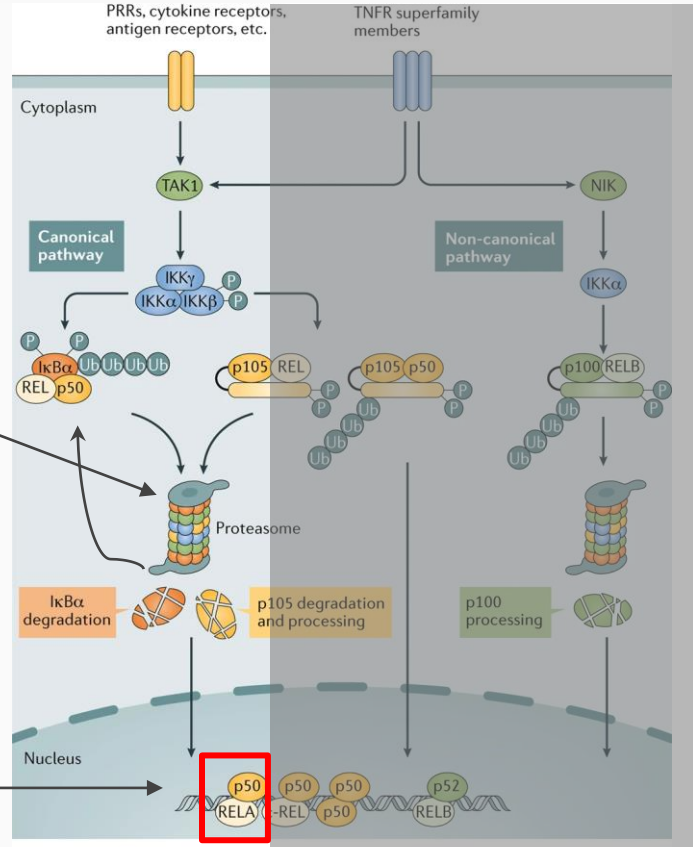


**Non-canonical**  
Adaptive immunity  
Cellular survival  
Differentiation





Active NF-κB  
transcription factor



## NFKB1

Encodes protein p105

Degraded to p50

NF-κB: p50/RelA

Inhibited by IκB

Degradation of IκB causes  
translocation, activation



Have patients  
with *NFKB1*  
mutations been  
described before?

Yes!

**AJHG**

Volume 97, Issue 3, 3 September 2015, Pages 389-403



Article

Haploinsufficiency of the NF- $\kappa$ B1 Subunit p50 in  
Common Variable Immunodeficiency



Journal of Allergy and Clinical Immunology

Volume 140, Issue 3, September 2017, Pages 782-796



Translational and clinical immunology

Damaging heterozygous mutations in *NFKB1*  
lead to diverse immunologic phenotypes





What did this research group do?



# Patient Population

231 total patients

105 different *NFKB1* mutations

Bioinformatic analysis: 56  
pathogenic / likely pathogenic

157 individual patients

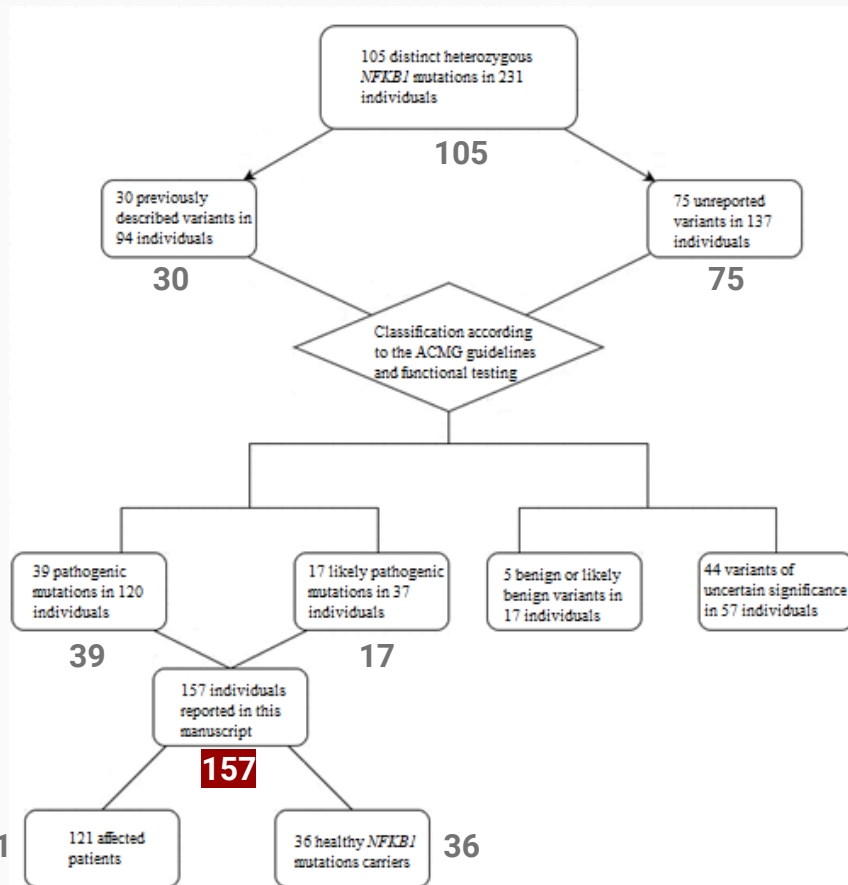


Fig. S1



# What kinds of mutations were found in this analysis?

56 pathogenic mutations

50% are novel

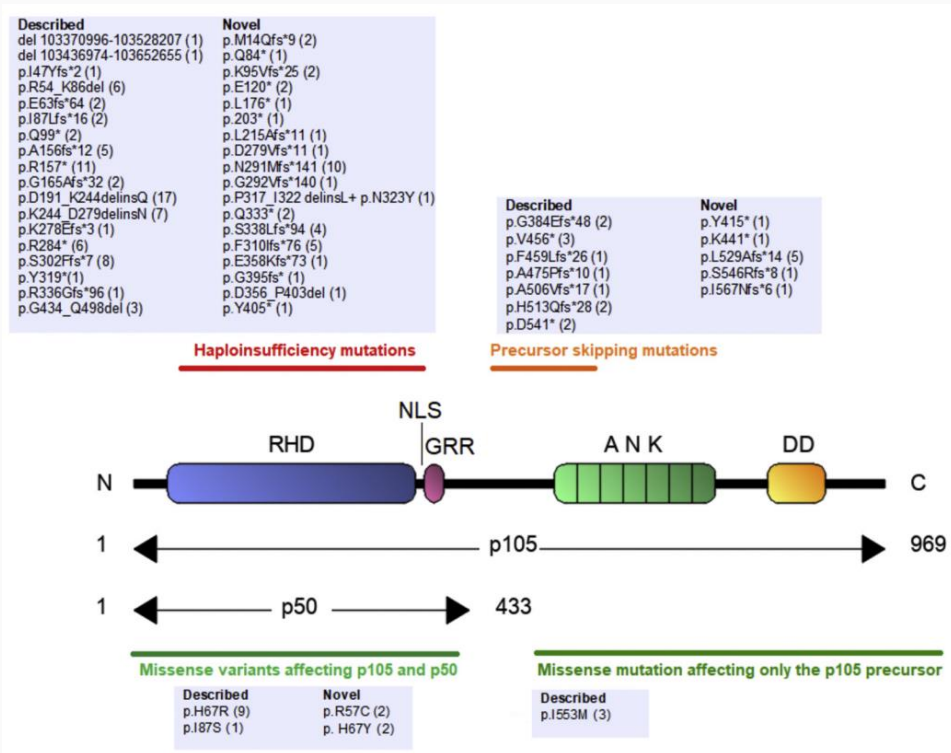


Fig. 1



# Did the novel mutations cause functional effects *in vitro*?

**Yes!**

Impaired p50 nuclear translocation

Decreased processing of p105 into p50

Decreased NF- $\kappa$ B transcription activity

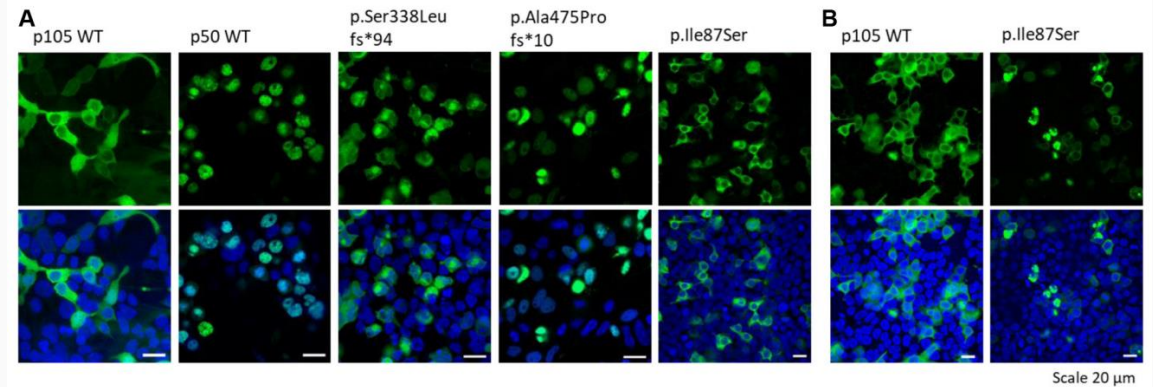


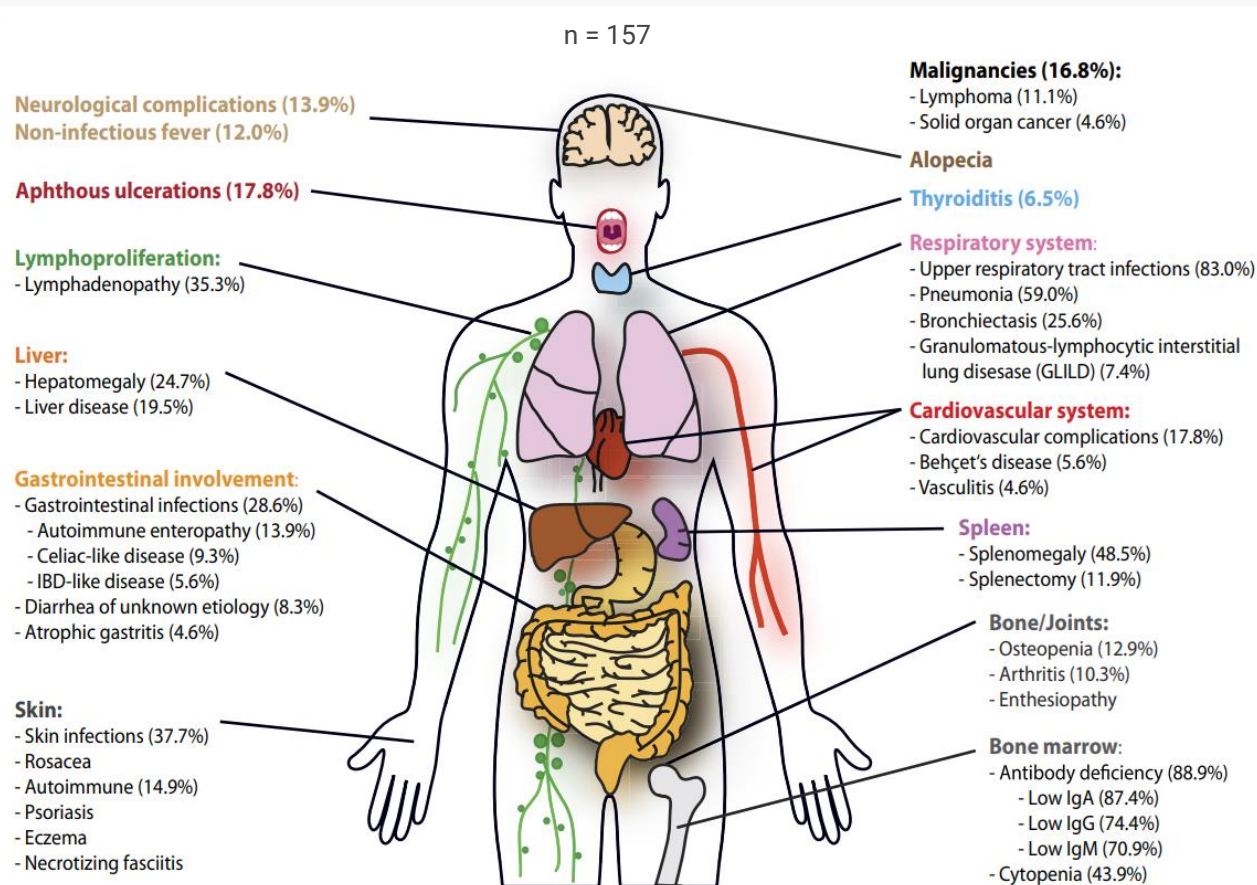
Fig. 2



What did patients with *NFKB1* mutations look like?



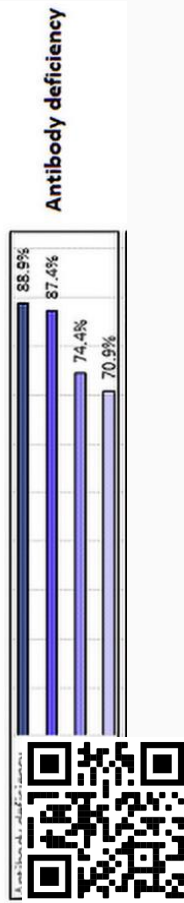
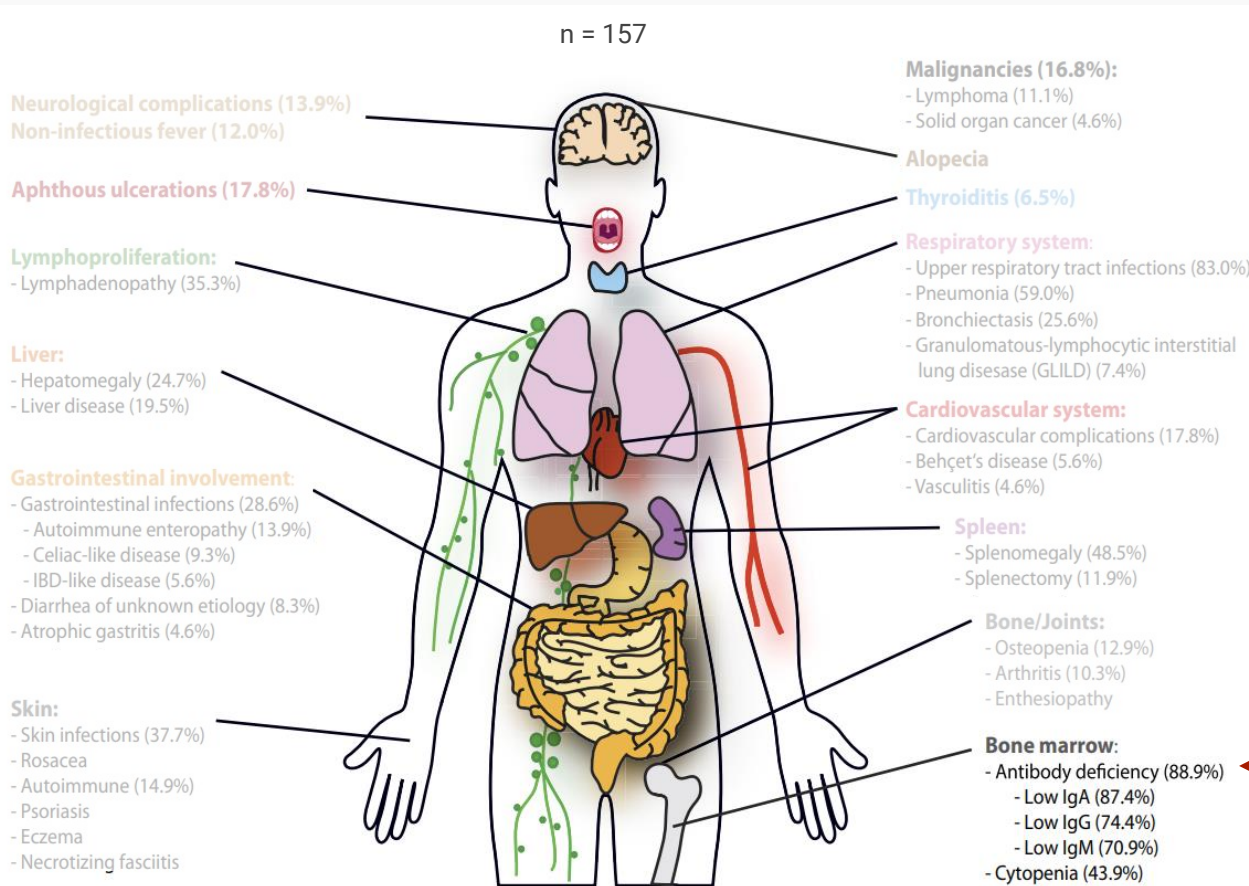
# The phenotype of *NFKB1* insufficiency



Adapted from graphical abstract



# Hypogammaglobulinemia



Adapted  
 Adapted  
 graphical  
 graphical  
 abstract  
 Page 5

# Lymphoproliferation



n = 157

**Neurological complications (13.9%)**

**Non-infectious fever (12.0%)**

**Aphthous ulcerations (17.8%)**

**Lymphoproliferation:**

- Lymphadenopathy (35.3%)

**Liver:**

- Hepatomegaly (24.7%)

- Liver disease (19.5%)

**Gastrointestinal involvement:**

- Gastrointestinal infections (28.6%)

- Autoimmune enteropathy (13.9%)

- Celiac-like disease (9.3%)

- IBD-like disease (5.6%)

- Diarrhea of unknown etiology (8.3%)

- Atrophic gastritis (4.6%)

**Skin:**

- Skin infections (37.7%)

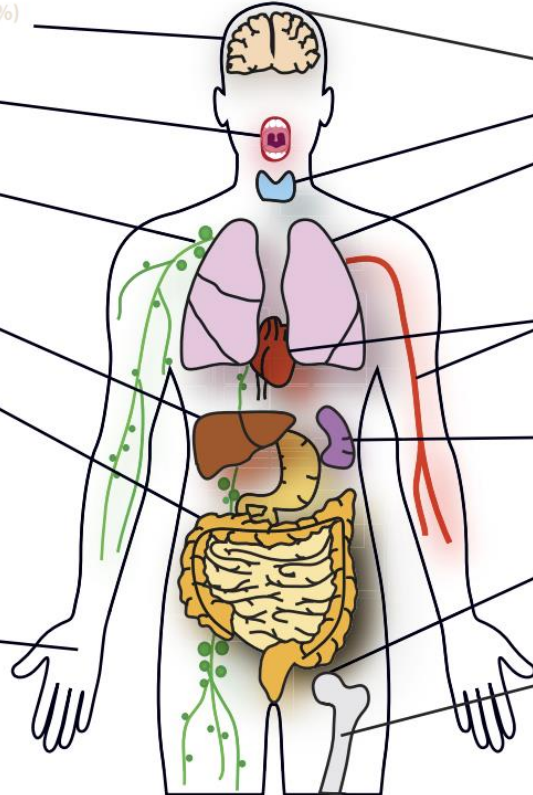
- Rosacea

- Autoimmune (14.9%)

- Psoriasis

- Eczema

- Necrotizing fasciitis



**Malignancies (16.8%):**

- Lymphoma (11.1%)

- Solid organ cancer (4.6%)

**Alopecia**

**Thyroiditis (6.5%)**

**Respiratory system:**

- Upper respiratory tract infections (83.0%)

- Pneumonia (59.0%)

- Bronchiectasis (25.6%)

- Granulomatous-lymphocytic interstitial lung disease (GLILD) (7.4%)

**Cardiovascular system:**

- Cardiovascular complications (17.8%)

- Behçet's disease (5.6%)

- Vasculitis (4.6%)

**Spleen:**

- Splenomegaly (48.5%)

- Splenectomy (11.9%)

**Bone/Joints:**

- Osteopenia (12.9%)

- Arthritis (10.3%)

- Enthesiopathy

**Bone marrow:**

- Antibody deficiency (88.9%)

- Low IgA (87.4%)

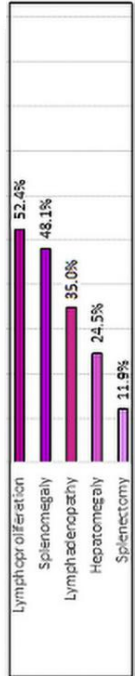
- Low IgG (74.4%)

- Low IgM (70.9%)

- Cytopenia (43.9%)



**Lymphoproliferation**



Adapted from graphical abstract and Fig. 5



# Recurrent infection

n = 157

**Neurological complications (13.9%)**

**Non-infectious fever (12.0%)**

**Aphthous ulcerations (17.8%)**

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- Enthesiopathy

**Bone marrow:**

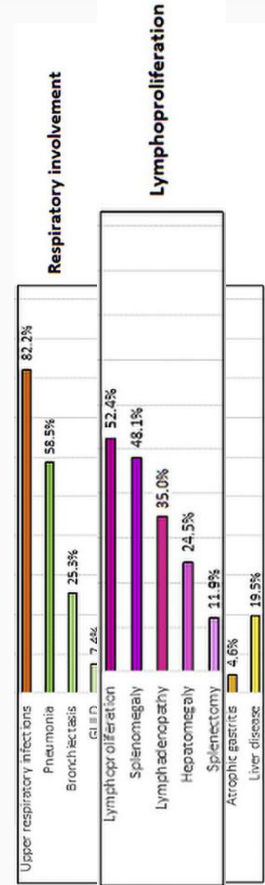
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- Cytopenia (43.9%)



Adapted from graphical abstract and Fig. 5

# Malignancy

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**Bone marrow:**

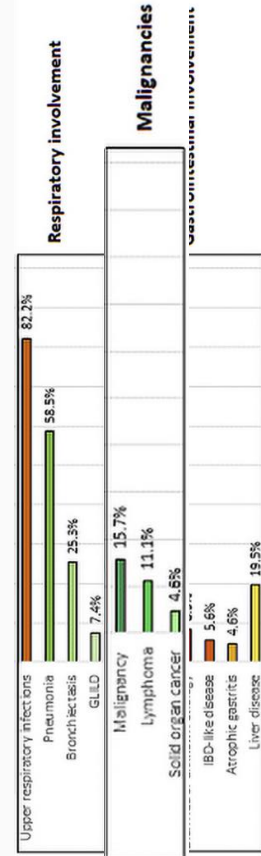
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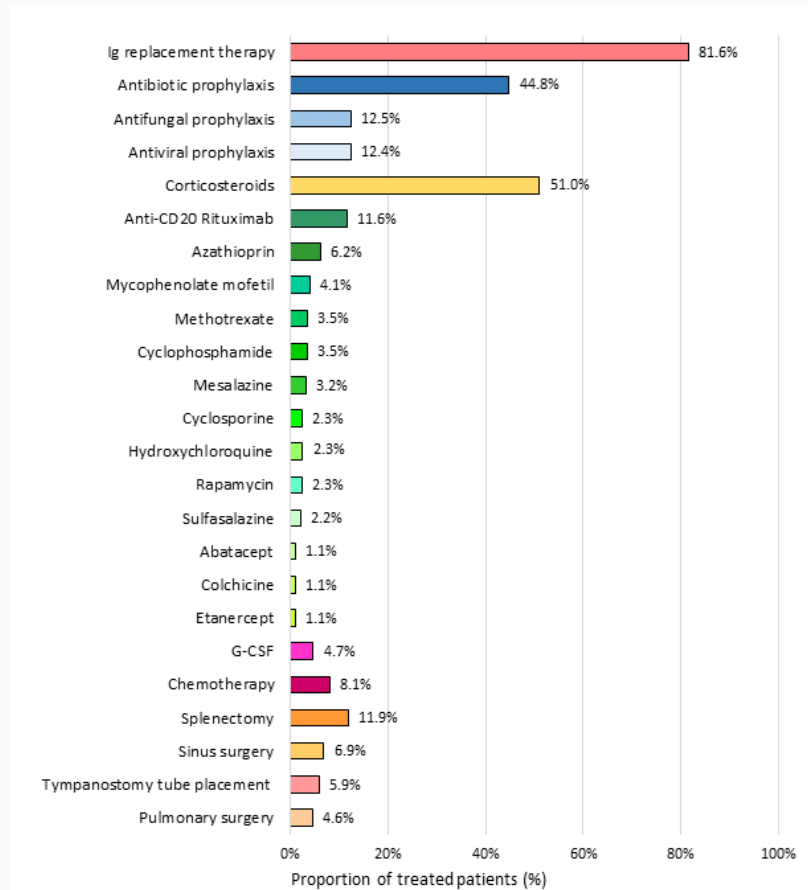
- Cytopenia (43.9%)



Adapted from graphical abstract and Fig. 5

# How were *NFKB1* mutation carriers treated?

Mostly immunosuppression and prophylaxis



82% IVIG

51% Steroids

45% Antibiotics

Fig. S4



# What happened to the cohort over time?

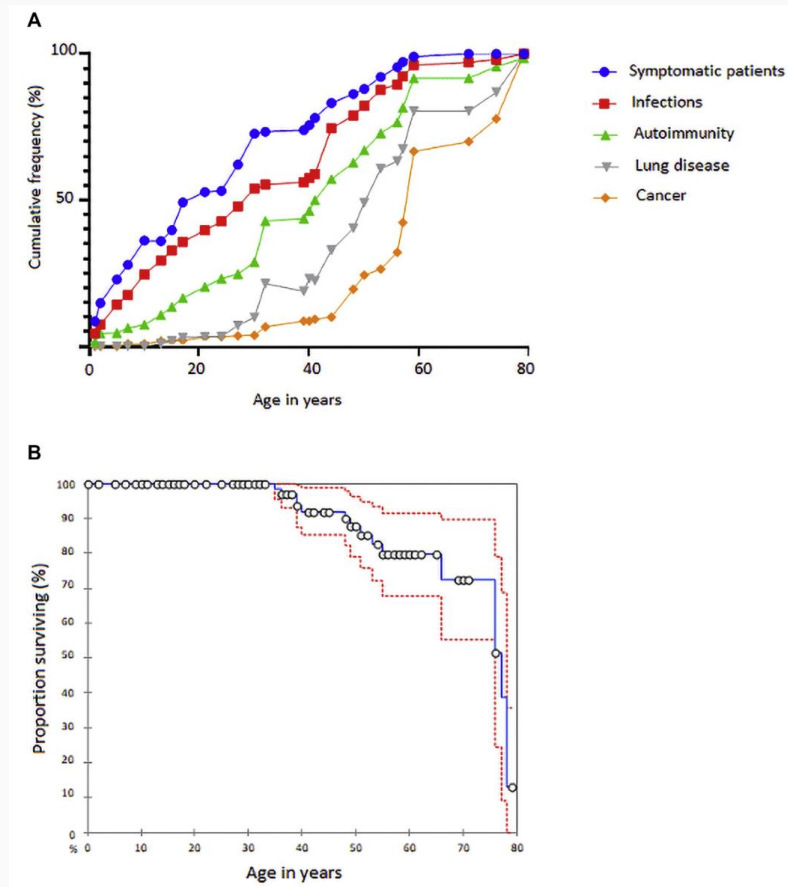


Fig. 3



# Takeaway:

## Major clinical findings

**Antibody deficiency**

**Recurrent respiratory /  
gastrointestinal infections**



# Takeaway:

When should I  
think about  
*NFKB1* mutation?

Suspect in patients with CVID-like phenotype

Autosomal dominant

Autoimmune component to presentation



# Takeaway:

How should I  
treat an *NFKB1*  
mutation carrier?

Immunoglobulin replacement

Antibiotic prophylaxis

Steroids if autoimmune

Other options need investigation:  
abatacept, proteasome inhibitors



# Questions

