Clinical and Immunologic Characterization of *NFKB1* Mutations

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

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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

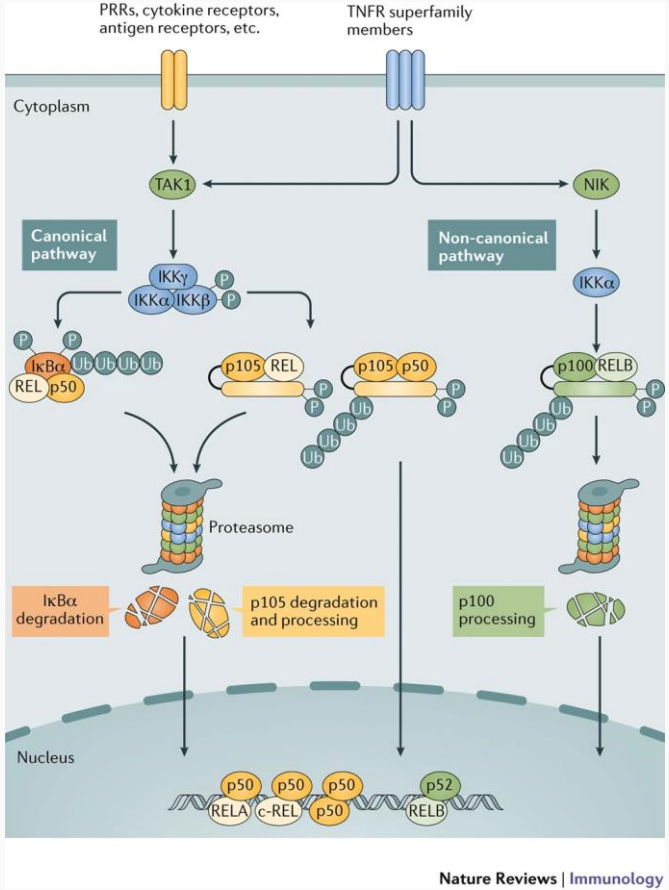
NF-kB

Canonical

Proliferation

Apoptosis

Inflammation



Non-canonical

Adaptive immunity

Cellular survival

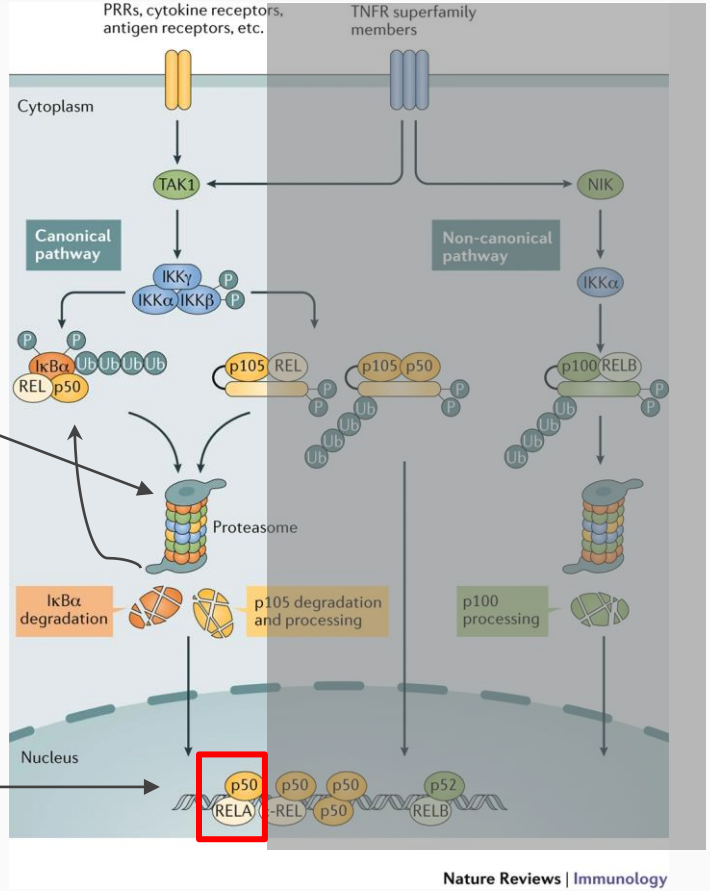
Differentiation

Sun, 2017

NF-kB

NFKB1

p105



Active NF-kB transcription factor

Sun, 2017

NFKB1

Encodes protein p105

Degraded to p50

NF-KB: p50/RelA

Inhibited by IKB

Degradation of IKB causes translocation, activation

Have patients with *NFKB1* mutations been described before?

Yes!

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

Article

Haploinsufficiency of the NF-κB1 Subunit p50 in Common Variable Immunodeficiency

ELSEVIER
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

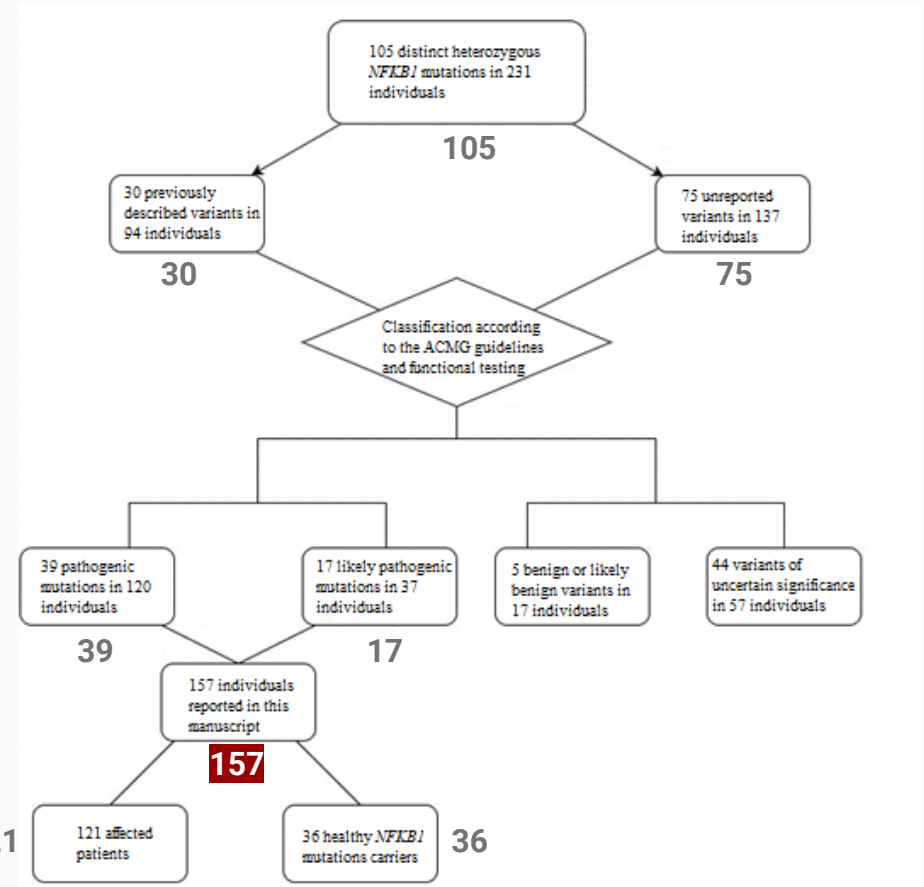


Fig. S1

What kinds of mutations were found in this analysis?

56 pathogenic mutations

50% are novel

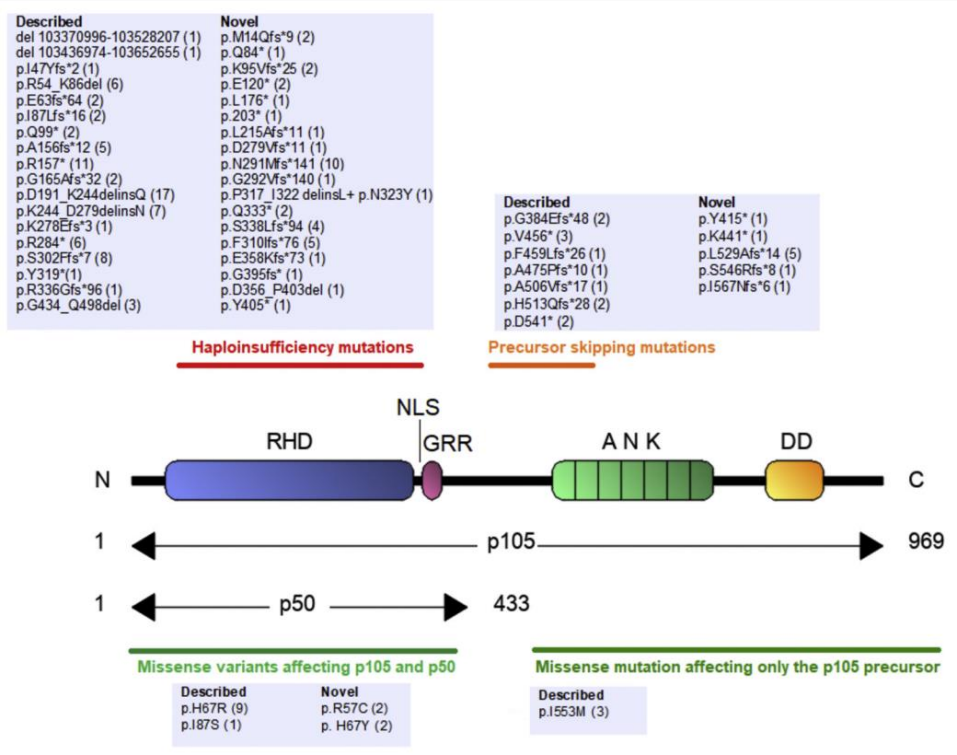


Fig. 1

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

Yes!

Impaired p50 nuclear translocation

Decreased processing of p105 into p50

Decreased NF-kB transcription activity

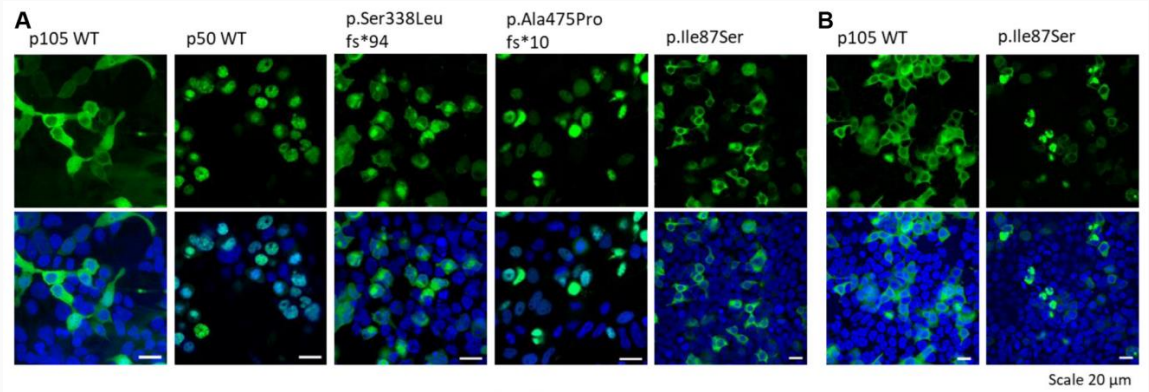
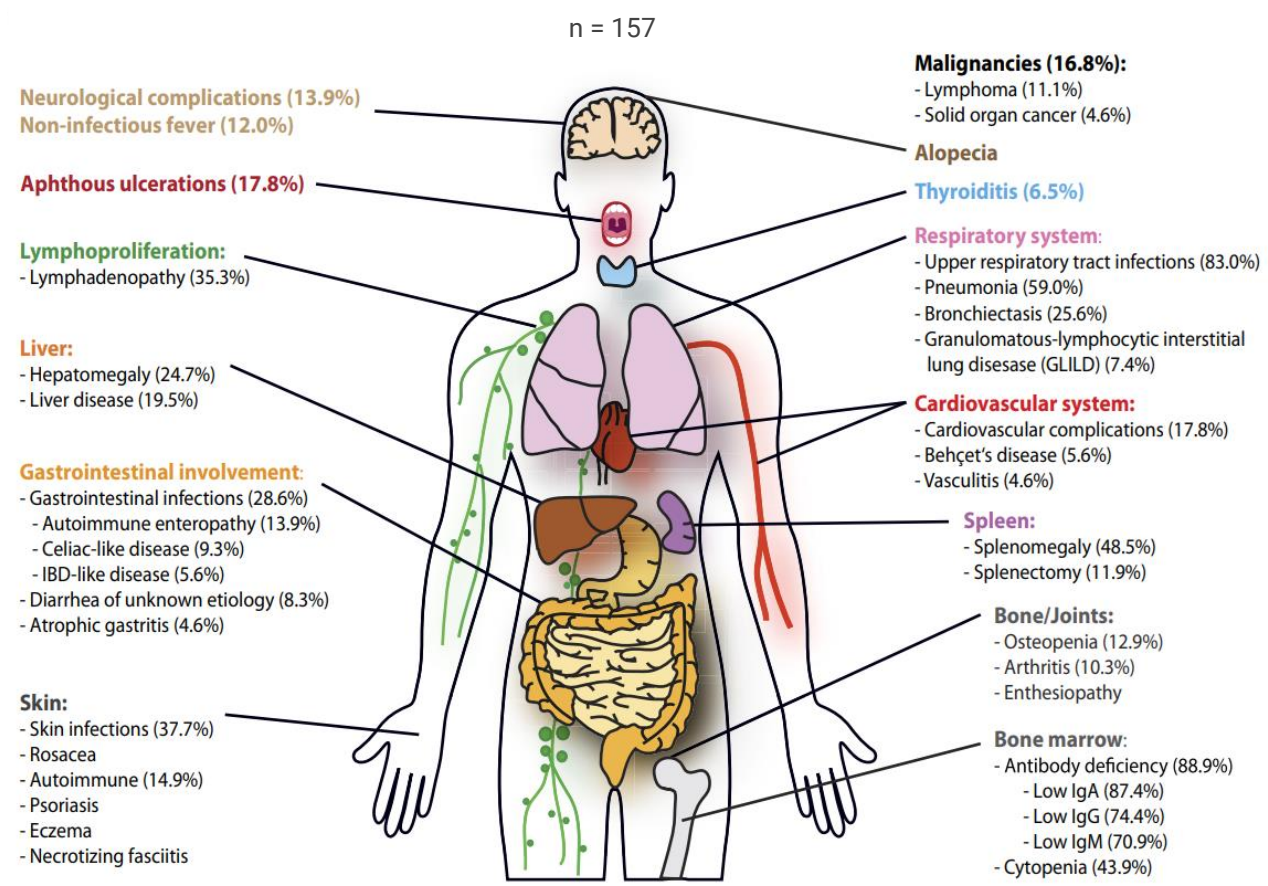


Fig. 2

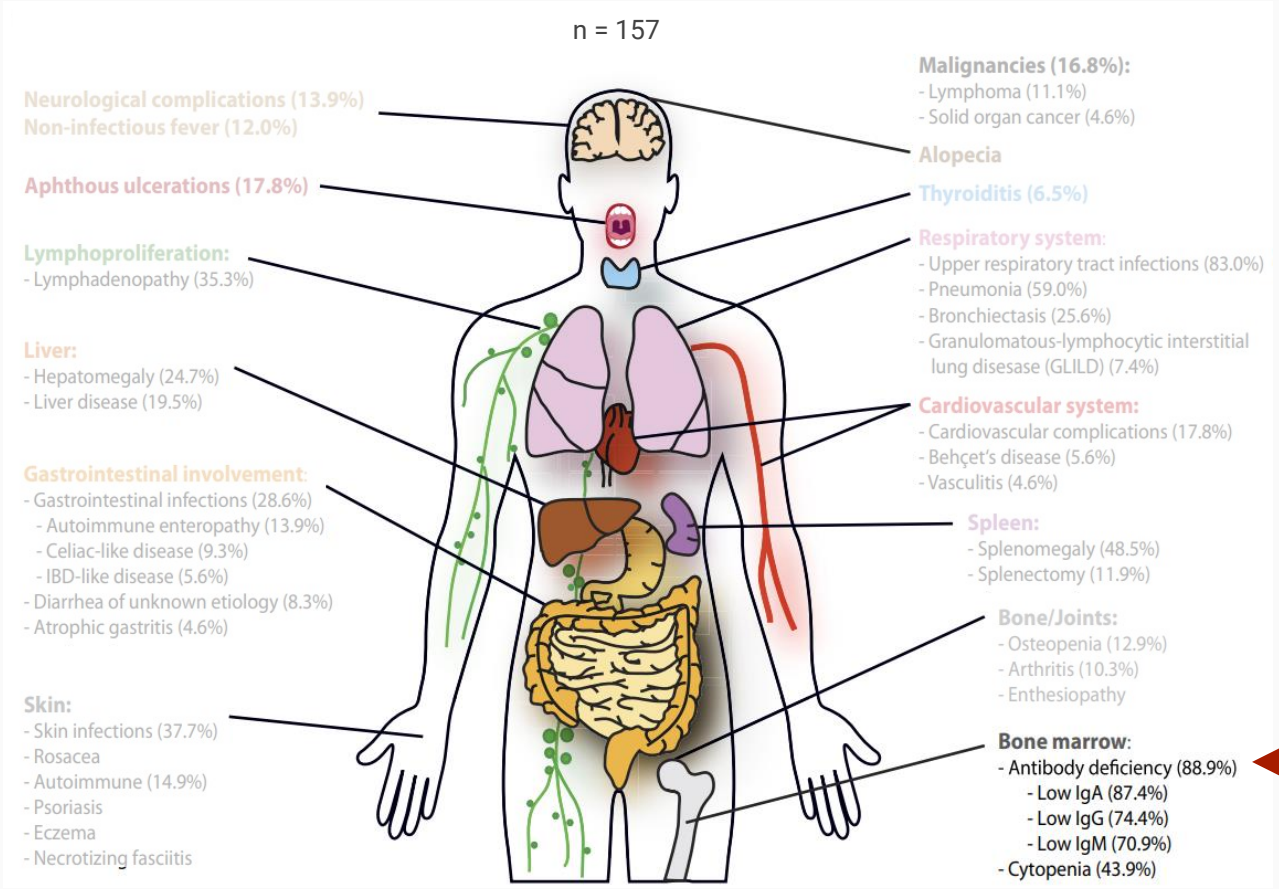
What did patients with *NFKB1* mutations look like?

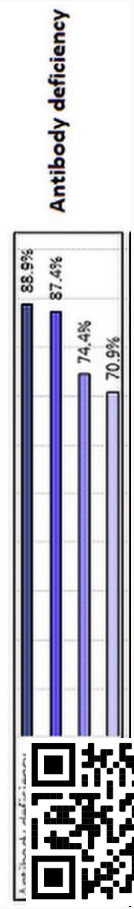
The phenotype of *NFKB1* insufficiency



Adapted from graphical abstract

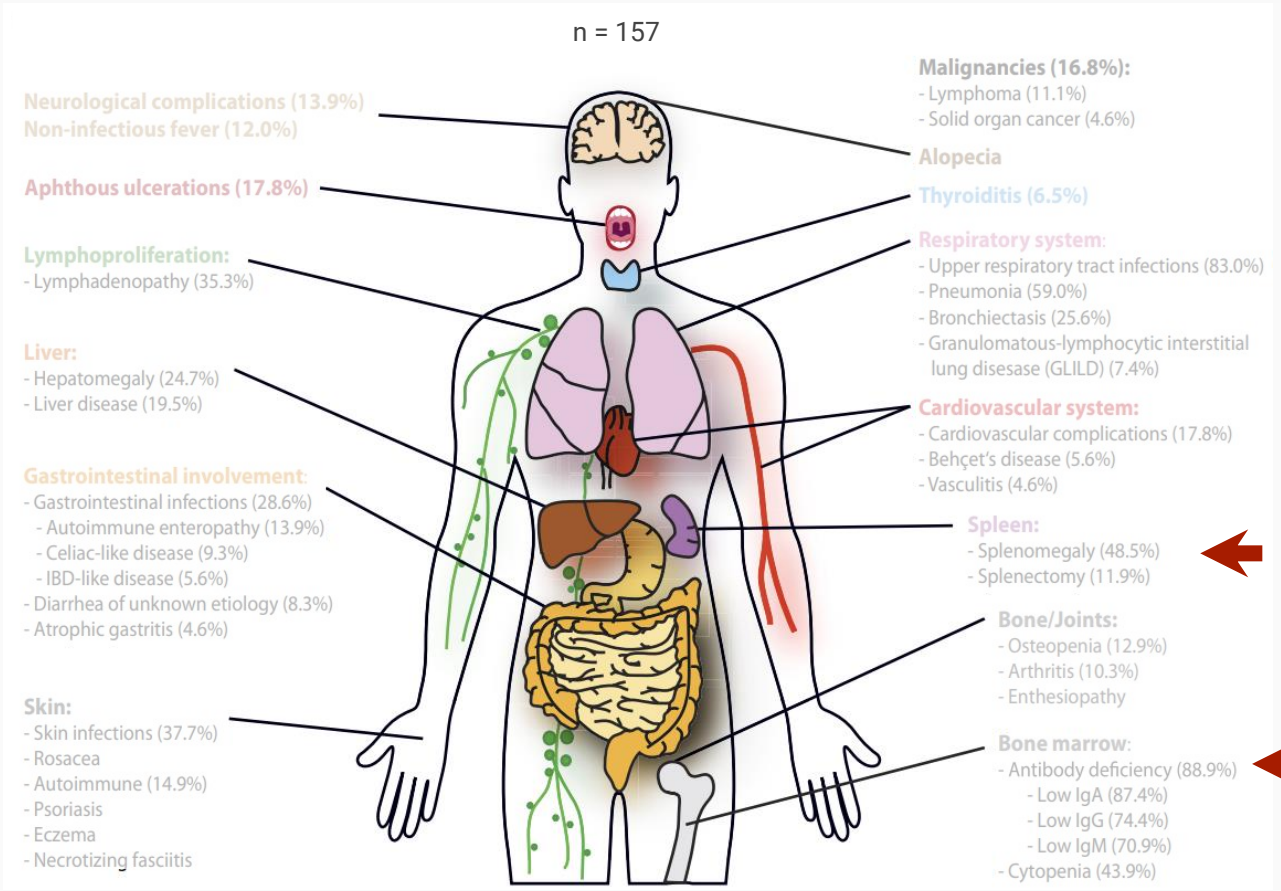
Hypogammaglobulinemia

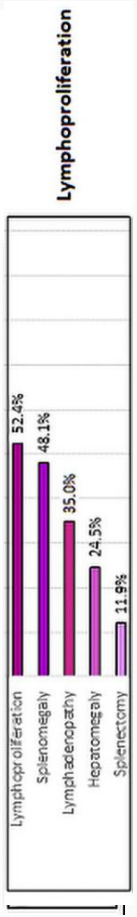




Adapted from graphical abstract 5

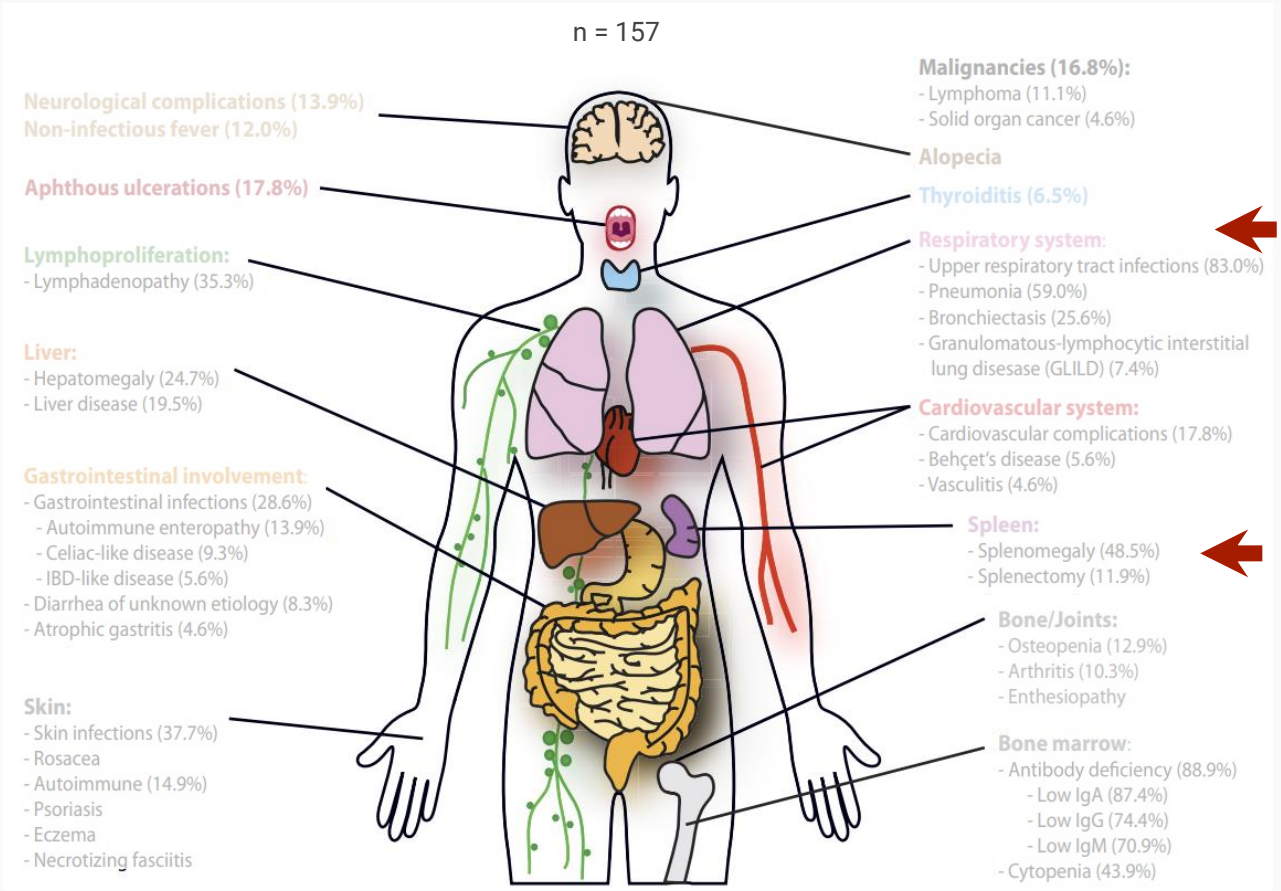
Lymphoproliferation





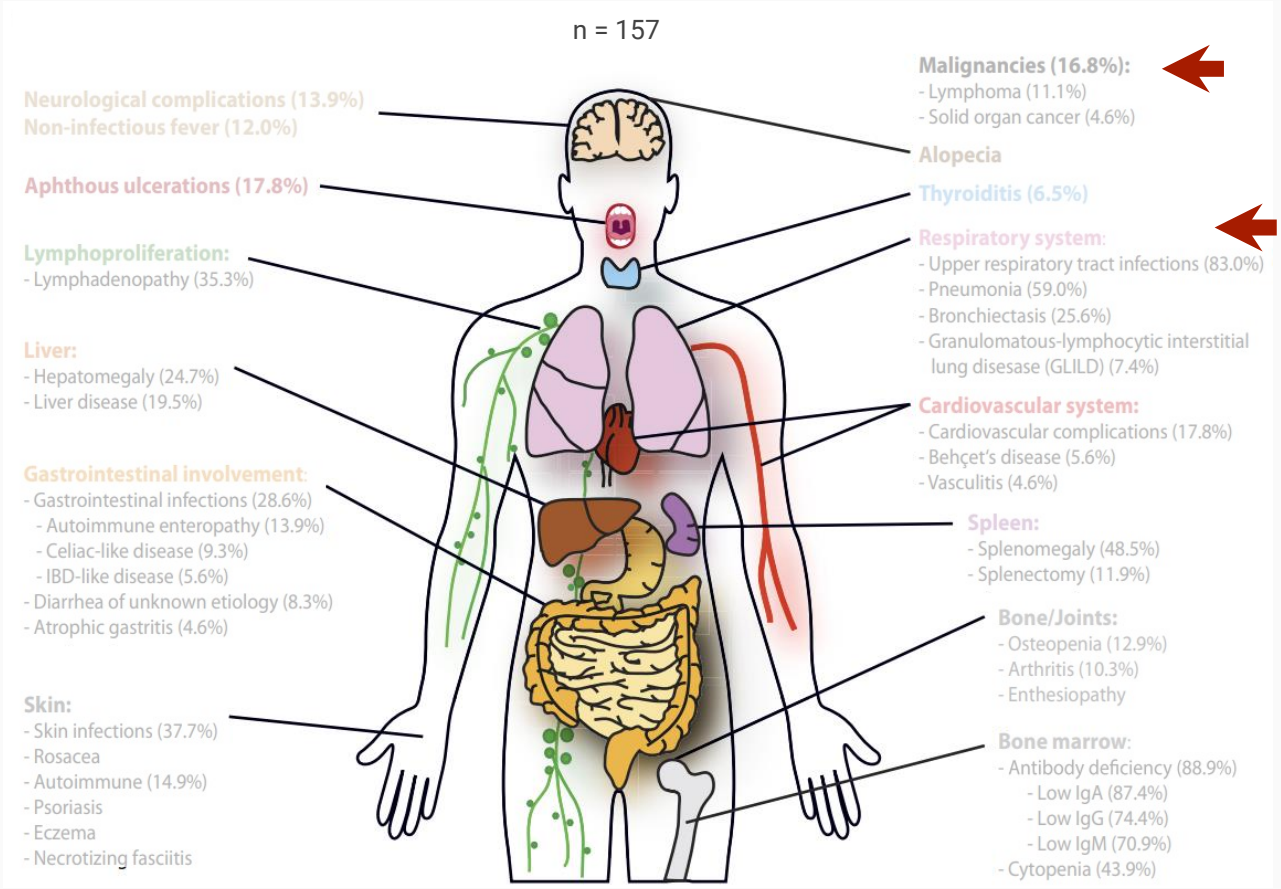
Adapted from graphical abstract and Fig. 5

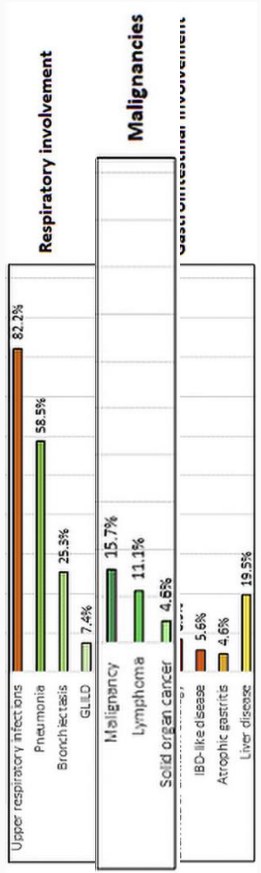
Recurrent infection



Adapted from graphical abstract and Fig. 5

Malignancy

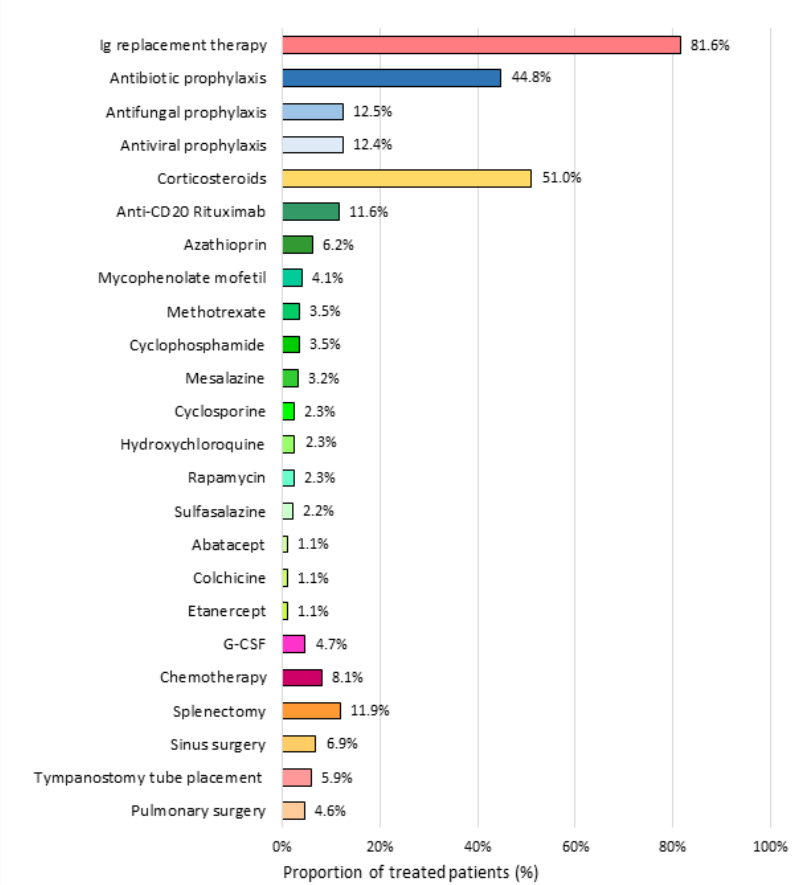




Adapted from graphical abstract and Fig. 5

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?

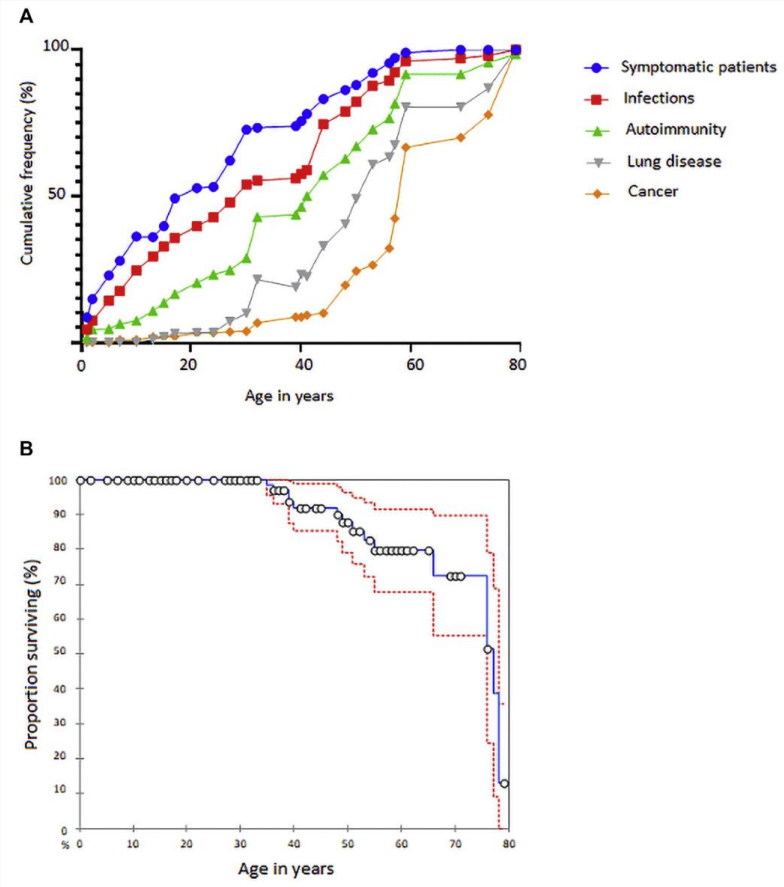


Fig. 3

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