

## The role of different genes in causing infection of ectodermal dysplasia patients: A systematic review

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### ABSTRACT

Ectodermal dysplasia (ED) is a genetic disorder which is characterized by deficient tissues from ectoderm and mesoderm. In this systematic review, two researchers searched keywords such as Ectodermal Dysplasia and Hypohidrotic Ectodermal Dysplasia (HED) in Medline (PubMed), Scopus, and Web of Science databases were searched until June 2020. In the first search 885 articles were found. After including and excluding criteria, included articles were reduced to 53 in Scopus, 11 in Web of Science, and 11 in PubMed. The point is that out of 75 selected studies, 52 articles were identified the cause of infection in ectodermal dysplasia as mutations in the NEMO gene and its subsets.

**Keywords:** Ectodermal dysplasia, infection, immunodeficiency, NEMO, NF-KB

### INTRODUCTION

Ectodermal Dysplasia (ED) is a heterogeneous group of disorders characterized by a deficiency of tissues

that originate from ectoderm and mesoderm. Therefore, sparse hair, peg-shaped teeth, and abnormal nails are typical in this congenital disorder. In this disorder, individuals are susceptible to

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severe infections. This rare disease happens in every 100/000 live births. More than 160 specific syndromes with different inheritance patterns are associated with this syndrome [1,2]. Two common forms of ED are: hidrotic and anhidrotic or hypohidrotic. Hypohidrotic Ectodermal Dysplasia (HED) is determined with a defect in hair growth, teeth, and sweat glands. Also, it shows a decrease in the production of mucus in the respiratory system. The difference between anhidrotic and hypohidrotic ectodermal dysplasia is the type of inheritance pattern and the reduction or absence of sweat glands [3]. HED can be inherited as X-linked recessive, autosomal dominant, and autosomal recessive that abnormal cell signaling cascade creates growth, which is essential for appropriate forming ectodermal-derived tissues function. X-link HED (the common form of HED; XLHED) caused by a mutation in the EDA gene mutation in EDAR and EDARADD genes causes autosomal recessive and dominant types. Many respiratory infections were reported in patients with an autosomal recessive mutation in EDARADD gene [4]. Ectodermal dysplasia with immunodeficiency (X-linked recessive) is a kind of immunological disorder caused by

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mutations in the coding genes of nuclear factor Kappa-B (NEMO). NF-KB is an essential transcription regulator factor of ectodermal growth and adaptive immune function [5].

Activation NF-KB is a critical signaling event in immune responses downstream of different immune receptors such as Toll-like, interleukin-1, T cell, and B cell receptors. Classic or regular NF-KB activation path depends on the phosphorylation of two serine residues (ser32 and ser36) of IKB $\alpha$ , mediated by IKKB. There is a mutation in many components involves NF-KB activation, which causes an immunodeficiency. Moreover, infection demonstrations as a combined immunodeficient, almost there are in all patients show EDA [6]. Mutation in one regulator subunit of NF- $\kappa$ B route is known as NEMO (NF kappa B) IKK gamma critical modifier that makes two different forms of X-linked recessive ectodermal dysplasia: Incontinentia Pigmenti (IP) which is fatal in men HED and immunodeficiency (HED-ID) in which, dysfunction of NEMO causes a disturbance in the immune response to bacterial and viral infection in addition to HED [7]. People suffering from XLHED are at risk of severe pneumonia and respiratory infections at young ages.

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Respiratory infections, wheezing, and frequent sinus infection can be continued in adults [5]. Immunodeficiency caused sensitivity to enclosed progenies bacteria, such as *Streptococcus pneumonia*, *Haemophilus influenza*, Mycobacteria, and Herpes virus infections. Repeated infections of the lower respiratory tract, which arising from enclosed bacteria, may cause permanent injury in body organs in patients with common variable immune deficiency (CVID). The bacterial disease can be partly due to the impact of NEMO mutation in the TIR signaling path [6]. Individuals with exon four deletion in EDARADD gene show frequent respiratory infections from childhood. Sometimes these chronic respiratory infections are seen in patients with X-linked recessive and in people who have p.Trp135 -Val136del EDARADD gene mutations. In Children with EDA ID, usually, lungs (pneumonia), ears (Otitis Media), sinuses (Sinusitis), Lymph nodes (lymphadenitis), skin, bones, and digestive system get infected. This study aimed to determine the role of genes causing infection in patients with ectodermal dysplasia [8].

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#### ***Search strategy***

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist was used as a template for this review. In this systematic review, English databases such as Medline (via PubMed), Scopus, and Web of Science studies were published in English until June 24, 2020, were searched. Search keywords were a combination of (Ectodermal dysplasia or ED and hypohidrotic ectodermal dysplasia OR HED) and (Infection or Infestation and Infections or Infestations). First, two separate researchers reviewed the titles and the abstracts of articles. Those studies that seemed to be related were extracted and reviewed in their full text. In the second stage, the full text of the remaining articles was carefully reviewed, and articles that met the inclusion and exclusion criteria were systematically reviewed for the quality assessment (Figure 1).

#### ***Study selection***

To avoid bias, two researchers performed the search independently. Database search was done for possible studies. Abstracts of the studies were screened to identify eligible studies, full-text articles were

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obtained, assessed, and finally listed of included studies was made. This process was done independently by two reviewers, and the 3rd reviewer resolved any disagreement.

### ***Data extraction***

Finally, for extracting data from these articles' text, reviewers collected the data independently, collected data were combined, and compared for accuracy, the third reviewer resolved any discrepancies. Data collected from the selected studies included: articles in which both keywords ectodermal dysplasia and infection can be seen, and there were more than one or two simple sentences about them. Also, we picked articles related to ectodermal dysplasia by NEMO and NF-KB mutation and there was a relationship between this immunodeficiency and infection.

Results of studies in this search strategy, 885 English language articles were identified. After applying the following restrictions, 75 articles were included in the study: years: 2014–2020, language: English, document type (Review), non-association of infection with ectodermal dysplasia, mention the ectodermal dysplasia only in reference, not in the text, partial reference to infection in one sentence, articles that are related to

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ectodermal dysplasia but do not mention infection, Infection is associated with other diseases and genetic defects, Articles about Aplasia cutis congenital, duplication of articles and articles related to ED syndromes and diseases such as aplasia cutis, EB, etc., were removed. During the search, 75 articles were selected according to including and excluding criteria.

### ***Nuclear factor KB (NF-KB)***

Of the total number of articles included, 52 were related to mutations in these patients' developmental gene. X-link recessive is a significant modulator (NEMO) with a defective immune system and mutation-induced growth in the nuclear factor KB (NF- KB) gene. NF KB is a primary transcriptional regulator of ectodermal growth and adaptive immune function. Hypomorphic mutations in NF KB (NEMO) encoded by the IKBKG / NEMO gene on the X chromosome lead to immunodeficiency HED. Immune deficiency leads to susceptibility to encapsulated pathogenic bacteria, such as *Streptococcus pneumonia* and *Haemophilus influenza*, mycobacteria, and herpes viruses. Recurrent lower respiratory tract infections caused by bacteria may cause permanent organ damage in patients with variable immunodeficiency. Common

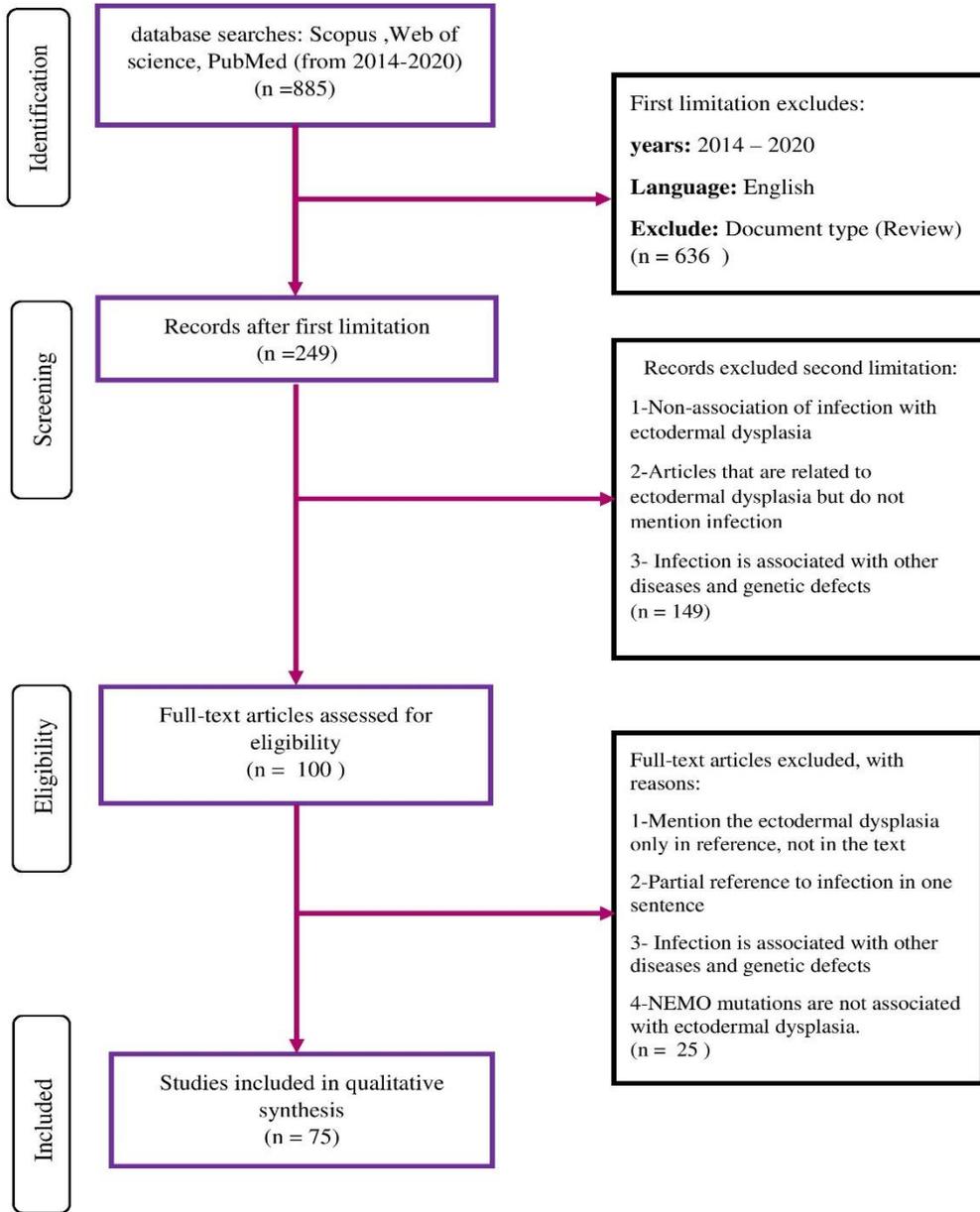
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Variable Immunodeficiency (CVID). Fungal infections have been described in 10 % of patients with HED ID. They also suffer from *Streptococcus pneumoniae*, meningitis, recurrent urinary tract infections, and recurrent upper and lower airway infections [6]. In one study, patients with HED-ID due to IKK-gamma NEMO mutation were also examined. They finally concluded that the BK virus could infect cortical nerve cells in humans and cause debilitating encephalopathy with minimal demyelination. *Human BK polyomavirus* (BKV) is activated under conditions of immune suppression that lead to nephropathy or inflammation of the bladder [8]. The IKBKB mutation (c. 1292dupG) in infants is characterized by the early onset of bacterial, viral, fungal, and mycobacterial infections. Genes in the IKK / NF  $\kappa$ B pathway, such as NEMO and I $\kappa$ B $\alpha$ , act in both hematopoietic and non-hematopoietic cells, leading to additional immune findings both disorders, such as

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ectodermal dysplasia and colitis. Reported infections include *Klebsiella*, *Pseudomonas*, *Haemophilus influenzae*, *Staphylococcus aureus*, Mycobacteria, and several viral infections (rotavirus, norovirus, parainfluenza, RSV, CMV) [9].

Furthermore, they are commonly encountered with infections caused by pyogenic bacteria (87 %), Mycobacteria (44 %), viruses (21 %), and fungal and opportunistic pathogens (10 %) [10]. *Pseudomonas aeruginosa* infection occurs in patients with EDA ID with IKBKG. They suffered from several debilitating infections, including gram-positive and gram-negative bacteria and Non-Tuberculous Mycobacterium (NTM), and one of the Patients with *Pneumocystis jirovecii pneumonia* [11] (Figure 2).



**Figure 1.** Flowchart of the systematic review based on the PRISMA checklist.

***PKP1***

Three articles described from the number of articles included Ectodermal Dysplasia-Skin Fragility Syndrome (ED SFS) is a rare genodermatosis caused by a mutation in the PKP1 gene that encodes plakophilin-1 protein. Mutations cause chest infections, pneumonia, skin infections, and other common infections [12,13].

***EDARADD***

Four articles described in connection with multiple lung infections. Patients who have exon four deletions in EDARADD show recurrent respiratory infections. Patients with X-linked HED, autosomal recessive and mutated EDARADDs had recurrent rhinitis and multiple respiratory infections. EDARADD interacts with the TAB2 RARAF6 /TAK1 set required by EDAR to activate NF $\kappa$ B [7,14].

***EDA***

Of the included articles, four were related to mutations in the EDA (most common ectodermal dysplasia) gene. That is, X-linked hypohidrotic ectodermal dysplasia (XLHED) in humans leads to lung infections. Upper respiratory tract

infections and infections of the eyes and airways are pneumonia, wheezing, respiratory infections, recurrent sinus infections, and group B streptococci (*Streptococcus agalactiae*) [5, 15–17].

**TP63**

Three Articles on Acro-Dermato-Ungual-Lacrimal-Tooth syndrome (ADULT) are part of a heterogeneous group of Ectodermal Dysplasia (ED) caused by TP63 mutations, indicating autosomal dominant inheritance. Chronic ear infections have been common in all patients with *Streptococcus pyogenes* and *Staphylococcus haemolyticus*. In patients with AEC syndrome due to a mutation in TP63, which encodes the p63 protein, it is essential to preserve epidermal stem cells reported by *S. aureus* and other gram-positive and gram-negative bacteria [18–20].

***Other genes***

A mutation in the BRAF gene and GJB2 and cause infections such as nail and skin infections [21,22]. Mutations in genes that encode components of the intraflagellar transport complex A (IFT-A) lead to Sensenbrenner syndrome, which is cranioectodermal dysplasia, and

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respiratory infections caused by viruses such as adenovirus and rhinovirus is seen [23]. Heterozygous mutations in IFT122, one of the IFT-A genes, also cause this syndrome, and hepatitis can be seen in these patients [24]. Biallelic mutations in WDR19 and TEK1, which express tektin-1, lead to ciliary dyskinesia, and mutations in WDR19 are associated with cranioectodermal dysplasia. This airway ciliary dyskinesia is associated with severe respiratory infections. Treatment is with siTEK1 [25]. Mutations in WDR35 also lead to cranioectodermal dysplasia (Sensenbrenner syndrome), a respiratory infection associated with *Pseudomonas aeruginosa tracheitis* [26].

Various types of epidermal disorders, along with approximately GJB2 mutations, include: Keratitis-ichthyosis-deafness (KID), defeating ectodermal syndrome (KID) is a rare debilitating ectodermal dysplasia. Infection is susceptible. Fungal infections increase susceptibility to skin infections. Common nail infections, cutaneous mycoses and common bacterial skin infections [21]. They studied salivary gland disorders and their effects on oral microbiota. HED is the most common form caused by a mutation in the EDA gene located on the X chromosome's extended arm. HED is

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caused by a mutation in the GJB6 gene, located on chromosome 13 (locus 13q12), encoding. In these patients, hypoplastic maxillary glands and abnormal growth of partial salivary glands have also been described. In this study, the number of the mutants streptococci and yeast was high. On the other hand, the number of lactobacilli was low. In the case of immunodeficiency disorder in the ED, we assume that patient two is diagnosed with *Candida albicans angular cheilitis* after confirmation of the diagnosis. Respiratory infections were also reported [27]. In an article, anhidrotic ectodermal dysplasia with immunodeficiency (AED ID) is a rare syndrome characterized by changes in the differentiation of ectoderm-derived structures such as teeth, hair, and sweat glands, and impaired immune function. Children with this defect and the X link develop a respiratory infection encapsulated with pyogenic bacteria, mycobacteria, viruses, and fungi. Patients with AD mutation in IKBA suffer from severe pyogenic bacterial infections, including pneumonia, due to *β hemolytic type A streptococcus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Serratia marcescens* [28]. In an article, Subungual Squamous Cell Carcinoma

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(SSCC) is a rare malignancy reported on the toe. Moreover, lesions can be treated topically; distal phalanx amputation is usually the recommended treatment option/radiation therapy [29]. An article Mutation in ORAI1 leads to the ablation of CRAC (Calcium-Release Activated Calcium) channel, characterized by SCID, autoimmunity, hypotension, and ectodermal dysplasia, and enamel defects and causes herpes virus infections including CMV, Pneumonia becomes *P.jirovecii* [30]. In an article, diseases such as Chronic Granulomatous isease (CGD) also infect, which is a skin manifestation of ectodermal dysplasia [31].

According to the PRISMA checklist in the first search in three databases, 885 articles were found from consideration search strategy. After including and excluding criteria, included articles was reduced to 53 in Scopus, 11 in Web of Science, and 11 in PubMed. The noteworthy point is that out of 75 selected studies, 52 articles identified the cause of infection in patients with ectodermal dysplasia as mutations in the NEMO gene and its subsets. Ectodermal dysplasia (ED) is a set of disorders in which the ectoderm or ectoderm-derived structures are involved in mutations in various

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genes. Most affected areas: skin, sweat glands, hair, nails. Moreover, it is the teeth that grow abnormally. Each person with ectodermal dysplasia may have a different phenotype. It depends on which part is involved. For example, in one patient, hair and nails may be involved, while in another, the sweat glands and teeth may be affected. In this heterogeneous disorder, mutations in some genes cause cystic immunodeficiency and infection [3]. Mutations in genes involved in the production of sweat glands cause the patient to lack or reduce sweating, leading to bacterial, viral, fungal infections and a weakened immune system. ED cannot be cured, but the symptoms can be treated or controlled. If not taken promptly, it can be life-threatening. Nikita Raje et al. Showed that mutations in NEMO and its subtypes cause ectodermal dysplasia, which is characterized by hypohidrosis, hair breakage, conical teeth, and premature tooth loss [79]. Kappa B (NEMO) is susceptible to bacterial infections such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, Mycobacterium and less viral and fungal infections [6]. They also showed that a

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defect in the NEMO gene increased IgM levels in 15 % of patients. They further found that mutations in one of the NEMO subsets called the NF-kappa B alpha Deficiency Inhibitor (IKBA in patients with) are susceptible to infection with *Pneumocystis jirovecii*, *mucosal candidiasis*, *Listeria monocytogenes*, *Serratia marcescens*, *Escherichia*

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Generally, candidiasis is a cutaneous mucosa and parainfluenza [51]. In a study, Elena Daniel *et al.* included 12 patients suspected of having ectodermal dysplasia and its subgroups. After studies, they found that mutations in different genes cause-specific organs' involvement that causes different infections [80].

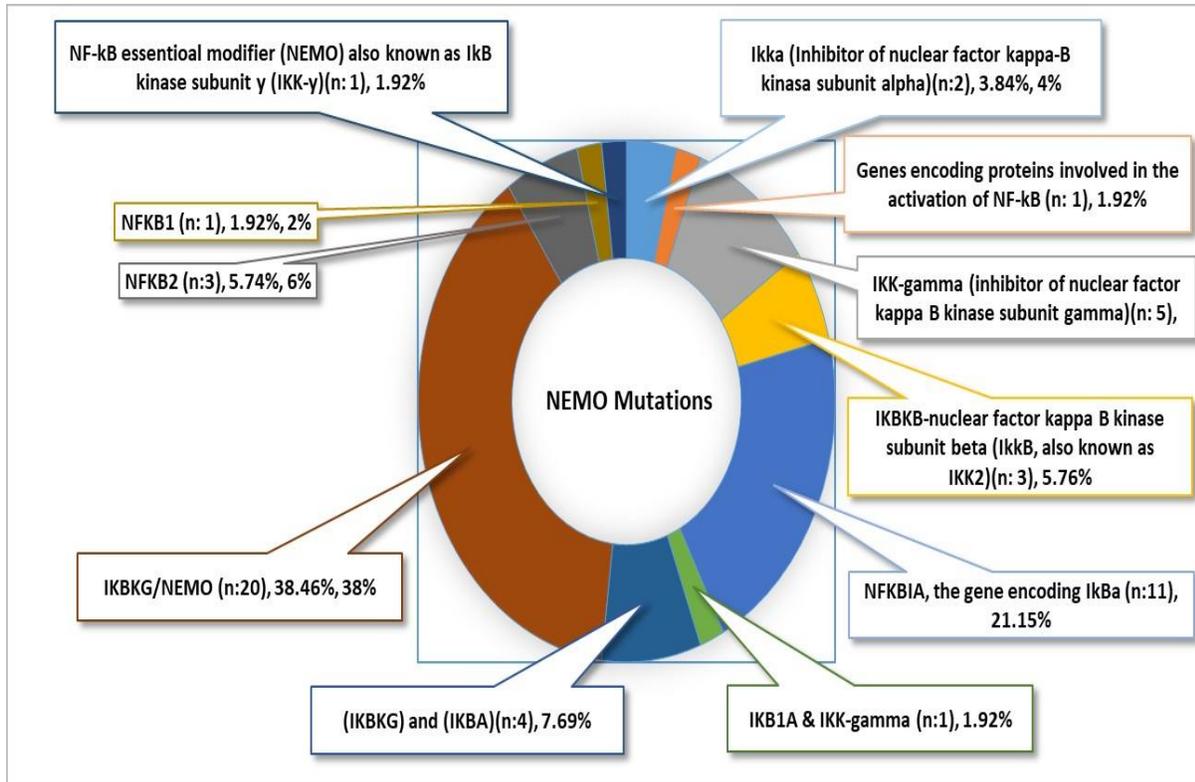


Figure 2. Types of Nuclear factor-KB (NF-KB) Mutations.

**CONCLUSION**

The results showed that mutations in various genes cause infection in ectodermal dysplasia patients, but the leading and most common cause of infection, which also causes a defect in the

immune system, can be considered mutations the NEMO gene.

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