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REVIEW

Ectodermal Dysplasias: A Clinical and Molecular Review☆

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Abstract The ectodermal dysplasias are a large group of hereditary disorders characterized by alterations of structures of ectodermal origin. Although some syndromes can have specific features, many of them share common clinical characteristics. Two main groups of ectodermal dysplasias can be distinguished. One group is characterized by aplasia or hypoplasia of ectodermal tissues, which fail to develop and differentiate because of a lack of reciprocal signaling between ectoderm and mesoderm, the other has palmoplantar keratoderma as its most striking feature, with additional manifestations when other highly specialized epithelia are also involved. In recent decades, the genes responsible for at least 30 different types of ectodermal dysplasia have been identified, throwing light on the pathogenic mechanisms involved and their correlation with clinical findings.

PALABRAS CLAVE
Genodermatosis;
Displasia ectodérmica;
Factor Nuclear kappa B;
Ectodisplasina;
Proteína p63

Displasias ectodérmicas: revisión clínica y molecular

Resumen Las displasias ectodérmicas son un amplio grupo de trastornos hereditarios que se caracterizan por la alteración de estructuras derivadas del ectodermo. Aunque algunos de estos síndromes poseen características específicas, determinados rasgos clínicos son comunes en muchos de ellos. De modo general, se diferencian 2 grupos de trastornos: uno caracterizado por la aplasia o hipoplasia de los derivados ectodérmicos, que fracasan en su desarrollo y diferenciación por la ausencia de señales recíprocas específicas entre ectodermo y mesénquima, y otro en el que la característica más llamativa es la queratodermia palmoplantar, que se presenta en asociación con otras manifestaciones cuando se afectan otros epitelios altamente especializados. En las últimas décadas se ha logrado identificar el gen responsable en al menos 30 entidades, permitiéndonos entender los mecanismos patogénicos y su correlación con la clínica.

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Introduction

The ectoderm is one of the primitive embryonic components. At around the third week of development, it undergoes a subdivision into the neuroectoderm, the origin of the nervous system, and the ectoderm, which will envelop the entire embryonic surface and form the epidermis, epidermal appendages, and tooth enamel. The ectoderm therefore gives rise not only to hair, teeth, nails, and sweat glands, but also to the central nervous system, peripheral nervous system, eyes, ears, and nose, as well as the eccrine, mammary, and pituitary glands.[1] During development, the ectoderm undergoes complex interactions with the mesoderm, so ectodermal disorders may lead to abnormalities in mesodermal structures such as the musculoskeletal and genitourinary systems.[2]

Ectodermal dysplasias (EDs) are a heterogenous group of hereditary disorders characterized by certain shared structural and functional abnormalities in tissues derived from the ectoderm. Most of these diseases are also associated with an abnormal development of structures derived from the mesoderm and, occasionally, mental retardation. They are considered rare conditions, with an estimated incidence of 7 cases per 10 000 births.[3] They can be transmitted by any of the possible Mendelian inheritance patterns,[4] and although many share certain clinical characteristics, some syndromes have specific clinical findings. To date, approximately 200 such conditions are known, and the causative gene mutation has been identified in around 30. Mutations in only 4 genes (*EDA1*, *EDAR*, *EDARADD*, and *WNT10A*) are responsible for most cases of ED.[5]

Historical Perspective

The first descriptions of clinical cases that might correspond to what we would now classify as ED date from 1792.[6] In 1848, Thurman defined anhidrotic ectodermal dysplasia (also known as hypohidrotic ectodermal dysplasia [HED]) as a condition in its own right.[7] Subsequently, similar cases were reported, such as the one presented by Weddernhorn and published in 1875 by the naturist Charles Darwin: ''I may give an analogous case, communicated to me by Mr. W. Weddenburn, of a Hindoo family in Scinde, in which ten men, in the course of four generations, were furnished, in both jaws taken together, with only four small and weak incisor teeth and with eight posterior molars. The men thus affected have very little hair on the body, and become bald early in life. They also suffer much during hot weather from excessive dryness of the skin. It is remarkable that no instance has occurred of a daughter being affected. . .though the daughters in the above family are never affected, they transmit the tendency to their sons: and no case has occurred of a son transmitting it to his sons. The affection thus appears only in alternate generations, or after long intervals.''[8] The above case described by Darwin corresponds to what we would describe today as X-linked HED, a term coined by Weech in 1929.[9]

Classification of Ectodermal Dysplasias

The classification of EDs is complex, and classification systems have come and gone in an attempt to accommodate clinical and genetic data.[10–15] Biomolecular findings have enabled the identification of the causative mutations that become manifest through 2 broad pathogenic mechanisms, associated with specific clinical features. Using these mechanisms as a starting point, in 2009, Priolo[2] established a clinical-functional classification, which will form the basis for this review. The author proposed the definition of 2 groups of disorders (Fig. 1).

Group 1

Group 1 corresponds to disorders in which defective interaction between the ectoderm and the mesenchyme is apparent. Two pathophysiologic mechanisms have been identified:

1. Changes in the signaling pathways that modulate activity of nuclear factor (NF) κB (ectodysplasin/ectodysplasin-A [EDA] receptor [EDAR]/EDAR associated death domain [EDARADD] signaling pathway and NEMO [NF-κB essential modulator] regulatory pathway).
2. Regulatory changes in transcription and/or expression of genes such as *p63*, *DLX3*, *MSX1*, *EVC2*, and *EVC*.

The resulting clinical phenotype is hypoplasia or aplasia of structures derived from the ectoderm. Development and differentiation of these structures fail due to the absence of specific reciprocal signals between the ectoderm and the mesenchyme (Table 1).

Group 2

Group 2 corresponds to disorders in which there is abnormal function of a structural protein in the cell membrane. Examples of structural proteins include nectin 1, connexins, and plakophilin, whose role in adhesion and cell-cell communication is essential for maintaining tissue homeostasis and controlling cell growth, development, and response to different stimuli.

Clinically, these disorders are mainly characterized by skin abnormalities such as palmoplantar keratoderma, with or without involvement of highly differentiated epithelia associated with deafness or retinal dystrophy (Table 2).

Group 1

Changes in the Signaling Pathways That Modulate NF-κB Activity

Ectodysplasin/EDAR/EDARADD Pathway

EDA, which consists of 391 amino acids, is a type 2 transmembrane protein belonging to the tumor necrosis factor (TNF) family.[16] The most biologically important isoforms of EDA are EDA-A1 and EDA-A2.[17] EDA-A1 binds to the EDA receptor (EDAR), whereas EDA-A2 binds to the X-linked EDAR A2 ligand (Fig. 2).[18] EDAR is a type 1 transmembrane protein