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Long-term follow up of families with pathogenic *NFKB1* variants reveals incomplete penetrance and frequent inflammatory sequelae

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ABSTRACT

Nuclear factor κ light-chain enhancer of activated B cells (NF-κB) family of evolutionarily conserved transcription factors are involved in key cellular signaling pathways. Previously, hypogammaglobulinemia and common variable immunodeficiency (CVID)-like phenotypes have been associated with *NFKB1* variants and loss-of-function *NFKB1* variants have been reported as the most common monogenic cause for CVID among Europeans. Here, we describe a Finnish cohort of *NFKB1* carriers consisting of 31 living subjects in six different families carrying five distinct heterozygous variants. In contrast to previous reports, the clinical penetrance was not complete even with advancing age and the prevalence of CVID/hypogammaglobulinemia was significantly lower, whereas (auto)inflammatory manifestations were more common (42% of the total cohort). At current stage of knowledge, routine genetic screening of asymptomatic individuals is not recommended, but counseling of potential adult carriers seems necessary.

Abbreviations: NF-κB, Nuclear factor κ light-chain enhancer of activated B cells; IEI, inborn errors of immunity; CVID, common variable immunodeficiency; ERCP, endoscopic retrograde cholangiopancreatography; WBC, white blood cell count; anti-PnP, anti-pneumococcal polysaccharide.

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1. Introduction

NF-κB pathway is an evolutionarily conserved signaling system regulating several cellular processes including survival, stress response, proliferation, inflammation, innate and adaptive immune responses, and ectodermal development [1–3]. Unsurprisingly, given the ubiquitous roles of NF-κB family members, variants in genes coding NF-κB pathway proteins are associated with inborn errors of immunity (IEIs) with immunodeficiency, autoimmunity, autoinflammation, ectodermal dysplasia, and malignancies [3–8]. *NFKB1* encodes for the precursor p105 belonging to the family of NF-κB transcription factors. Upon activation, p105 is proteolytically cleaved into p50 further dimerizing with p65, c-Rel or with itself, as a part of canonical NF-κB pathway activation [2,3,9]. Monoallelic variants encoding either p105 or p50are sufficient to lead to signaling dysregulation and cause IEI, by affecting the formation and nuclear entrance of either or both dimers [10–12].

Hypogammaglobulinemia and CVID-like phenotypes have been associated with *NFKB1* variants [10,11,13–17]. Among Europeans, loss-of-function variants in *NFKB1* have been reported as the most common monogenic cause for CVID (clinically presenting with symptomatic hypogammaglobulinemia and recurrent infections), accounting for 4% of cases [13]. Clinical penetrance for hypogammaglobulinemia or CVID associated with disease-causing variants in *NFKB1* has been reported to range from 50 to 100% [10,13–15,17], with an age-dependent increase, and eventually to reach full 100% [14].

Besides a CVID -like phenotype or other types of hypogammaglobulinemia, variants in *NFKB1* have so far been associated with a wide spectrum of manifestations ranging from various kinds of organ involvement to autoinflammation [6,11,18,19]. Previously, heterozygous truncating variants in *NFKB1* have been associated with necrotizing cellulitis incited by tissue trauma or surgical procedures, and missense variants with Behçet-like disease [11].

Because genetic screening in mildly symptomatic or asymptomatic *NFKB1* deficient family members has rarely included extended families [15], we wanted to perform wider screening of all consenting family members in Finnish pedigrees with an identified *NFKB1* loss-of-function variant. To facilitate knowledge-based clinical family counseling, we focused on potential infectious and inflammatory complications and on clinical penetrance. Our findings suggest incomplete penetrance of B cell deficiencies and clinically meaningful severe disease overall, as well as previous relative underrepresentation of potential inflammatory manifestations associated with *NFKB1* variants.

2. Materials and methods

2.1. Patients/cohort

Our cohort consisted of 36 consenting individuals in six different families, carrying five distinct heterozygous *NFKB1* variants. All consenting, potential living carriers in these families were systematically interviewed, screened genetically, and their available patient records studied. Five deceased, often decades earlier, tested or obligate variant carriers were excluded from analyses due to incomplete remaining data. Thus, altogether 31 consenting Finnish individuals carried functionally proven pathogenic variants in *NFKB1* and were included, of whom 24 have been published previously [11,12]. Here, we provide longer follow-up data on families and additional data on carriers. An individual was defined clinically healthy/asymptomatic if she or he had not displayed any clinical signs suggesting IEI. Abnormalities in laboratory parameters were recorded but were not used to determine whether the individual was clinically healthy or not. For more detailed information on the cohort, on excluded individuals, and clinical data, see Supplementary text.

2.2. Genetics and validation

WES and Sanger sequencing were performed at the sequencing core facilities of Science for Life Laboratory, Stockholm, Sweden and the Institute for Molecular Medicine Finland, Helsinki, Finland, as described elsewhere [11].

2.3. Statistics

Statistics were performed on R Studio (R-4.1.1) using Fisher's exact and Mann-Whitney *U* tests. *P* values <0.05 were considered significant.

3. Results

3.1. Patients/cohort

Study subjects carried five distinct heterozygous *NFKB1* variants in six different families: c.2041C > T;p.(Gln681*), c.469C > T;p.Arg157*, c.778_779insCTGTC;p.(Gly261Valfs*5), c.1659C > G;p.Ile553Met and c.200A > G;p.His67Arg (see Supplementary figs. 1–5). The pathogenicity for the previously reported variants p.Ile553Met, His67Arg and Arg157* has been shown in in vitro experiments [11,12]. Two heterozygous variants (c.2041C > T;p.(Gln681)* and c.778_779insCTGTC;p.(Gly261Val fs*5)) were validated functionally elsewhere (*manuscript submitted*). For more detailed information on classification of the variants, see Supplementary Table 1. Variant annotations refer to RefSeq transcript NM_003998.4.

Of the studied 31 *NFKB1* variant carriers, 16 (52%) were women and 15 (48%) men, with mean age of 52 (median 55, range 13–90) years. Altogether 12 (39%) were considered clinically healthy/asymptomatic, 19 affected, resulting in clinical penetrance of 61% (Fig. 1a). The median age of asymptomatic individuals was 63 range 13–90) years and for the affected patients 48 (range 31–73) years. No significant age difference was noted between these groups ($p = 0.9838$; Mann-Whitney *U* test). Median age at the onset of first symptoms (recurrent or prolonged infections, autoinflammation, complex aphthae) was 25 (range 0.5–56) years. Median follow-up time was 23 (range 1–90) years. Follow-up of asymptomatic individuals was significantly higher: 63(range 13–90 years) years compared to that in affected 18 (range 1–62) years ($p < 0.01$; Mann-Whitney *U* test). Hence, in our cohort, the clinical penetrance of NFκB1 deficiency was incomplete, did not reach 100% with increasing age and was not explained by age differences between the healthy and affected.

3.2. Clinical and laboratory findings

Clinical symptoms of the affected individuals are listed in Supplementary table 2 and described in more detail in the Supplementary text and supplementary figs. 6–17. We further analyzed potential differences between affected and unaffected study subjects. Data included blood counts with absolute WBC counts, plasma/serum immunoglobulin levels and vaccine responses. However, not all subjects and/or physicians accepted further testing when the carrier was asymptomatic. We had access to at least one blood count with absolute WBC count in 28/31 subjects/carriers. Immunoglobulin levels and vaccine responses were assessed in 28/31 and 21/31 individuals, respectively.

Altogether 12 variant carriers (39% of the total cohort) displayed abnormalities in total leukocytes, neutrophils and/or lymphocytes, three of whom were asymptomatic. Permanent or fluctuating blood count changes did not seem to associate with the clinical phenotype (Supplementary table 2). Of note, only two individuals (11%) presented with permanent or prolonged cytopenia requiring treatment.

Altogether 22 variant carriers (71% of the total cohort) displayed decreases in at least one of the immunoglobulin classes and 14 of them were defined as affected. Furthermore, hypogammaglobulinemia in terms of low total IgG level was observed in 15 individuals (48%), five of

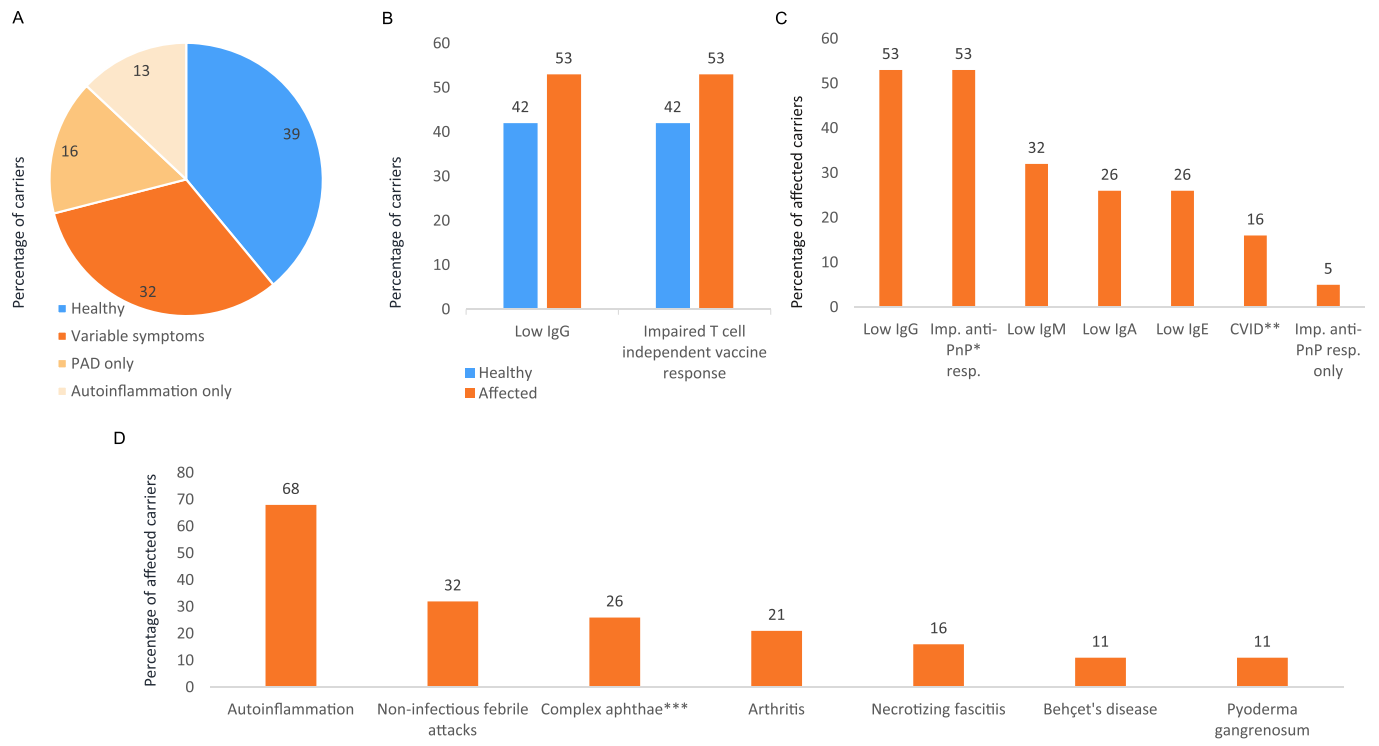

Fig. 1. Phenotypic features among Finnish *NFKB1* variant carriers.
A) Distribution of asymptomatic carriers (blue) or affected (different shades of orange) subjects displaying individuals presenting with only primary antibody deficiency (PAD) or autoinflammatory symptoms.
B) Prevalence of PAD and impaired T cell independent vaccine responses among the asymptomatic (blue) and affected (orange).
C) Prevalence of primary antibody deficiencies among the affected variant carriers.
D) Prevalence of various autoinflammatory manifestations among the affected carriers.
*anti-PnP, anti-pneumococcal polysaccharide **CVID: Common Variable Immunodeficiency; *** including two subjects diagnosed with Behçet's disease; proportions/prevalence displayed as percentages.
Autoinflammation comprises otherwise unexplained sudden, recurring febrile attacks, complex aphthae, Behçet's disease, inappropriate inflammatory reactions including PG and/or NF in response to tissue injury and (mono)arthritis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

whom (14%) were asymptomatic and considered clinically healthy (Fig. 1b). Hypogammaglobulinemia in other Ig classes was variable in the affected (Fig. 1c; Supplementary table 2). CVID (impaired anti-PnP responses with low IgG together with decreased IgA and/or IgM), was present in only three affected individuals (16%) (Fig. 1c; Supplementary table 2).

Impaired responses to anti-PnP were detected in 10 affected individuals (53%), one of whom displayed no infection susceptibility (5%; Supplementary table 2). Interestingly, impaired anti-PnP responses were detected also in five completely asymptomatic subjects (42% of the unaffected group; Fig. 1b). Of note, two fully asymptomatic individuals even presented with decreased IgG (and IgA) plus impaired responses to pneumococcal antigens [20]. No statistical differences in the prevalence of IgG hypogammaglobulinemia or impaired anti-PnP responses between the asymptomatic and affected ($p = 0.716$ for both cases, Fisher's Exact test) were noted. No tested carriers displayed long-term impairment of antibody responses to tetanus or diphtheria.

Twelve individuals (63% of the affected) suffered from both upper and lower recurrent respiratory tract infections, some with other pyogenic infections as well (Supplementary table 2). More than one episode of pneumonia was noted in four affected individuals (21%). One individual (F3:II:1; Fig.S3) required intensive care for severe necrotizing pneumonia of unknown etiology without previous abnormal susceptibility to pyogenic infections or hypogammaglobulinemia. No opportunistic infections to suggest T cell deficiency were observed in our patients. Variable gastrointestinal symptoms were observed in ten affected individuals (53%; Supplementary table 2).

Autoimmune manifestations were observed in nine affected individuals (47%). Autoinflammatory manifestations were present in 13 individuals (42% of the total cohort; 68% of the affected). Clinical severity ranged from complex aphthous stomatitis, often accompanied by fever and abdominal pain, to life threatening sterile necrotizing fasciitis incited by tissue injury, requiring aggressive and often repeated surgical revisions (Fig. 1d; Supplementary table 2). Immune dysregulation including autoimmunity and autoinflammatory disorders were present in 18 affected individuals (95%; Supplementary table 2).

4. Discussion

Here, we report the clinical features associated with all identified and consenting Finnish individuals with pathogenic variants in *NFKB1*. Clinical penetrance of *NFKB1* variants has previously been reported to range between 50 and 100% [11,14,15,17] and the penetrance in our cohort (61%) is in line with this. However, the most common clinical feature in our cohort was autoinflammation presenting with various manifestations and with significantly higher prevalence than previously reported. In the large international patient cohort by Lorenzini et al., penetrance was age-dependent, eventually reaching full 100% in individuals ≥60 years. Interestingly, in our cohort, the penetrance didn't reach 100% even with aging. Of note, one asymptomatic carrier has deceased at the age of 92 with no evident signs of immunodeficiency or immune dysregulation. Our cohort included altogether seven living, asymptomatic subjects aged 62–90 years. Thus, our data suggests incomplete clinical penetrance of *NFκB1* variants even with advancing

age.

Further comparing our observations to this large international patient (not screening) focused cohort reported by Lorenzini et al. [14], the prevalence of autoinflammatory manifestations among the affected was significantly higher (68% vs. 29.6%; $p < 0.01$, Fisher's Exact test). The prevalence of cytopenia ($p < 0.01$) and lymphoproliferation ($p < 0.001$) appeared also lower in our partly overlapping series. In the larger patient cohort, the prevalence of hypogammaglobulinemia in terms of low IgG and a marked decrease in IgA or IgM among affected carriers was 88.9% while only four affected individuals in our genetically screened family cohort met these criteria for hypogammaglobulinemia (21%; $p < 0.0001$). Also, the prevalence of low IgG in our family cohort (53% in the affected) was significantly lower ($p < 0.001$) than in Lorenzini et al. and in another report by Fliegauf et al. ($p < 0.01$) who screened three unrelated families with three distinct *NFKB1* variants associated with CVID/hypogammaglobulinemia. [15].

This significantly lower prevalence of CVID/hypogammaglobulinemia – so far, the most reported clinical feature associated with *NFKB1* variants – likely reflects different inclusion criteria. Interestingly, in Fliegauf et al., phenocopies not harboring variants in *NFKB1* yet with hypogammaglobulinemia were reported [15] and suggests that potential other genetic, epigenetic, or environmental factors may play a role in the development of CVID. Thus, we hypothesize that previous studies might have been influenced by sampling error by focusing on detecting *NFKB1* variants in patients with hypogammaglobulinemia and/or CVID. Likely NFKB1 deficiency has not been actively searched in patients with mainly autoimmune or autoinflammatory manifestations, often treated by other specialties than Clinical Immunology. We cannot however rule out unknown confounding factors in our comparisons above since these were based on different studies.

Impaired response to vaccine in terms of T cell independent antigens was comparable to the international cohort [14] and might reflect frequent subclinical defects in B cell function in carriers of pathogenic variants. Interestingly, impaired responses to pneumococcal antigens were observed both in affected and asymptomatic subjects in nearly equal levels, as reported in previous reports on primary antibody deficiencies [20]. Low numbers of switched memory B cells have been reported in individuals carrying *NFKB1* variants [10,13,14,17] and were detected also in our cohort [11]. However, we were not able to ethically assess B cell differentials systematically due to highly lacking data in asymptomatic carriers.

Further limitations of our family study include its relatively small size when compared to larger patient cohorts [14]. However, our sample size was sufficient to detect differences between an approach to actively screen affected families versus mostly “patient only testing” due to suspected antibody deficiency. Importantly, functional characterization of *NFKB1* variants in these individuals have confirmed their pathogenicity [11,12]. Our observed clinical penetrance was well in line with most previous reports; however, our family screening approach suggests a remarkably high prevalence of autoinflammatory manifestations in carriers. Furthermore, incomplete penetrance, long asymptomatic periods, and lack of associations between widely available laboratory parameters and phenotypic findings make follow-up and genetic counseling challenging. While routine screening of asymptomatic carriers does not seem warranted, genetic counseling of adult family members does appear advisable. Due to the severity of certain complications like fasciitis, development of targeted therapies and prophylactic measures during invasive procedures seems highly desirable. Further studies to elucidate which of the putative (auto)inflammatory complications are indeed associated with *NFKB1* variants and respond to targeted therapy will be needed. Studies on NFKB1 deficiency to unravel potential genotype-phenotype correlations and additional screening methods to aid in assessing lifetime risk of various severe complications, for example by focusing on the molecular mechanisms behind these in affected tissues and immune cell types, seem also warranted. Whether some *NFKB1* variants act more as risk alleles rather than directly causative will require large population-based studies.

5. Conclusions

Our cohort of 31 *NFKB1* variant carriers, found mostly by active genetic screening, displayed variable clinical manifestations and frequent immune dysregulation of both innate and adaptive immune systems. A high frequency of (auto)inflammatory complications (42%) in carriers was noted. As the penetrance is incomplete – and may potentially only decrease with more active screening – we do not encourage screening of asymptomatic family members. However, first degree relatives of NFKB1 carriers should be informed of potential consequences of the variant and screened if symptoms suggesting of IEI appear. Consenting carriers could be monitored to detect illness early and to anticipate possible complications for example in case of surgical procedures.

Compliance with ethical standards

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from patients and healthy control subjects. The study protocols were approved by the Coordinating Ethics Committee of The Hospital District of Helsinki and Uusimaa (HUS/182/2021) and the Ethics Committee for Gynecology, Obstetrics, Pediatrics and Psychiatry (138/13/03/00/2013, HUS/2107/2020).

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Authors' contributions

Conceptualization: ET, MS, TH; Data curation: ET, MS, TH, OK, LS; Formal analysis: ET, MS, TH, OK, MK, JSa; Funding acquisition: ET, JSa, MV, JK, TH, MS, MS, KKE; Investigation: LS, TM, SH, HV, JS, UW-K, OK, TH, JSa, MK, KKE, MV; Methodology: ET, MS, MK, JSa, MV, KKE, TH; Project Administration: ET, MS, TH, OK, KKE, JK; Resources: MS, TH, KKE, MV, JK; Software: ET, MS; Supervision: MS, TH, JK; Validation: LS, TM, SH, HV, JS, UW-K, OK,TH, MK, JSa; Visualization: ET, MS, OK; Writing – original draft: ET, MS; Writing – review and editing: all authors

Declaration of Competing Interest

JSa has received speaker fees from Sanofi-Genzyme.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2022.109181.

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