

Medical genetics

## Hypohidrotic ectodermal dysplasia: clinical and molecular review

Julia Reyes-Real<sup>1</sup>, BC, María Isabel Mendoza-Ramos<sup>1</sup>, MD, Efraín Garrido-Guerrero<sup>2</sup>, PhD, Claudia F. Méndez-Catalá<sup>3</sup>, PhD, Adolfo R. Méndez-Cruz<sup>1</sup>, MD, PhD, and Glustein Pozo-Molina<sup>4</sup>, MD, PhD

<sup>1</sup>Laboratorio de Inmunología, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla, Mexico, <sup>2</sup>Laboratorio de Investigación en Biología Molecular y Celular del Cáncer, Departamento de Genética y Biología Molecular, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Ciudad de México, Mexico, <sup>3</sup>Laboratorio Nacional de Enfermedades Crónico-Degenerativas/ Unidad de Biomedicina (UBIMED), Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla, Mexico, and <sup>4</sup>Carrera de Médico Cirujano, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla, Mexico

### Correspondence

Glustein Pozo Molina, MD, PhD  
Carrera de Médico Cirujano  
Facultad de Estudios Superiores Iztacala  
Universidad Nacional Autónoma de México  
Ave. de los Barrios 1  
Los Reyes Iztacala  
Tlalnepantla, 54090  
Edo. de México, México.  
E-mails: glustein@campus.iztacala.unam.mx; glustein@hotmail.com

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The XL-HED is a genetic disease caused by mutations in the EDA1 gene that encodes the protein ectodysplasin-A. We report a clinical and molecular review of a hypohidrotic ectodermal dysplasia based on both available literature and our experience from the XL-HED family previously reported in this journal.

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### Introduction

Ectodermal dysplasia (EDs) is a term used to describe a large group of clinically and congenitally heterogeneous disorders characterized by developmental failure in two or more ectodermal

### Abstract

Hypohidrotic Ectodermal Dysplasia (HED) is a genetic human disorder which affects structures of ectodermal origin. Although there are autosomal recessive and dominant forms, X-linked (XL) is the most frequent form of the disease. This XL-HED phenotype is associated with mutations in the gene encoding the transmembrane protein ectodysplasin-1 (*EDA1*), a member of the TNF $\alpha$ -related signaling pathway. The proteins from this pathway are involved in signal transduction from ectoderm to mesenchyme leading to the development of ectoderm-derived structures in the fetus such as hair, teeth, skin, nails, and eccrine sweat glands. The aim of this review was to update the main clinical characteristics of HED regarding to recent molecular advances in the comprehension of all the possible genes involved in this group of disorders since it is known that Eda-A1-Edar signaling has multiple roles in ectodermal organ development, regulating their initiation, morphogenesis, and differentiation steps. The knowledge of the biological mechanisms that generate HED is needed for both a better detection of possible cases and for the design of efficient prevention and treatment approaches.

structures involving alterations in hair, teeth, nails, or sweat glands. This group of disorders decreases the quality of life of patients.<sup>1,2</sup>

There are other ectodermal structures that could be involved in ED, such as mammary glands, thyroid glands, thymus,

anterior pituitary, adrenal medulla, central nervous system, melanocytes, external ear, lacrimal gland and duct, conjunctiva, cornea, and Meibomian glands.<sup>1</sup>

More than 200 types of ED have been described,<sup>3,4</sup> but the most common phenotype is the anhidrotic or hypohidrotic ectodermal dysplasia (HED/EDA 1) (OMIM 305100); this disorder is an X-linked hypohidrotic form of ED, which has a frequency of one per 17,000 live births in the general population.<sup>5</sup> The HED is characterized by reduced ability to sweat (hypohidrosis), abnormal or lack of several teeth (anodontia or hypodontia), and sparse hair (hypotrichosis).<sup>5</sup> Thus, HED could be differentiated from other types of ectodermal dysplasia by these triad of signs.

HED comprises a genetically heterogeneous group of disorders due to mutations in one of several genes that encode components of the tumor necrosis factor  $\alpha$  (TNF $\alpha$ )-related pathway, specifically the ectodysplasin A (EDA) signaling pathway that plays an important role in the embryonic ectodermal development.<sup>6</sup> Mutations in genes involved in this pathway disturb the interaction between surface-located epithelial cells and the underlying mesenchyme<sup>7</sup> during embryonic development which causes alterations of the initiation, formation, and differentiation of skin appendages.

The most frequent form of HED results from mutations in EDA1 gene, located on chromosome Xq12-q13.1 encoding the ligand ectodysplasin A-A1 (EDA-A1) (MIM#300451). Mutations in Eda receptor encoding by gene EDAR, located on chromosome 2q11-q13 (MIM#604095), or in the Edar-associated death domain encoding gene EDARADD, located on chromosome 1q42-q43 (MIM#606603), have been implicated in the autosomal recessive and dominant HED forms, respectively.<sup>8</sup>

According to Trzeciak *et al.* (2016),<sup>5</sup> there have been 345 reported cases of HED, of which 206 are due to EDA gene mutations. Until 2017, the Human Gene Mutation Database (HGMD Professional 2017.2) has registered 314 mutations in EDA gene. Table 1 shows the mutation types reported on HED patients involving this gene. As can be observed, the most frequent mutation type is the missense/nonsense which consists of single base-pair substitutions in coding regions.

### Clinical Manifestations

As it was mentioned, the main HED-clinical characteristics include hypohidrosis, hypodontia, and hypotrichosis. The male affected

**Table 1** EDA gene mutations reported until 2017 according to the human gene mutation database professional 2017.02

Mutation type	Number of mutations reported
Missense/nonsense	176
Splicing	28
Small deletions	47
Small insertions	20
Small indels	5
Gross deletions	33
Gross insertions	5

newborns may exhibit a collodion membrane and an intense scaling as in ichthyosis. The newborns may suffer increases in central temperature that leads them to develop febrile seizures. The patients have problems with the thermoregulation due to a reduction in the ability to sweat causing overheating, particularly in Summer season and/or geographical regions with high average temperature,<sup>9,10</sup> resulting in about 30% mortality rate in early childhood.<sup>11</sup> In fact, the children that we reported<sup>10</sup> had to take showers every hour to decrease their body temperature. They also had a history of frequent hospitalization due to high fevers during infancy.

The hair is thin scalp, sparse, light-colored, and fragile. The patients show generalized hypotrichosis and may have mosaic patchy distribution of body hair; in the pubis and axilla, the hair is sparse; in addition, there may be eyebrows and eyelashes missing. The skin is thin, pale, dry, and exfoliating like ichthyosis, with hypopigmentation. The skin from around the eyes and mouth shows linear wrinkled and is hyperpigmented. Other manifestations include dryness of eyes, airways, and mucosal membranes due to the defective development of exocrine glands (Fig. 1a).

The patients show hypodontia or anodontia. The teeth are small, conical, bulbous or taurodontic, and widely spaced. The enamel is prone to caries and mechanical damage. There could be atrophic inflammation of oral cavity mucosa, a hoarse voice, and, sometimes, swallowing difficulties (Fig. 1b).

Some patients may exhibit dysmorphic features like prominent forehead, forehead bumps, rings under the eyes, hypertelorism, epicanthic fold, everted nose, depressed nasal bridge, prominent lips, and prognathism. The skin on palms and soles shows characteristic dermatoglyphic patterns. Moreover, we recently reported a family that presented feet with broad toes, short and widely spaced, with wide and thick tips, with convex, hypoplastic, unpolished and thin toenails, besides mild or severe plantar-fissured hyperkeratosis (Fig. 1c, d).<sup>10</sup>

Female carriers showed defective dentition or a patchy distribution of sweating. Some physical signs are overt with sparse, patchy scalp hair or with marked hypodontia. These heterozygote patients may exhibit abnormal skin temperature patterns consistent with altered peripheral vascular perfusion and mosaic hypohidrosis.<sup>12</sup> The heterozygote patients could be identified by the starch and iodine sweat testing; if this test is performed on backs of females, it generates V-shaped patterns of streaks that conformed the lines of Blaschko. In the heterozygous female, expression of the symptoms varies considerably due to different levels of inactivation of the X-chromosome.<sup>13</sup>

### Diagnosis

HED can be diagnosed after infancy on the basis of physical features. Identification of a hemizygous EDA pathogenic variant in an affected male or biallelic EDAR, EDARADD, or WNT10A pathogenic variants in an affected male or female confirms the diagnosis.



**Figure 1** Clinical phenotype of the XL-HED patients. (a) Facial features including hypotrachosis with hypo pigmentation of hair, scanty eyelashes and eyebrows, low implanted ears, and skin pigmentation in the nasolabial region. (b) Oral manifestation shows conical and widely-spaced teeth. (c) Feet features including broad, short, and widely-spaced toes with wide and thick ends. Nails are convex, hypoplastic, unpolished, and thin. (d) Severe plantar fissured hyperkeratosis

HED patients show hypohidrosis or anhidrosis of the hands which is deduced by the scarcity or absence of purple color after starch-iodine test; however, they may have Blaschko lines on back (Fig. 2a–c). Normal subjects had purple color in their hands, making it clear they have enough sweat glands (Fig. 3a–c). The histopathology analysis of skin biopsies from the hypothenar region in HED patients showed compact orthokeratotic hypertrophy of the *stratum corneum* as well as moderate acanthosis of interpapillary processes could be found. The papillary dermis showed a mild lymphocyte infiltrate, and atrophic or immature eccrine sweat glands could be observed in the reticular dermis. Carriers exhibited orthokeratotic hypertrophy of the *stratum corneum*, and reticular dermis shows mixed, normal, and hypotrophic sweat glands with diminished subcutaneous fat. A non-HED patient shows no alterations of these structures. The molecular diagnostic is the key to find the cause of ED since there are several genes that could be responsible for the clinical manifestation, as mentioned early, mutations on EDA gene generate the majority of HED cases. The search for mutations in any of the genes involved on EDA pathway is made by DNA genotyping through direct sequencing of each exon from the genes that participate in this pathway. Whole exome sequencing (exome-seq) is a new technology that enables rapid detection of mutations in exons across many patients. Exome sequencing can be used to search for mutations in any of the genes involved in HED phenotype, constituting a better option for molecular diagnosis.

## Treatment

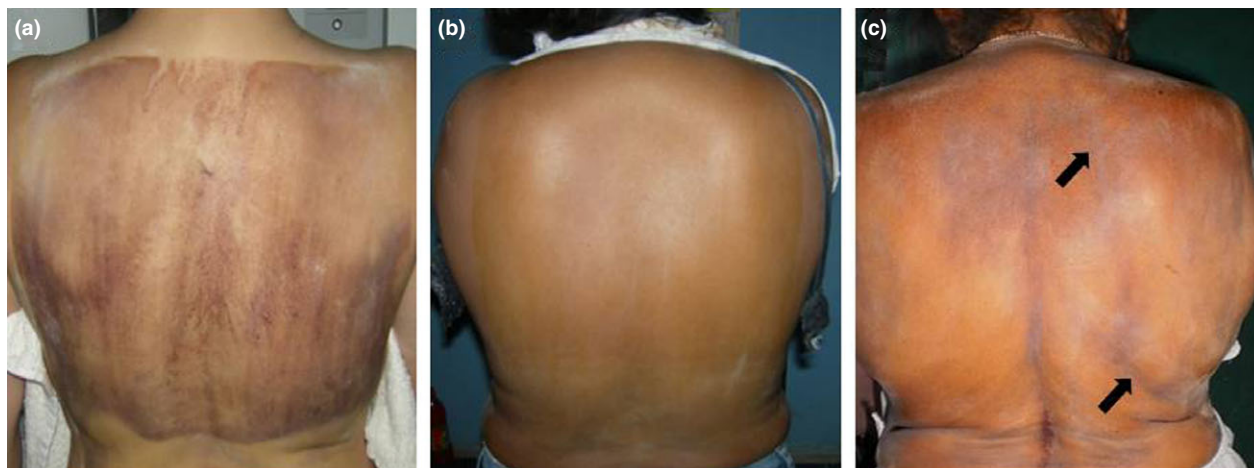
To date no gene therapy for humans has been reported for this disease. However, there are some reports in HED animal models showing evidence for a potential short-term treatment with a

recombinant ectodysplasin protein that can correct some of the developmental genetic defects observed in HED patients.<sup>14–17</sup> Unfortunately, there is not much that medicine can offer to HED patients. Treatment involves some general medical actions such as avoidance of overheating through wetting the skin several times a day, and application of some skin care products (moisturizing creams) is useful for management of eczema, rashes, and for dry skin.<sup>18</sup> Teeth abnormalities may be corrected by prosthetic treatment.

## Molecular Bases of Ectodermal Dysplasias

HED is caused by mutations in at least one of several genes: *EDA1*, encoding ectodysplasin A (EDA), *EDAR*, coding for Eda receptor, *EDARADD*, EDAR-associated death domain protein, and *NEMO* (NF $\kappa$ B essential modulator) that indirectly activates the nuclear factor  $\kappa$ B (NF $\kappa$ B). Both the *EDA1* and *NEMO* genes are localized on the X chromosome, and the other genes encoding components of the TNF $\alpha$  related signaling pathway involved in differentiation of skin appendages are localized on autosomes. There has been significant progress in understanding the pathogenesis of HED mainly due to the discovery of the proteins that participate in signal transduction from TNF $\alpha$  related pathway since mutations on these genes are responsible for systemic tooth agenesis and defects on the other ectodermal structures.<sup>5,19,20</sup>

The *EDA1* gene encodes for different transcripts, although the Eda-A1 and Eda-A2 are the isoforms with biological relevance.<sup>7</sup> These transcripts differ from each other by two amino acids that are generated according to the site of splicing. They are transmembrane type II proteins with the C-terminus projecting outward. This protein region of Eda-A1 and Eda-A2 (last 62



**Figure 2** Starch-iodine test on back. (a) Healthy control; (b) Carrier showing hypohidrosis; (c) Carrier showing Blaschko lines (black arrows)

or 60 amino acids, respectively) is highly homologous to the C-terminal sequence of TNF $\alpha$  receptor ligands.<sup>21</sup>

Eda-A1 encodes for a 391 amino acid residues protein produced as a trimeric type II transmembrane protein. Ectodysplasin has a short collagen domain and a TNF domain in its extracellular region suffering a furin-mediated proteolytic cleavage near the collagen domain that release it from cell surface, a stalk region of uncharacterized function, a short positively-charged sequence required for interactions with heparin-sulfate proteoglycans and a 150 amino acid residues long C-Terminal TNF homology domain (THD) responsible for receptor binding.<sup>22</sup>

EDA mutations identified in HED patients comprise particular regions of the protein that are important to its function. Some lie at the beginning of the stalk region. The second region is the furin consensus cleavage site, showing the importance that ectodysplasin must be released to a soluble form to be active. Third, the mutations in the THD region interfere both with the trimer formation or the receptor binding. Mutations in the collagen domain interfere with the capacity to keep the Eda trimers in close proximity, compromising its ability to stimulate Edar signaling. Finally, the proteoglycan-binding domain could restrict Eda diffusion in tissues once it is released in the soluble form (Fig. 4).<sup>22</sup>

Eda-A1 and Eda-A2 contain the THD that interact with receptors with an identifying biological activity, and both isoforms are functionally important and critical for EDA pathology.<sup>23</sup> Eda-A1 binds to Edar, while Eda-A2 (two amino acids shorter with respect to A1 isoform) interacts with Xedar, another TNF receptor family member.<sup>24</sup>

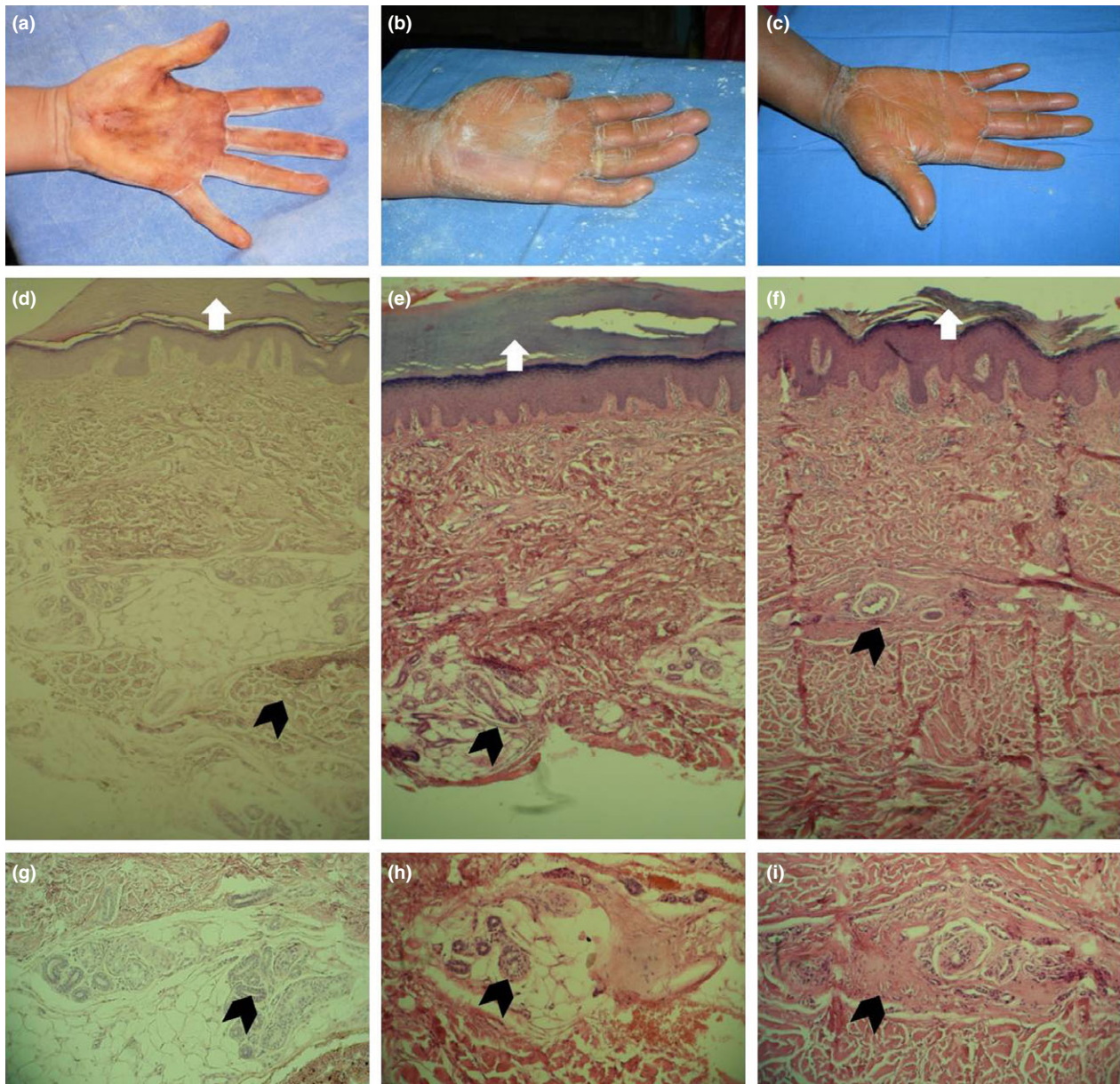
The Eda ligands form active ligand-trimers comparable to those seen for other TNF ligand family members.<sup>7,25</sup> Eda-A1 protein binds and activates Edar, while Eda-A2 signals via Xedar (member of the TNF receptor superfamily).<sup>24</sup> Any type of EDA gene mutation found in TNF, collagen, furin, and transmembrane protein domain could cause HED syndrome.<sup>26</sup>

Ectodysplasin is an early regulator of placode formation that acts downstream of the primary inductive signal. Upon initiation of skin appendage development, expression of the Eda receptor Edar becomes restricted to the placodes, whereas Eda shows complementary expression in the flanking epithelium.<sup>25</sup> Edar activates the transcription factor NF $\kappa$ B. The trimeric Eda binds to Edar receptor which recruits the EDARADD mediated by death domains (DD) present in both proteins.<sup>27</sup> The other DD-containing TNFR (tumor necrosis factor receptor) members are able to induce cell death.

The DD region is responsible for Edar binding to its cytoplasmic signaling adaptor EDARADD. EDARADD links Edar to downstream pathways via TNFR-associated factors (TRAFs), the adaptor molecules utilized by different TNFRs. Although EDARADD can bind to several TRAFs, its signaling *in vivo* is mostly dependent on Traf6.<sup>28</sup> EDARADD is co-expressed with Edar in epithelial cells during the formation of skin appendages.<sup>5</sup> The interaction between Edar-ADARADD strongly activates the NF $\kappa$ B pathway and weakly activates the JNK pathway.<sup>19</sup> Participation of TRAF2 is also suspected since EDARADD contains a TRAF2-binding sequence in addition to a TRAF6-binding sequence.<sup>29</sup>

In the case of Eda-A2, this protein interacts with Xedar leading to an interaction with TRAF3 and/or TRAF6, promoting the activation of both c-Jun N-terminal kinase (JNK) and NF $\kappa$ B pathways.<sup>30</sup>

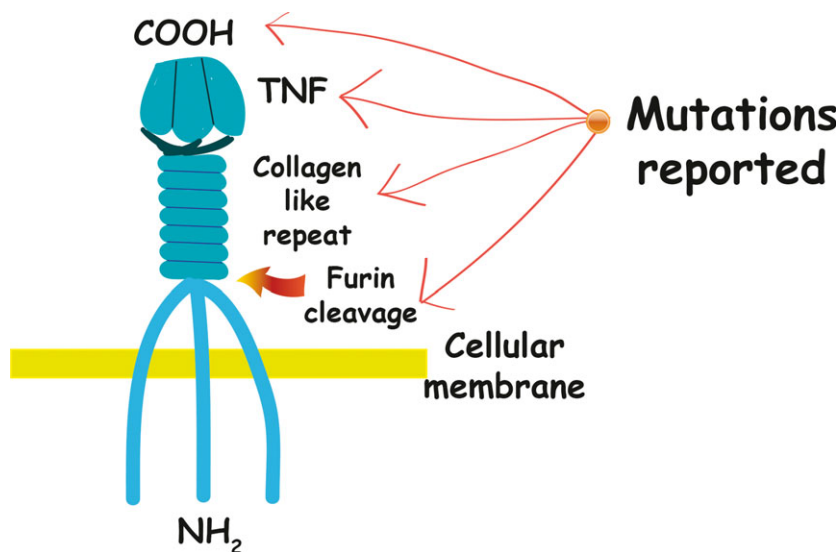
When TRAF6 is activated, it recruits TGF $\beta$ -activated kinase (TAK1)-binding protein 2 (TAK2) that links TRAF6 to TAK1; this interaction leads to its activation which stimulates I $\kappa$ B kinase (IKK) complex,<sup>29</sup> a key step in the canonical NF $\kappa$ B pathway. In cytoplasm, I $\kappa$ B proteins sequester NF $\kappa$ B. The release of NF $\kappa$ B is generated by activation of the IKK complex, composed of two kinase subunits (IKK1/ $\alpha$  and IKK2/ $\beta$ ), along with an obligate regulatory component NEMO (or IKK $\gamma$ ), leading to phosphorylation and degradation of I $\kappa$ B.<sup>31</sup> This complex phosphorylates the downstream I $\kappa$ B complex leading NF $\kappa$ B to the nucleus to activate its responsive genes.



**Figure 3** Starch-iodine test in hands and histopathology skin biopsies. (a) Hand of a relative female from HED patient as a control shows normal hidrosis, with purple color of sweat reacting with iodine-starch; (b) Carrier with hypohidrosis; (c) HED patient with hypohidrosis; (d) and (g) Biopsy of a non-HED family related subject shows epidermis with orthokeratotic hypertrophy of *stratum corneum* (white arrow), and sweat eccrine normal gland (black arrowhead). (e) and (h) biopsy of a carrier shows epidermis with orthokeratotic hypertrophy of *stratum corneum* (white arrow), and normal and hypotrophic eccrine sweat glands (black arrowhead). (f) and (i) biopsy of an HED patient shows epidermis with orthokeratotic hypertrophy of *stratum corneum* (white arrow), and immature or atrophic eccrine sweat glands (black arrowhead). (d), (e) and (f)  $\times 10$ ; (g), (h) and (i)  $\times 25$

The alterations in *EDA1*, *EDAR*, and *EDARADD* genes account for almost 90% of HED cases. These three forms are clinically indistinguishable, probably because they alter a single signal transduction pathway but differ in their inheritance patterns.<sup>6</sup> All these factors are upstream of NEMO-IKK.

Incontinentia pigmenti (IP) is associated with malfunctions of NEMO because most of the identified mutations lead to a truncated NEMO.<sup>32</sup> A total of 70–80% of IP patients carry the same genomic deletion of *IKBK*G from exon 4–10 caused by a recurrent genomic rearrangement that involves a pseudo-NEMO gene located nearby.<sup>33,34</sup>



**Figure 4** Representation of ectodysplasin. Schematic representation of the trimeric form of ectodysplasin with the TNF domain, the furin-mediated proteolytic cleavage site, and the collagen domain. The arrows indicate the sites where most mutations have been observed

Thirteen mutations have been identified in exon 10 of NEMO/IKBKG gene in IP patients.<sup>35</sup> From those mutations, only two are also related to EDA-ID (frameshifts c.1167dup and c.1183\_1184del) and one to OL-EDA-ID (nonstop c.1259A>G). Despite current research of NEMO-associated diseases IP and EDA-ID, they cannot be precisely distinguished because distinct geno- and phenotypes of EDA-ID cannot be assigned confidently to these diseases.<sup>32,36</sup> It should be noted that the symptoms of HED due to in-frame mutations in NEMO are often accompanied with immunodeficiency and incontinentia pigmenti (EDA-ID, IP). In mutations that lead to truncation of NEMO, the immunodeficiency is accompanied by osteoporosis and lymphedema (OL-EDA-ID).<sup>5</sup>

EDA signaling activates the canonical NF $\kappa$ B pathway for skin appendage formation (Fig. 5). The activation of NF $\kappa$ B is essential to Edar signaling leading to skin appendage development.<sup>37</sup> The inhibition of this pathway through I $\kappa$ B $\alpha$  in transgenic mice results in a phenotype similar to HED.<sup>38</sup> In addition to EDA, EDAR, and EDARADD, other molecules of EDA pathway have been implicated with HED.<sup>39</sup>

The genetic studies demonstrate the importance of the ectodysplasin-EDAR-EDARADD-TRAF6-NEMO-I $\kappa$ B $\alpha$ -NF $\kappa$ B signaling pathway in skin appendage development, apparently working through the NEMO/I $\kappa$ B $\alpha$ .<sup>7</sup>

The implication of NF $\kappa$ B signaling in ectodermal appendages is quite interesting because this factor is well known for its major role during inflammation and immunity, acting downstream of the activation of TNF immune receptors,<sup>39</sup> contrasting with its role when it is activated by EDA pathway, where it does not seem to induce inflammation. However, recent data suggests the participation of the EDA pathway in the induction of chemokines transcription.<sup>40</sup>

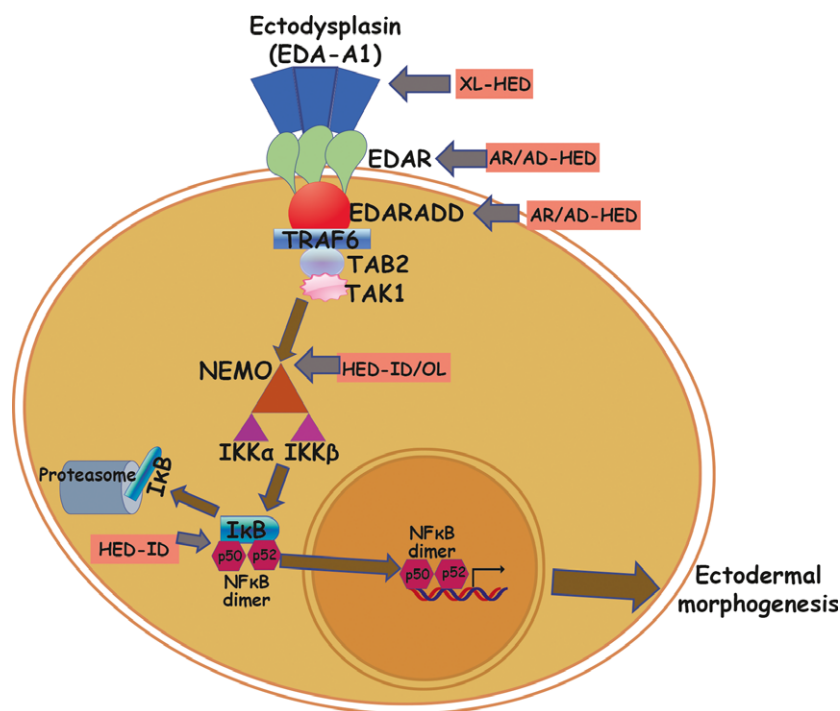
The organs affected in ectodermal dysplasias develop as ectodermal appendages. Their development is regulated by

interactions between the epithelium and mesenchyme through a sequence of inductive signals. The interaction between these two adjacent embryonic layers constitutes the mechanisms of organ-specific morphogenesis and regulates many types of cellular functions including proliferation, differentiation, and cell death. All these functions and interactions are mediated by signaling molecules.<sup>37</sup>

Defects in EDA pathway affect the development of ectodermal appendage and generally do not avoid it. Instead, these appendages typically present defects in shape, size, position, or number in the organism.<sup>27</sup> The onset of skin appendage formation is marked by the development of placodes. This placode then invaginates to form a bud. For example, the hair follicle bud grows rapidly downwards and encases a cluster of dermal cells that form the dermal papilla.<sup>37</sup>

There are many reports showing that placodes development is the result of complex reciprocal interactions between different pathways including the Wnt, FGF, BMP, and EDA signaling.<sup>19,25</sup> During early development, Eda and Edar are colocalized in the simple ectodermal sheet covering the embryo. At this stage of development, the EDA expression and its downstream targets are strictly confined to placodes.<sup>20</sup> Overexpression of EDA increase the size of placodes,<sup>41</sup> while the absence of Edar signaling generates a rudimentary pre-placode formation.<sup>8</sup> Interestingly, ectopic tooth and mammary placodes and consequently supernumerary organs are induced in mice overexpressing EDA gene.<sup>41,42</sup> In the case of mammary gland, this is through the ectodysplasin/NF $\kappa$ B pathway that potentially activates several Wnt pathway components.<sup>42</sup> These data show that in addition to hair follicles, Eda-A1 is also involved in the initiation of mammary glands and tooth development involving different pathways.

Finally, the phenotype of HED patients in which EDA signaling is inhibited indicates the pathway is required for normal



**Figure 5** EDA signaling pathway. The EDA-EDAR interaction results in the activation of the NF $\kappa$ B pathway implicated in the ectodermal appendages development. XL-X linked; AR, autosomal recessive; AD, autosomal dominant; ID, immunodeficiency; OL, osteopetrosis and lymphedema; HED-ID/OL, hypohidrotic ectodermal dysplasia-Immunodeficiency/Osteopetrosis and lymphedema; HED-ID, hypohidrotic ectodermal dysplasia-Immunodeficiency

development of ectodermal organs including hair, teeth, and exocrine glands. Moreover, members of EDA pathway are expressed in different tissues besides ectodermal organs, suggesting the existence of redundant TNF pathways in other tissues.

### Concluding Remarks

Accumulated evidence indicates that development of skin appendages is driven by some signaling pathways that are activated through different developmental stages. The EDA pathway is specific for ectodermal appendage development where it controls the fine-tune growth. This characteristic possibly allowed it to regulate the morphological changes during evolution, because the activation of this pathway is not vital and therefore could be modified without causing lethal effects. The function of EDA during placode formation is known in detail as well as the role of NF $\kappa$ B downstream of Edar activation. Obviously, the target genes in the EDA pathway could be excellent candidates in searching for novel genes causing ectodermal dysplasia.

However, several questions remain. What other genes could be regulated by EDA, and could these genes be candidates for some manifestations in HED patients? Could the genes targeted by EDA pathway be involved in the development of different ectodermal organs or being novel candidate genes for ectodermal dysplasia? As more and more targets of EDA are recognized, the understanding of the functions of EDA pathway will probably increase in the near future, in part due to modern genetic and genomic tools.

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