A database for immunodeficiency due to mutations in nuclear factor kappa B pathway genes

Arnon Broides*

ABSTRACT

Nuclear factor kappa B (NFκB) pathway defects are associated with immunodeficiency; however, multiple phenotypes for mutations in genes encoding for NFκB proteins have been reported. We sought to create a database of published mutations in the genes encoding for IKKα and IKKβ and the regulatory subunit IKKγ, also referred to as NFκB essential modulator (NEMO). All published mutations were reviewed. The clinical and laboratory phenotypes were recorded and yearly updates of new mutations and phenotypes will be performed. Multiple immunodeficiency and infectious phenotypes were recorded particularly for patients with NEMO gene mutations. Even patients with the same NEMO mutation tended to have somewhat different phenotypes. In patients with primary immunodeficiency, the clinical phenotype may not direct the clinician to the genetic cause of the disease. Therefore, a comprehensive database will expand our knowledge and enhance the clinician's ability to predict which gene mutation is the cause of the immunodeficiency. This database can assist clinicians in the diagnoses of patients with specific features of immunodeficiency.

Statement of novelty: A comprehensive database of published mutations in the genes encoding for IKKα, IKKβ, and IKKγ was created. This database may aid the clinician in recognizing specific immunodeficiency phenotypes.

Introduction

The nuclear factor kappa B (NFκB) family of transcription factors is essential for a variety of biological functions including response to stress, infection, and inflammation. The NFκB is normally found in the cytoplasm due to the effects of the inhibitor of NFκB, (IκB). Upon canonical stimulation of the NFκB pathway, the IκB components are phosphorylated by the IκB kinase (IKK) which is composed of 2 catalytic subunits (IKKα and IKKβ) and a regulatory subunit (IKKγ, also referred to as NEMO, NFκB essential modulator, IKBKG), leading to the degradation of the IκB which allows for translocation of the NFκB into the nucleus and transcription of pro-inflammatory genes (Gilmore 2006).

As expected, mutations within this pathway have a deleterious effect on susceptibility to malignancies, development, and the immune system. Mutations in genes encoding for NEMO, IκKα, and IKKβ cause a wide variety of immunodeficiency phenotypes. The NEMO gene is found at the Xq28 region, males born with hypomorphic mutations in the NEMO gene usually suffer from combined immunodeficiency with or without ectodermal dysplasia. Null mutations in males are lethal in utero and female carriers of mutations in the NEMO gene have a typical skin condition with streaks of hyperpigmentation known as incontinenta pigmenti. Diseases from mutations in IκKα and IKKβ are inherited in an autosomal recessive manner (Courtois and Gilmore 2006). We have created a database (Tables 1–3) of published mutations in NEMO,

Pediatric Immunology Clinic, Soroka University Medical Center, Beer Sheva, Israel

Submitted 23 August 2016
Accepted 10 November 2016
Available online 14 November 2016

*Corresponding author: Arnon Broides/broides@bgu.ac.il

LymphoSign Journal 3:165–178 (2016)
[dx.doi.org/10.14785/lymphosign-2016-0009](https://doi.org/10.14785/lymphosign-2016-0009)

Table 1: NFκB essential modulator (NEMO).

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
Splice site defect at bp 4257, +1 of exon1B splice site	—	T+B+ Antibody deficiency Dysgammaglobulinemia	Normal proliferation to PHA, pokeweed mitogen, anti-CD3; low proliferation to tetanus; impaired cytokine production after TLR activation	Normal or low IgM, normal IgG and elevated IgA; waning antibodies to <i>Streptococcus Pneumoniae</i> ; no response to Hepatitis B, mumps, and measles vaccines	Otitis, adenitis, bronchitis/ bronchopneumonia, bronchiectasis, recurrent diarrhea	Mooster et al. 2010
110-111insC	ΔNterm37	T+B+NK+ (with progressive decline of T cells with age) Combined immunodeficiency	Normal to borderline proliferation to PHA, pokeweed mitogen; low response to OKT3. Very low IFN-γ production	Elevated IgM, low IgG, absent IgA, IgE; no antibodies to tetanus toxoid, Diphtheria toxoid, Pneumococcus, <i>Haemophilus influenzae</i> B	<i>Mycobacterium avium</i> lymphadenitis, Bronchiectasis (<i>Hemophilus Influenzae</i> and <i>Streptococcus pneumoniae</i> in sputum), <i>Mycobacterium Avium</i> osteomyelitis, lethal herpes encephalitis. <i>Salmonella enteritidis</i> bacteremia and enteritis, no ectodermal dysplasia	Niehues et al. 2004 ; Puel et al. 2006 ; Hanson et al. 2008
239T>C	80L>P	T+B+NK+Combined immunodeficiency	Low proliferation to PHA poor IL-6 production from fibroblasts after TNF-α and IL1-β stimulation	Low IgM, normal IgA and IgG; no antibodies to Pneumococcus	Recurrent pneumococcal infections, pneumonia, episodes of orbital cellulitis (<i>Staphylococcus aureus</i> and candida), hypodontia, conical incisor teeth, no ectodermal dysplasia	Ku et al. 2005 ; Hanson et al. 2008
337G>A	113D>N	T+B+NK+Decreased T-cell function, low NK-cell activity	Normal to slightly low proliferation to PHA, ConA, pokeweed mitogen; TCR-induced NFκB activation diminished; low NK cytolytic activity	Normal IgM and IgG, absent IgA; normal antibodies to <i>Hemophilis influenzae</i> B, Pneumococcus	<i>Pneumocystis jiroveci</i> pneumonia, CMV viremia, no ectodermal dysplasia	Hanson et al. 2008 ; Salt et al. 2008
6IVs6 + 5G>A (1027 + 5G>A)	Δ134-256	T+ B+ Hypogammaglobulinemia	Impaired IκB-α degradation after TNF-α stimulation	Hypogammaglobulinemia (or hypergammaglobulinemia); hyper IgA, no antibodies to <i>Streptococcus pneumoniae</i>	Ectodermal dysplasia, inflammatory bowel disease, pyogenic and mycobacterial infections, Small for gestational age, failure to thrive, hypodontia, conical incisor teeth, immune dysregulation (multiple patients with varied phenotype)	Orstavik et al. 2006 ; Hanson et al. 2008

(continued)

Table 1: (Continued)

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
437T>G	146V>G	T+B+NK+ Hypogammaglobulinemia	—	Absent IgG and IgM, elevated IgA	<i>Staphylococcus aureus</i> subdural empyema, ectodermal dysplasia, conical incisor tooth, failure to thrive, eosinophilia	Devora et al. 2010
458T>G	153L>R	T+Hypogammaglobulinemia	Normal proliferation to PHA, pokeweed mitogen; reduced proliferation to ConA; reduced response to tetanus and diphtheria; low NK activity; normal antibody directed cell cytotoxicity	Hypogamma- globulinemia; low IgM, elevated IgA	Ectodermal dysplasia, CMV colitis, <i>Listeria</i> <i>monocytogenes</i> sepsis, <i>Streptococcus bovis</i> meningitis	Orange et al. 2002, 2004a; Brodeur et al. 2003; Deering and Orange 2006; Ku et al. 2007; Hanson et al. 2008; Salt et al. 2008
518C>G	173R>G	T+B+Antibody deficiency (Dysgammaglobulinemia)	Reduced IL-10 production after TNF- α stimulation; slightly reduced IL-6 production after LPS and IL-1 β stimulation	Normal immunoglobulins; specific antibody defects (<i>Streptococcus pneumoniae</i> , tetanus, <i>Hemophilis influenza</i> B, pertussis toxoid)	Ectodermal dysplasia, Immune dysregulation, <i>Streptococcus pneumoniae</i> cellulitis	Ku et al. 2007; Hanson et al. 2008
524G>C	175R>P	T+B+Dysgammaglobulinemia	Normal responses	Normal IgM, low IgG2, elevated IgG4, IgA; specific antibody defects (<i>Streptococcus pneumoniae</i>)	Ectodermal dysplasia, Immune dysregulation, <i>Streptococcus pneumoniae</i> meningitis	Abinun et al. 1996; Doffinger et al. 2001; Carrol et al. 2003; Hanson et al. 2008
Non-specified	217R>G	T+B+Dysgamma- globulinemia	—	Normal to elevated IgG, IgM, IgA	Ectodermal dysplasia, recurrent pneumonia, recurrent otitis/sinusitis	Lee et al. 2005; Hanson et al. 2008
Exon 4-5 dup	K224fsX9	T+ (low CD4)Combined immunodeficiency	Low proliferation to PHA, ConA; normal response to PMA-ionomycin; low response to LPS stimulation	Low PHA, ConA; normal PMA-ionomycin; low response to LPS stimulation	Ectodermal dysplasia, transient lymphedema, diarrhea, delayed teeth, pneumonia, <i>Staphylococcus aureus</i> cellulitis, <i>Pseudomonas</i> <i>aeruginosa</i> sinusitis/otitis, diarrhea	Nishikomori et al. 2004; Hanson et al. 2008
667_669del	Δ E223	T+B+NK+ Dysgammaglobulinemia	Normal responses to mitogens and antigens; low NK activity; Impaired TLR signaling to agonists	Normal IgG, low IgM and elevated IgG; Partial antibodies to <i>Streptococcus pneumoniae</i> , low tetanus and diphtheria antibodies	Ectodermal dysplasia, recurrent sinopulmonary infections, 2 pneumonias	Karamchandani-Patel et al. 2011

(continued)

Table 1: (Continued)

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
667G>A	223E>K	T+B+NK+ Dysgammaglobulinemia	Low NK activity; impaired TLR signaling to agonists	Low IgM, normal IgG and IgA; tetanus toxoid and diphtheria antibodies low to normal	Ectodermal dysplasia, necrotizing MRSA soft tissue infection, brain abscess, <i>Streptococcus anginosus</i> bacteremia, conical teeth	Karamchandani-Patel et al. 2011
680T>C	227L>P	Hypogammaglobulinemia	Low NK activity	Normal to low immunoglobulins; no antibodies to <i>Streptococcus pneumoniae</i>	Ectodermal dysplasia, inflammatory bowel disease, immune dysregulation, pyogenic infections (multiple patients with varied phenotype)	Schweizer et al. 1999 ; Doffinger et al. 2001 ; von Bernuth et al. 2005 ; Hanson et al. 2008
769-1G>C	IVS6	T+B+NK+ (low B cells) Dysgammaglobulinemia	Low NK activity; impaired TNF- α production after LPS stimulation	Normal immunoglobulins, impaired antibody production to measles and <i>Streptococcus pneumoniae</i> , normal antibodies to CMV/EBV, measles, varicella	Recurrent <i>Streptococcus pneumoniae</i> meningitis, septic arthritis, cellulitis, measles, osteomyelitis, hypodontia, conical teeth	Karakawa et al. 2011
760C>G	254R>G	T+ (low CD4) T cell deficiency	Normal delayed type hypersensitivity and antibody directed cell cytotoxicity, low NK activity	Normal to elevated immunoglobulins	<i>Mycobacterium avium</i> intracellulare infections of skin, muscle and lungs, HPV	Haverkamp et al. 2004 ; Hanson et al. 2008
1049dupA	Fs264-284X	T+ B+ (low CD8, low naïve T cells) Combined immunodeficiency	Low anti-CD3 and CD40L stimulation	Elevated IgM, low IgG, normal IgA	Incontinentia pigmenti, pneumonia (RSV, <i>Streptococcus pneumoniae</i> , <i>Candida albicans</i> sepsis/ bacteremia, <i>Aspergillus fumigatus</i> osteomyelitis, EBV infection	Martinez-Pomar et al. 2005 ; Hanson et al. 2008
811_828del	Δ 271-276	T+B+NK+ Dysgammaglobulinemia	Normal proliferation to PHA and PMA/ionomycin; reduced TNF- α and IL-1 stimulation	Elevated IgA, normal IgG and IgM; no antibodies to <i>Pneumococcus</i>	Recurrent pneumococcal infections, pneumonia, hypodontia, conical incisor teeth	Ku et al. 2005
863C>G	288A>G	Combined immunodeficiency	Normal PHA, normal PMA/I; reduced TNF- α and LPS stimulation, reduced NF κ B activation	—	Ectodermal dysplasia, immune dysregulation, <i>Streptococcus pneumoniae</i> infection	Doffinger et al. 2001 ; Vinolo et al. 2006 ; Hanson et al. 2008
931G>A	311D>N	—	Impaired IL12p40 production from EBV transformed B cells after PMA stimulation	—	Ectodermal dysplasia, immune dysregulation, <i>Streptococcus pneumoniae</i> infection, <i>Mycobacterium avium</i> infections	Doffinger et al. 2001 ; Hanson et al. 2008

(continued)

Table 1: (Continued)

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
932A>G	311D>G	T+B+	Normal T-cell proliferation to PHA and antigens; reduced NFκB activity, IκB-α degradation, impaired IL-6 and IL-8 production from fibroblasts after TNF-α and IL-1β stimulation; impaired IL12p40 production from EBV transformed B cells after PMA stimulation	Normal IgM and IgG, elevated IgA; normal anti-A antibody, low anti-B antibody	<i>Streptococcus pneumoniae</i> pneumonia and otitis. <i>Mycobacterium avium</i> adenitis and later <i>Mycobacterium abscessus</i> , absent adult maxillary lateral incisors and right premolar	Hubeau et al. 2011
932A>G	311D>E	T+B+NK+	Normal proliferation to PHA, ConA; slightly reduced NK activity; impaired PBMC release of IFN-γ after IL-12 stimulation and TNF-α after LPS stimulation	Low IgM, normal IgG, elevated IgA; no antibodies to measles, positive for rubella.	Disseminated <i>Bacillus Calmette-Guérin</i> , generalized lymphadenopathy, parotitis, <i>Streptococcus pneumoniae</i> sepsis	Imamura et al. 2011
944A>C	315E>A	T+ B+	Normal proliferation to PHA; reduced interferon γ production in response to PMA/ionomycin; normal response to LPS	Normal immunoglobulins or elevated IgG	<i>Ectodermal dysplasia</i> , <i>Mycobacteria avium</i> intracellular infections, diarrhea, hypodontia, conical incisor teeth, failure to thrive (multiple patients with varied phenotype)	Holland et al. 1994 ; Haverkamp et al. 2004 ; Filipe-Santos et al. 2006 ; von Bernuth et al. 2006 ; Hanson et al. 2008
956G>A	319R>Q	T+ B+	Reduced response to CD40L stimulation; normal TLR and IL-1 stimulation; normal to reduced response to TNF-α stimulation	Normal to elevated IgG, IgM; normal IgA	<i>Mycobacteria avium</i> intracellular cellulitis/ abscess, <i>Haemophilus influenzae</i> cellulitis/ abscess, diarrhea, Pulmonary tuberculosis	Filipe-Santos et al. 2006 ; von Bernuth et al. 2006 ; Hanson et al. 2008
991del9	E3331del3	T+ (low CD4)T-cell deficiency	—	Elevated IgG; IgM not elevated	Recurrent <i>Streptococcus pneumoniae</i> infections, warts, <i>Mycobacteria avium</i> intracellular infections	Haverkamp et al. 2004 ; Hanson et al. 2008
1056G>A	Δ353-373	T+B+ Dysgammaglobulinemia	Reduced NK activity; reduced response to IL-1 and TLR stimulation	Normal IgG and IgM, elevated IgA; no antibodies to tetanus toxoid, <i>Haemophilus influenzae B</i>	Recurrent pneumonia, <i>Haemophilis influenzae</i> bacteremia/sepsis, <i>Mycobacterium bovis</i> infections	Dai et al. 2004 ; Orange et al. 2004a, 2004b ; Hanson et al. 2008

(continued)

Table 1: (Continued)

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
1161insC	P389fsX4	Hypogammaglobulinemia	Reduced NFκB activation	Low IgG, elevated IgE	Ectodermal dysplasia, hypodontia, conical incisor teeth, abdominal pain, failure to thrive, pneumonia, bronchiectasis, cellulitis, <i>Mycobacteria avium</i> intracellular infections	Aradhya et al. 2001 ; Kosaki et al. 2001 ; Hanson et al. 2008
1167insC	E390fsX5	T+B+T-cell deficiency	Normal proliferation to mitogens; no proliferation to anti-CD3, tetanus toxoid, diphtheria; low NK activity; reduced response to LPS	Elevated to low IgM, normal or low IgG, low IgA	Ectodermal dysplasia, osteopetrosis, hypodontia, conical incisor teeth, immune dysregulation, failure to thrive, diarrhea, <i>Pneumocystis jiroveci</i> pneumonia, <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> infections, <i>Mycobacterial avium</i> intracellular infections, CMV infection	Hanson et al. 2008 ; Mancini et al. 2008
1171G>T	391E>X	T+B+ Dysgammaglobulinemia	Normal proliferation to mitogens	Normal IgM, elevated IgG IgA; no antibodies to <i>Streptococcus pneumoniae</i>	Ectodermal dysplasia, conical teeth, inflammatory bowel disease, immune dysregulation, recurrent pneumonia, cellulitis, <i>Streptococcus Pneumoniae</i> infections (meningitis, pneumonia), giardiasis (multiple patients with varied phenotype)	Zonana et al. 2000 ; Hanson et al. 2008
1426insC	S387fsX8	T+B+Hypogammaglobulinemia	Normal proliferation to mitogens and to tetanus, candida, diphtheria	Normal IgM, low IgG IgM	Ectodermal dysplasia, diarrhea, failure to thrive, meningitis/encephalitis, recurrent pneumonia and sinusitis, diarrhea, <i>Molluscum contagiosum</i> virus	Lee et al. 2005 ; Hanson et al. 2008

(continued)

Table 1: (Continued)

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
1182_1183delTT	420X>W	Hypogammaglobulinemia	—	Elevated IgM, low IgG, normal IgA	Ectodermal dysplasia, osteopetrosis, lymphedema, <i>Enterobacter cloacae</i> sepsis, pustulosis, Group A streptococcus septic arthritis, Salmonella and adenovirus gastroenteritis, multiple skin abscesses, <i>Molluscum contagiosum</i> , otitis media (multiple patients)	Roberts et al. 2010
1207C>T	403Q>X	T+B+ (low CD4 later in life) Combined immunodeficiency	Normal proliferation to PHA, pokeweed mitogen, low ConA; reduced proliferation to antigens; low NK activity, normal ADCC, reduced response to CD40L stimulation	Low IgM and IgG, elevated IgA	Ectodermal dysplasia, immune dysregulation, <i>Streptococcus pneumoniae</i> , <i>Pseudomonas aeruginosa</i> meningitis/encephalitis and osteomyelitis. Herpes simplex virus oral infection, Pneumonia, <i>Mycobacterium avium</i> intracellular infection of blood, bone marrow and skin	Orange et al. 2002, 2004a ; Dai et al. 2004 ; Hanson et al. 2008
1217A>T	406D>V	T+B+Combined immunodeficiency	Low proliferation to CD3; normal response to TNF- α and LPS stimulation; reduced CD40L stimulation, reduced IFN- γ production	Normal IgM, low IgG and IgA	Ectodermal dysplasia, <i>Streptococcus pneumoniae</i> infections, sinusitis/otitis	Jain et al. 2001 ; Hanson et al. 2008
1218insA	D406fsX12	T+B+Combined immunodeficiency	—	—	Ectodermal dysplasia, immune dysregulation, <i>Streptococcus pneumoniae</i> infections	Doffinger et al. 2001 ; Hanson et al. 2008
1235insC	I412fsX6	—	—	Low IgG, IgM and IgA; no tetanus antibodies	Ectodermal dysplasia, <i>Mycobacterium avium</i> intracellular infection	Orange et al. 2005 ; Hanson et al. 2008

(continued)

Table 1: (Continued)

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
1249T>C	417C>R	T+B+Dysgamma-globulinemia	Normal proliferation to PHA, normal anti-CD3; no proliferation to tetanus toxoid and diphtheria; low NK activity; reduced DTH and IFN-γ production; normal antibody directed cell cytotoxicity	Normal or elevated IgM, low IgG, low or elevated IgA; no tetanus antibodies after immunization	Ectodermal dysplasia, hypodontia, conical incisor teeth, immune dysregulation, pneumonia, bronchiectasis, osteomyelitis, cellulitis/abscess, sinusitis/otitis, <i>Molluscum contagiosum</i> , <i>Staphylococcus aureus</i> adenitis, <i>Klebsiella</i> pneumonia bacteremia/sepsis, <i>Mycobacterium abscessus</i> osteomyelitis (multiple patients with varied phenotype)	Zonana et al. 2000 ; Doffinger et al. 2001 ; Jain et al. 2001 ; Hanson et al. 2008
1250G>T	417C>F	Hypogamma-globulinemia	—	Elevated IgM and IgA, low IgG; no antibodies to <i>Streptococcus pneumoniae</i> after immunization	Ectodermal dysplasia, conical incisors, hypodontia, immune dysregulation, <i>Streptococcus pneumoniae</i> infections, recurrent viral and <i>Streptococcus Pneumoniae</i> meningitis, bronchiectasis	Zonana et al. 2000 ; Doffinger et al. 2001 ; Hanson et al. 2008
1250G>A	417C>Y	Hypogamma-globulinemia	Normal proliferation to mitogens and tetanus toxoid; low NK activity; normal DTH; low NFκB activation and CD40L stimulation	Normal IgM, low IgG and IgA	Ectodermal dysplasia, conical incisors, <i>Streptococcus pneumoniae</i> meningitis (multiple patients with varied phenotype)	Brodeur et al. 2003 ; Orange et al. 2004a ; Hanson et al. 2008
1259A>G	X420WroX447	T+B+Hypogamma-globulinemia	Normal proliferation to antigens; low IFN-γ production; low response to TNF-α, IL-1, LPS, CD40L stimulation and NFκB activation	Low IgM, IgG and IgA or normal IgM and IgA with low IgG; low <i>Streptococcus pneumoniae</i> antibodies after immunization	Ectodermal dysplasia, osteopetrosis, lymphedema, immune dysregulation, delayed eruption of teeth, vancomycin resistant <i>enterococci</i> , <i>Staphylococcus aureus</i> cellulitis/abscess, atypical mycobacteria osteomyelitis, adenovirus infection, oral herpes simplex virus (multiple patients with varied phenotype)	Doffinger et al. 2001 ; Mansour et al. 2001 ; Dupuis-Girod et al. 2002 ; von Bernuth et al. 2005 ; Hanson et al. 2008

Table 2: IκB kinase α (IKKα).

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
25C>T	9Q>X	T+B+	Low to normal proliferation to PHA ConA; reduced TNF-α production after LPS stimulation in CD14 positive cells	High IgA, normal IgM and IgG	Ectodermal dysplasia, <i>Cytomegalovirus</i> , <i>Rotavirus</i> , pneumonia, otitis media	Ohnishi et al. 2012
110T>A	37M>K	T+B+ Hypogamma-globulinemia	Normal proliferation to PHA, ConA, pokeweed mitogen and antigens; reduced proliferation to CD3; reduced IL-6 production in whole blood after IL-1β, TLR2/6 agonist; reduced responses to LPS and PMA/Ionomycin; absent IL-10 production following TNF-α stimulation	High IgM, absent IgG and IgA; no specific antibodies to diphtheria, tetanus, <i>Haemophilus influenzae</i> B, <i>Streptococcus pneumoniae</i>	Hyper IgM syndrome/SCID; polyendocrinopathy (autoimmune thyroiditis, hypothalamic hypopituitarism), ectodermal dysplasia, chronic mucocutaneous candidiasis, chronic diarrhea, failure to thrive	Schimke et al. 2013
40G>T	14E>X	T+B+NK–	Normal proliferation to PHA, ConA, pokeweed mitogen; low IFN-γ production after anti-CD3 stimulation (restored by addition of IL-12)	Normal immunoglobulins	<i>Pneumocystis jiroveci</i> pneumonia, oral candidiasis, failure to thrive, recurrent pyogenic bacterial infections, anhidrosis	Lopez-Granados et al. 2008
32G>A	11W>X	T+B+NK+	Normal proliferation to PHA, anti-CD3, anti-CD3+anti-CD28, PMA, tetanus and diphtheria; reduced TNF-α production after stimulation with TLR3, TLR4, TLR5, TLR9 agonists; normal TNF-α production after TLR7 agonist; reduced IFN-α production after TLR3 and TLR9 agonists	Normal immunoglobulins; normal antibodies to tetanus toxoid; no specific antibodies to <i>Pneumococcus</i>	Recurrent pneumonia with bronchiectasis, no episodes of bacteremia	McDonald et al. 2007
94G>T	32S>I	T+B+ NK+ Combined immunodeficiency	Low to normal proliferation to PHA; low proliferation to anti-CD3, OKT3; normal proliferation to PHA+IL-2, OKT3+IL-2; no proliferation to tetanus toxoid and candida; reduced IL12p40 production in monocytes after LPS stimulation; reduced IL-6 production from whole blood after LPS stimulation; normal TNF-α and IL-1β production after LPS stimulation; normal NK activity	High IgM, absent IgG and IgA; no specific antibodies after immunizations	<i>Pneumocystis jiroveci</i> pneumonia, <i>Streptococcus</i> A meningitis, neurodevelopmental regression, ectodermal dysplasia, periodic diarrhea, candidiasis, failure to thrive, bronchopneumonitis, hepatosplenomegaly	Courtois et al. 2003 ; Janssen et al. 2004

Table 3: IκB kinase β (IKKβ).

Nucleotide	Amino acid	Deficiency	Cellular immune function	Serum immunoglobulin levels	Presenting features	References
—	286R>X	T+B+NK+/- (normal to low B cells, normal to low NK cells) Combined immunodeficiency	Normal proliferation to PHA; low proliferation to pokeweed mitogen, ConA; no proliferation to tetanus toxoid, candida or anti-CD3; low Tregs; reduced NK activity	Low to absent immunoglobulins	Candida/ <i>Bacillus Calmette-Guérin</i> and (or) viral and gram negative bacterial infections	Mousallem et al. 2014
814C>T	272R>X	T+B+NK+ (with absent isotype switched memory B cells) Combined immunodeficiency	No proliferation to anti-CD3/CD28, corrected with addition of IL-2; partial proliferation to PHA	Elevated IgM, undetectable IgG and IgA	Hyper IgM syndrome, <i>Pneumocystis jiroveci</i> pneumonia, fatal <i>Mycobacterium bovis</i> infection	Nielsen et al. 2014
321C>A	107Y>X	T+B+NK+ Hypogammaglobulinemia	Normal proliferation to PHA; reduced to absent production of IFN-γ, TNF-α, IL-17A, IL-6 and IL-12 after multiple stimuli	Elevated IgM, low IgG, IgA	<i>Salmonella</i> sepsis, recurrent bacterial infections, rash, conical incisor teeth, skin and gut BCG-osis, hepatosplenomegaly	Burns et al. 2014
1292dupG	Q432fsX	T+B+NK+/- (normal to low B cells, normal to absent NK cells) Severe combined immunodeficiency	Normal to low proliferation to PHA, pokeweed mitogen, ConA; no response to anti-CD3; reduced IL-6 production by fibroblasts after stimulation with LPS or flagellin	Low to absent immunoglobulins	Failure to thrive, oral thrush, recurrent viral and bacterial infections	Pannicke et al. 2013

IκKα, and IKKβ and we show a wide clinical spectrum of immunodeficiency and infectious phenotypes. This database can aid the clinician in recognizing specific immunodeficiency phenotypes and promote the diagnosis of NFκB pathway defects.

REFERENCES

- Abinun, M., Spickett, G., Appleton, A.L., Flood, T., and Cant, A.J. 1996. Anhidrotic ectodermal dysplasia associated with specific antibody deficiency. *Eur. J. Pediatr.* **155**(2):146–147. PMID: [8775234](#). doi: [10.1007/BF02075774](#).
- Aradhya, S., Bardaro, T., Galgoczy, P., Yamagata, T., Esposito, T., Patlan, H., Ciccodicola, A., Munnich, A., Kenwrick, S., Platzer, M., D'Urso, M., and Nelson, D.L. 2001. Multiple pathogenic and benign genomic rearrangements occur at a 35 kb duplication involving the NEMO and LAGE2 genes. *Hum. Mol. Genet.* **10**(22):2557–2567. PMID: [11709543](#). doi: [10.1093/hmg/10.22.2557](#).
- Brodeur, S.R., Angelini, F., Bacharier, L.B., Blom, A.M., Mizoguchi, E., Fujiwara, H., Plebani, A., Notarangelo, L.D., Dahlback, B., Tsitsikov, E., and Geha, R.S. 2003. C4b-binding protein (C4BP) activates B cells through the CD40 receptor. *Immunity.* **18**(6):837–848. PMID: [12818164](#). doi: [10.1016/S1074-7613\(03\)00149-3](#).
- Burns, S.O., Plagnol, V., Gutierrez, B.M., Al Zahrani, D., Curtis, J., Gaspar, M., Hassan, A., Jones, A.M., Malone, M., Rampling, D., McLatchie, A., Doffinger, R., Gilmour, K.C., Henriquez, F., Thrasher, A.J., Gaspar, H.B., and Nejentsev, S. 2014. Immunodeficiency and disseminated mycobacterial infection associated with homozygous nonsense mutation of IKKβ. *J. Allergy Clin. Immunol.* **134**(1):215–218. PMID: [24679846](#). doi: [10.1016/j.jaci.2013.12.1093](#).
- Carrol, E.D., Gennery, A.R., Flood, T.J., Spickett, G.P., and Abinun, M. 2003. Anhidrotic ectodermal dysplasia and immunodeficiency: The role of NEMO. *Arch. Dis. Child.* **88**(4):340–341. PMID: [12651765](#).
- Courtois, G., and Gilmore, T.D. 2006. Mutations in the NF-kappaB signaling pathway: Implications for human disease. *Oncogene.* **25**(51):6831–6843. PMID: [17072331](#). doi: [10.1038/sj.onc.1209939](#).
- Courtois, G., Smahi, A., Reichenbach, J., Doffinger, R., Cancrini, C., Bonnet, M., Puel, A., Chable-Bessia, C., Yamaoka, S., Feinberg, J., Dupuis-Girod, S., Bodemer, C., Livadiotti, S., Novelli, F., Rossi, P., Fischer, A., Israel, A., Munnich, A., Le Deist, F., and Casanova, J.L. 2003. A hypermorphic IkappaBalpha

- mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. *J. Clin. Invest.* **112**(7):1108–1115. PMID: [14523047](#). doi: [10.1172/JCI18714](#).
- Dai, Y.S., Liang, M.G., Gellis, S.E., Bonilla, F.A., Schneider, L.C., Geha, R.S., and Orange, J.S. 2004. Characteristics of mycobacterial infection in patients with immunodeficiency and nuclear factor-kappaB essential modulator mutation, with or without ectodermal dysplasia. *J. Am. Acad. Dermatol.* **51**(5):718–722. PMID: [15523349](#). doi: [10.1016/j.jaad.2004.05.032](#).
- Deering, R.P., and Orange, J.S. 2006. Development of a clinical assay to evaluate toll-like receptor function. *Clin. Vaccine Immunol.* **13**(1):68–76. PMID: [16426002](#). doi: [10.1128/CVI.13.1.68-76.2006](#).
- Devora, G.A., Sun, L., Chen, Z., van Oers, N.S., Hanson, E.P., Orange, J.S., and de la Morena, M.T. 2010. A novel missense mutation in the nuclear factor-kappaB essential modulator (NEMO) gene resulting in impaired activation of the NF-kappaB pathway and a unique clinical phenotype presenting as MRSA subdural empyema. *J. Clin. Immunol.* **30**(6):881–885. PMID: [20652730](#). doi: [10.1007/s10875-010-9445-y](#).
- Doffinger, R., Smahi, A., Bessia, C., Geissmann, F., Feinberg, J., Durandy, A., Bodemer, C., Kenwrick, S., Dupuis-Girod, S., Blanche, S., Wood, P., Rabia, S.H., Headon, D.J., Overbeek, P.A., Le Deist, F., Holland, S.M., Belani, K., Kumararatne, D.S., Fischer, A., Shapiro, R., Conley, M.E., Reimund, E., Kalhoff, H., Abinun, M., Munnich, A., Israel, A., Courtois, G., and Casanova, J.L. 2001. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. *Nat. Genet.* **27**(3):277–285. PMID: [11242109](#). doi: [10.1038/85837](#).
- Dupuis-Girod, S., Corradini, N., Hadj-Rabia, S., Fournet, J.C., Faivre, L., Le Deist, F., Durand, P., Doffinger, R., Smahi, A., Israel, A., Courtois, G., Brousse, N., Blanche, S., Munnich, A., Fischer, A., Casanova, J.L., and Bodemer, C. 2002. Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency in a boy and incontinentia pigmenti in his mother. *Pediatrics.* **109**(6):e97. PMID: [12042591](#).
- Filipe-Santos, O., Bustamante, J., Haverkamp, M.H., Vinolo, E., Ku, C.L., Puel, A., Frucht, D.M., Christel, K., von Bernuth, H., Jouanguy, E., Feinberg, J., Durandy, A., Senechal, B., Chapgier, A., Vogt, G., de Beaucoudrey, L., Fieschi, C., Picard, C., Garfa, M., Chemli, J., Bejaoui, M., Tsolia, M.N., Kutukculer, N., Plebani, A., Notarangelo, L., Bodemer, C., Geissmann, F., Israel, A., Veron, M., Knackstedt, M., Barbouche, R., Abel, L., Magdorf, K., Gendrel, D., Agou, F., Holland, S.M., and Casanova, J.L. 2006. X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. *J. Exp. Med.* **203**(7):1745–1759. PMID: [16818673](#). doi: [10.1084/jem.20060085](#).
- Gilmore, T.D. 2006. Introduction to NF-kappaB: Players, pathways, perspectives. *Oncogene.* **25**(51):6680–6684. PMID: [17072321](#). doi: [10.1038/sj.onc.1209954](#).
- Hanson, E.P., Monaco-Shawver, L., Solt, L.A., Madge, L.A., Banerjee, P.P., May, M.J., and Orange, J.S. 2008. Hypomorphic nuclear factor-kappaB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. *J. Allergy Clin. Immunol.* **122**(6):1169–1177.e16. PMID: [18851874](#). doi: [10.1016/j.jaci.2008.08.018](#).
- Haverkamp, M.H., Arend, S.M., Lindeboom, J.A., Hartwig, N.G., and van Dissel, J.T. 2004. Nontuberculous mycobacterial infection in children: A 2-year prospective surveillance study in the Netherlands. *Clin. Infect. Dis.* **39**(4):450–456. PMID: [15356803](#). doi: [10.1086/422319](#).
- Holland, S.M., Eisenstein, E.M., Kuhns, D.B., Turner, M.L., Fleisher, T.A., Strober, W., and Gallin, J.I. 1994. Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma. A preliminary report. *N. Engl. J. Med.* **330**(19):1348–1355. PMID: [7908719](#). doi: [10.1056/NEJM199405123301904](#).
- Hubeau, M., Ngadjeu, F., Puel, A., Israel, L., Feinberg, J., Chrabieh, M., Belani, K., Bodemer, C., Fabre, I., Plebani, A., Boisson-Dupuis, S., Picard, C., Fischer, A., Israel, A., Abel, L., Veron, M., Casanova, J.L., Agou, F., and Bustamante, J. 2011. New mechanism of X-linked anhidrotic ectodermal dysplasia with immunodeficiency: Impairment of ubiquitin binding despite normal folding of NEMO protein. *Blood.* **118**(4):926–935. PMID: [21622647](#). doi: [10.1182/blood-2010-10-315234](#).
- Imamura, M., Kawai, T., Okada, S., Izawa, K., Takachi, T., Iwabuchi, H., Yoshida, S., Hosokai, R., Kanegane, H., Yamamoto, T., Umez, H., Nishikomori, R., Heike, T., Uchiyama, M., and Imai, C. 2011. Disseminated BCG infection mimicking metastatic nasopharyngeal carcinoma in an immunodeficient child with a novel hypomorphic NEMO mutation. *J. Clin. Immunol.* **31**(5):802–810. PMID: [21755389](#). doi: [10.1007/s10875-011-9568-9](#).
- Jain, A., Ma, C.A., Liu, S., Brown, M., Cohen, J., and Strober, W. 2001. Specific missense mutations in NEMO result in hyper-IgM syndrome with

- hypohidrotic ectodermal dysplasia. *Nat. Immunol.* **2**(3):223–228. PMID: [11224521](#). doi: [10.1038/85277](#).
- Janssen, R., van Wengen, A., Hoeve, M.A., ten Dam, M., van der Burg, M., van Dongen, J., van de Vosse, E., van Tol, M., Bredius, R., Ottenhoff, T.H., Weemaes, C., van Dissel, J.T., and Lankester, A. 2004. The same IκappaBα mutation in two related individuals leads to completely different clinical syndromes. *J. Exp. Med.* **200**(5):559–568. PMID: [15337789](#). doi: [10.1084/jem.20040773](#).
- Karakawa, S., Okada, S., Tsumura, M., Mizoguchi, Y., Ohno, N., Yasunaga, S., Ohtsubo, M., Kawai, T., Nishikomori, R., Sakaguchi, T., Takihara, Y., and Kobayashi, M. 2011. Decreased expression in nuclear factor-κB essential modulator due to a novel splice-site mutation causes X-linked ectodermal dysplasia with immunodeficiency. *J. Clin. Immunol.* **31**(5):762–772. PMID: [21720903](#). doi: [10.1007/s10875-011-9560-4](#).
- Karamchandani-Patel, G., Hanson, E.P., Saltzman, R., Kimball, C.E., Sorensen, R.U., and Orange, J.S. 2011. Congenital alterations of NEMO glutamic acid 223 result in hypohidrotic ectodermal dysplasia and immunodeficiency with normal serum IgG levels. *Ann. Allergy Asthma Immunol.* **107**(1):50–56. PMID: [21704885](#). doi: [10.1016/j.anai.2011.03.009](#).
- Kosaki, K., Shimasaki, N., Fukushima, H., Hara, M., Ogata, T., and Matsuo, N. 2001. Female patient showing hypohidrotic ectodermal dysplasia and immunodeficiency (HED-ID). *Am. J. Hum. Genet.* **69**(3):664–665. PMID: [11484156](#). doi: [10.1086/323003](#).
- Ku, C.L., Dupuis-Girod, S., Dittrich, A.M., Bustamante, J., Santos, O.F., Schulze, I., Bertrand, Y., Couly, G., Bodemer, C., Bossuyt, X., Picard, C., and Casanova, J.L. 2005. NEMO mutations in 2 unrelated boys with severe infections and conical teeth. *Pediatrics.* **115**(5):e615–e619. PMID: [15833888](#). doi: [10.1542/peds.2004-1754](#).
- Ku, C.L., Picard, C., Erdos, M., Jeurissen, A., Bustamante, J., Puel, A., von Bernuth, H., Filipe-Santos, O., Chang, H.H., Lawrence, T., Raes, M., Marodi, L., Bossuyt, X., and Casanova, J.L. 2007. IRAK4 and NEMO mutations in otherwise healthy children with recurrent invasive pneumococcal disease. *J. Med. Genet.* **44**(1):16–23. PMID: [16950813](#). doi: [10.1136/jmg.2006.044446](#).
- Lee, W.I., Torgerson, T.R., Schumacher, M.J., Yel, L., Zhu, Q., and Ochs, H.D. 2005. Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. *Blood.* **105**(5):1881–1890. PMID: [15358621](#). doi: [10.1182/blood-2003-12-4420](#).
- Lopez-Granados, E., Keenan, J.E., Kinney, M.C., Leo, H., Jain, N., Ma, C.A., Quinones, R., Gelfand, E.W., and Jain, A. 2008. A novel mutation in NFKBIA/IKBA results in a degradation-resistant N-truncated protein and is associated with ectodermal dysplasia with immunodeficiency. *Hum. Mutat.* **29**(6):861–868. PMID: [18412279](#). doi: [10.1002/humu.20740](#).
- Mancini, A.J., Lawley, L.P., and Uzel, G. 2008. X-linked ectodermal dysplasia with immunodeficiency caused by NEMO mutation: Early recognition and diagnosis. *Arch. Dermatol.* **144**(3):342–346. PMID: [18347290](#). doi: [10.1001/archderm.144.3.342](#).
- Mansour, S., Woffendin, H., Mitton, S., Jeffery, I., Jakins, T., Kenwrick, S., and Murday, V.A. 2001. Incontinentia pigmenti in a surviving male is accompanied by hypohidrotic ectodermal dysplasia and recurrent infection. *Am. J. Med. Genet.* **99**(2):172–177. PMID: [11241484](#).
- Martinez-Pomar, N., Munoz-Saa, I., Heine-Suner, D., Martin, A., Smahi, A., and Matamoros, N. 2005. A new mutation in exon 7 of NEMO gene: Late skewed X-chromosome inactivation in an incontinentia pigmenti female patient with immunodeficiency. *Hum. Genet.* **118**(3–4):458–465. PMID: [16228229](#). doi: [10.1007/s00439-005-0068-y](#).
- McDonald, D.R., Mooster, J.L., Reddy, M., Bawle, E., Secord, E., and Geha, R.S. 2007. Heterozygous N-terminal deletion of IκappaBα results in functional nuclear factor κB haploinsufficiency, ectodermal dysplasia, and immune deficiency. *J. Allergy Clin. Immunol.* **120**(4):900–907. PMID: [17931563](#). doi: [10.1016/j.jaci.2007.08.035](#).
- Mooster, J.L., Cancrini, C., Simonetti, A., Rossi, P., Di Matteo, G., Romiti, M.L., Di Cesare, S., Notarangelo, L., Geha, R.S., and McDonald, D.R. 2010. Immune deficiency caused by impaired expression of nuclear factor-κB essential modifier (NEMO) because of a mutation in the 5′ untranslated region of the NEMO gene. *J. Allergy Clin. Immunol.* **126**(1):127–132.e7. PMID: [20542322](#). doi: [10.1016/j.jaci.2010.04.026](#).
- Mousallem, T., Yang, J., Urban, T.J., Wang, H., Adeli, M., Parrott, R.E., Roberts, J.L., Goldstein, D.B., Buckley, R.H., and Zhong, X.P. 2014. A nonsense mutation in IKBKB causes combined immunodeficiency. *Blood.* **124**(13):2046–2050. PMID: [25139357](#). doi: [10.1182/blood-2014-04-571265](#).
- Niehues, T., Reichenbach, J., Neubert, J., Gudowius, S., Puel, A., Horneff, G., Lainka, E., Dirksen, U.,

- Schroten, H., Doffinger, R., Casanova, J.L., and Wahn, V. 2004. Nuclear factor kappaB essential modulator-deficient child with immunodeficiency yet without anhidrotic ectodermal dysplasia. *J. Allergy Clin. Immunol.* **114**(6):1456–1462. PMID: [15577852](#). doi: [10.1016/j.jaci.2004.08.047](#).
- Nielsen, C., Jakobsen, M.A., Larsen, M.J., Muller, A.C., Hansen, S., Lillevang, S.T., Fisker, N., and Barington, T. 2014. Immunodeficiency associated with a nonsense mutation of IKBKB. *J. Clin. Immunol.* **34**(8):916–921. PMID: [25216719](#). doi: [10.1007/s10875-014-0097-1](#).
- Nishikomori, R., Akutagawa, H., Maruyama, K., Nakata-Hizume, M., Ohmori, K., Mizuno, K., Yachie, A., Yasumi, T., Kusunoki, T., Heike, T., and Nakahata, T. 2004. X-linked ectodermal dysplasia and immunodeficiency caused by reversion mosaicism of NEMO reveals a critical role for NEMO in human T-cell development and/or survival. *Blood*. **103**(12):4565–4572. PMID: [14726382](#). doi: [10.1182/blood-2003-10-3655](#).
- Ohnishi, H., Miyata, R., Suzuki, T., Nose, T., Kubota, K., Kato, Z., Kaneko, H., and Kondo, N. 2012. A rapid screening method to detect autosomal-dominant ectodermal dysplasia with immune deficiency syndrome. *J. Allergy Clin. Immunol.* **129**(2):578–580. PMID: [22078572](#). doi: [10.1016/j.jaci.2011.09.042](#).
- Orange, J.S., Brodeur, S.R., Jain, A., Bonilla, F.A., Schneider, L.C., Kretschmer, R., Nurko, S., Rasmussen, W.L., Kohler, J.R., Gellis, S.E., Ferguson, B.M., Strominger, J.L., Zonana, J., Ramesh, N., Ballas, Z.K., and Geha, R.S. 2002. Deficient natural killer cell cytotoxicity in patients with IKK-gamma/NEMO mutations. *J. Clin. Invest.* **109**(11):1501–1509. PMID: [12045264](#). doi: [10.1172/JCI0214858](#).
- Orange, J.S., Jain, A., Ballas, Z.K., Schneider, L.C., Geha, R.S., and Bonilla, F.A. 2004a. The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. *J. Allergy Clin. Immunol.* **113**(4):725–733. PMID: [15100680](#). doi: [10.1016/j.jaci.2004.01.762](#).
- Orange, J.S., Levy, O., Brodeur, S.R., Krzewski, K., Roy, R.M., Niemela, J.E., Fleisher, T.A., Bonilla, F.A., and Geha, R.S. 2004b. Human nuclear factor kappa B essential modulator mutation can result in immunodeficiency without ectodermal dysplasia. *J. Allergy Clin. Immunol.* **114**(3):650–656. PMID: [15356572](#). doi: [10.1016/j.jaci.2004.06.052](#).
- Orange, J.S., Levy, O., and Geha, R.S. 2005. Human disease resulting from gene mutations that interfere with appropriate nuclear factor-kappaB activation. *Immunol. Rev.* **203**:21–37. PMID: [15661019](#). doi: [10.1111/j.0105-2896.2005.00221.x](#).
- Orstavik, K.H., Kristiansen, M., Knudsen, G.P., Storhaug, K., Vege, A., Eiklid, K., Abrahamsen, T.G., Smahi, A., and Steen-Johnsen, J. 2006. Novel splicing mutation in the NEMO (IKK-gamma) gene with severe immunodeficiency and heterogeneity of X-chromosome inactivation. *Am. J. Med. Genet. A.* **140**(1):31–39. PMID: [16333836](#). doi: [10.1002/ajmg.a.31026](#).
- Pannicke, U., Baumann, B., Fuchs, S., Henneke, P., Rensing-Ehl, A., Rizzi, M., Janda, A., Hese, K., Schlesier, M., Holzmann, K., Borte, S., Laux, C., Rump, E.M., Rosenberg, A., Zelinski, T., Schrezenmeier, H., Wirth, T., Ehl, S., Schroeder, M.L., and Schwarz, K. 2013. Deficiency of innate and acquired immunity caused by an IKBKB mutation. *N. Engl. J. Med.* **369**(26):2504–2514. PMID: [24369075](#). doi: [10.1056/NEJMoa1309199](#).
- Puel, A., Reichenbach, J., Bustamante, J., Ku, C.L., Feinberg, J., Doffinger, R., Bonnet, M., Filipe-Santos, O., de Beaucoudrey, L., Durandy, A., Horneff, G., Novelli, F., Wahn, V., Smahi, A., Israel, A., Niehues, T., and Casanova, J.L. 2006. The NEMO mutation creating the most-upstream premature stop codon is hypomorphic because of a reinitiation of translation. *Am. J. Hum. Genet.* **78**(4):691–701. PMID: [16532398](#). doi: [10.1086/501532](#).
- Roberts, C.M., Angus, J.E., Leach, I.H., McDermott, E.M., Walker, D.A., and Ravenscroft, J.C. 2010. A novel NEMO gene mutation causing osteopetrosis, lymphoedema, hypohidrotic ectodermal dysplasia and immunodeficiency (OL-HED-ID). *Eur. J. Pediatr.* **169**(11):1403–1407. PMID: [20499091](#). doi: [10.1007/s00431-010-1206-7](#).
- Salt, B.H., Niemela, J.E., Pandey, R., Hanson, E.P., Deering, R.P., Quinones, R., Jain, A., Orange, J.S., and Gelfand, E.W. 2008. IKBKG (nuclear factor-kappa B essential modulator) mutation can be associated with opportunistic infection without impairing Toll-like receptor function. *J. Allergy Clin. Immunol.* **121**(4):976–982. PMID: [18179816](#). doi: [10.1016/j.jaci.2007.11.014](#).
- Schimke, L.F., Rieber, N., Rylaarsdam, S., Cabral-Marques, O., Hubbard, N., Puel, A., Kallmann, L., Sombke, S.A., Notheis, G., Schwarz, H.P., Kammer, B., Hokfelt, T., Repp, R., Picard, C., Casanova, J.L., Belohradsky, B.H., Albert, M.H., Ochs, H.D., Renner, E.D., and Torgerson, T.R. 2013. A novel gain-of-function IKBA mutation underlies ectodermal dysplasia with immunodeficiency and polyendocrinopathy.

- J. Clin. Immunol. **33**(6):1088–1099. PMID: [23708964](#). doi: [10.1007/s10875-013-9906-1](#).
- Schweizer, P., Kalhoff, H., Horneff, G., Wahn, V., and Diekmann, L. 1999. [Polysaccharide specific humoral immunodeficiency in ectodermal dysplasia. Case report of a boy with two affected brothers]. *Klin. Padiatr.* **211**(6):459–461. PMID: [10592927](#). doi: [10.1055/s-2008-1043834](#).
- Vinolo, E., Sebban, H., Chaffotte, A., Israel, A., Courtois, G., Veron, M., and Agou, F. 2006. A point mutation in NEMO associated with anhidrotic ectodermal dysplasia with immunodeficiency pathology results in destabilization of the oligomer and reduces lipopolysaccharide- and tumor necrosis factor-mediated NF-kappa B activation. *J. Biol. Chem.* **281**(10):6334–6348. PMID: [16379012](#). doi: [10.1074/jbc.M510118200](#).
- von Bernuth, H., Ku, C.L., Rodriguez-Gallego, C., Zhang, S., Garty, B.Z., Marodi, L., Chapel, H., Chrabieh, M., Miller, R.L., Picard, C., Puel, A., and Casanova, J.L. 2006. A fast procedure for the detection of defects in Toll-like receptor signaling. *Pediatrics.* **118**(6):2498–2503. PMID: [17142536](#). doi: [10.1542/peds.2006-1845](#).
- von Bernuth, H., Puel, A., Ku, C.L., Yang, K., Bustamante, J., Chang, H.H., Picard, C., and Casanova, J.L. 2005. Septicemia without sepsis: Inherited disorders of nuclear factor-kappa B-mediated inflammation. *Clin. Infect. Dis.* **41**(Suppl 7):S436–S439. PMID: [16237643](#). doi: [10.1086/431994](#).
- Zonana, J., Elder, M.E., Schneider, L.C., Orlow, S.J., Moss, C., Golabi, M., Shapira, S.K., Farndon, P.A., Wara, D.W., Emmal, S.A., and Ferguson, B.M. 2000. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am. J. Hum. Genet.* **67**(6):1555–1562. PMID: [11047757](#). doi: [10.1086/316914](#).