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The Genetics of Ectodermal Dysplasia: A review

Saliha Samiullah[1*], Kifayat-ullah[2], Hina Ishtiaq[3]

[1]*Institute of Biochemistry, University of Baluchistan, Quetta, Pakistan*

[2]*Institute of Microbiology, University of Baluchistan, Quetta, Pakistan*

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Abstract

Ectodermal dysplasia is permeated by defected development of ectodermal layer. This ectoderm forms the organs of embryo like skin, hair, nails, teeth and sweat glands. It is a heterogeneous type of genetic syndrome. The aim of this works is signaling and morphogenesis of ectodermal organs. About more than 180 various types of ectodermal dysplasia prevail. Ranging from forbearing to acute, almost all types dispense certain common sign and might involve irregular digit nails, fragile, scarce or lacking hair, denticle deformities, incapable to sweat and numerous skin diseases. Ectodermal dysplasia is caused by mutations in different types of genes. The divergent kinds of hereditament patterns ascertain, depends on the particular form of ectodermal dysplasia in a line include X-linked recessive, autosomal dominant, and autosomal recessive.

* **Corresponding Author:** Saliha Samiullah ✉ salihakhan67@gmail.com

Introduction

Ectodermal dysplasia's narrates huge and complex categories of disorders distinguished by abnormal growth of the skin and appendages (Nails, Hairs, Sweet glands, and teeth's). They are associated with different organs developing from the primordial external germ layer. Among Species developmental mechanisms are conserved eminently (Chuong *et al*., 2001). Freire-Maia explained 117 possible variations of ectodermal dysplasia expressed by all possible inheritance (Mendelian modes). Freire-Maia redefined it as a pathogenic developmental defect that influence the ectoderm at the embryologic level, hence the structure and tissues derived from it. Thus, the epidermis is affected by it and it is responsible for causing aberrations and development of keratinocytes in sebaceous glands, hairs, nails, eccrine, teeth and apocrine glands, lenses conjunctiva of eye, nipples, anterior pituitary gland and the ear (Deshmukh and Prashanth, 2012).

Ectodermal dysplasia may arise isolated or related with other clinical manifestations. In ectodermal dysplasia, some syndromic forms are identified by particular clinical features (Itin and Fistarol, 2004). The group of genetic disorders forms the ectodermal dysplasia syndromes that are recognized by the weak insufficient function of at least two derivatives of the ectoderm such as Hair, Teeth, Sweat glands and Nails.

The possible pathologies may comprise trichodyplasias, dental anomalies, dyshidrotic and onychodysplasias (Kaercher, 2004). Many ectodermal dysplasia cases were revealed in recent years with noticeable overlapping phenotypes in disorders that were assessed to be different (Bertola *et al*., 2000).

Ectodermal dysplasia

Hypohidrotic Ectodermal Dysplasia (HED)

It is also known as CHRIST-SIEMENS-TOURAINE SYNDROME and the hypohidrotic form appears in the classic triad hypohidrosis/anhidrosis (sweat glands), Hypotrichosis hair and hypodontia/anodontia teeth. Males are severely affected, whereas females reveals insignificant defects and in patchy distribution. The disease is usually inherited as autosomal recessive disorder. Protruding lips, hyper keratinized skin about eyes, hyperthermia, dryness of skin, air ways, eyes, converse nose and prominent forehead are associated with hypohydrotic ectodermal dysplasia (Ahmad, 2018).

Hypohidrotic ectodermal dysplasia is most commonly disseminated in an X-linked recessive fashion; dominant transmission and autosomal recessive also appears. All participants' genes encode proteins in a single signaling pathway. Ectodysplasin-A (MIM#300451), the tumor necrosis factor ligand superfamily member, was recognized as the influenced protein coded in the Xq12-q13.1 region. Ectodysplasin-A is expressed in adult skin, normal fetal, hair and in adult teeth. The autosomal recessive form, localized to 2q11-q13, was linked with receptor that is defected for ectodysplasin-A, EDAR (MIM604095), a Trans-membrane protein. Recently in families a third genotype was recognized i.e. affected by HED and immunodeficiency (Rouse *et al*., 2004).

Hidrotic ectodermal dysplasia

HED (hidrotic ectodermal dysplasia) further more studied as Clouston syndrome, a sporadic autosomal ascendant condition. Hyperkeratosis of soles and palms, alopecia and nail dystrophy is the medical features of this disorder. Patients of HED usually have normal teeth and sweat glands (Yang *et al*., 2016).

Components of ectodermal signaling

Organogenesis in utmost organs is started by the signals supplied by mesenchyme, and it known as the "first dermal message" to make epithelial appendages. First dermal messages evenly expressed all over the mesenchyme has been described by reaction-diffusion model a certain by the molecular indicators, both the positive and negative placodes controllers outcomes are activated. The information for placodes formation may be induced by mesenchyme or preplacode by its very nature which affects initiation or placodes

growth. Presently BMP Bone morphogenetic protein is paramount placode clogs. First dermal message identity is unknown Wnt (Wingless/Integrated) family is suspected to be involved. Wnt signaling inhibited by Dickkopf-1 protein stops tooth, mammary gland development and hair (Pispa *et al*., 2003).

Ectodysplasin (TNF family representative) in Ectodermal Structures as New player

Ectodermal dysplasia (developmental syndrome) particularly damages the ectodermal organs. HED (hypohydrotic ectodermal dysplasia) patients and mouse models (Tabby (Ta), downless (dl), and crinkled (cr)) have defective hair, teeth, lacrimal glands, salivary glands and sweat gland (Blakes *et al*., 2002). Mutant genes are associated to TNF (TUMOR NECROSIS FACTOR) signaling pathway: EDA (ectodysplasin), TNF ligand, Edar (its receptor), and Edaradd intracellular adaptor protein (Mikkola and Thesleff, 2002).

ED Signaling

New tumor necrosis factor (TNF) (MIM191160) pathways and ectodysplasin pathway discovery in past few years playing important role in development of embryonic layers. Deformity syndrome called HED (hypohidrotic or anhidrotic ectodermal dysplasia) is the result of mutations in the signaling pathway components. Most common form of HED is X-linked hypohydrotic ectodermal dysplasia in approximately 150 clinically marked hereditary ectodermal dysplasia which is caused by the mutations in TNF ligand ectodysplasin protein (product of ED1 and Eda gene). Signaling of Eda-EDAR controls developing and functioning of ectodermal placode and initiating the development of ectodermal organs. In several other signaling pathways of placodes progresses it lies upstream (Mikkola and Thesleff, 2003).

Hair signaling

Signals from the embryonic epidermis initiates the morphogenesis of hair follicle that commands over ectoderm for initiation of placode genesis. Messages are sent back by placodes to core mesenchyme, here dermal contractions occur and signals are sent to epithelial keratinocytes for directive of follicular morphogenesis. To regulate the formation of ectodermal-mesodermal interaction for the formation of hair follicle effect signal molecules are same as for other epithelium projections. Mostly these signals are parts of four preserved families: hedgehog family (HH), WNT family, TRANSFORMING GROWTH FACTOR β family (TGFβ) and FIBRO BLAST GROWTH FACTOR (FGFs). Within the sections of ectodermal and mesenchymal tissues lateral signaling is facilitated by Notch pathway. In adult's implication and facilitation of hair cycles, most of the same signaling molecules are phrased (Laurikkala *et al.,* 2002).

Nail signaling

In developing human embryo day 14-15(E14-15), primitive nails begin to appear about dorsal surface. From the epidermis the nail fold lengthens and folds inmost to shield proximal nail plate. Nail matrix comprising of proliferating keratinocytes displace nail folds. Epithelial keratins (Krts) are expressed by keratinocytes dorsal to matrix and encounter apoptosis, and leaves nail plate keratinized. In keratinization initial stages Krt1(MIM139350) and Krt10(148080) are expressive Krt5(MIM148040) and Krt14(148040) replaces them that provide cytoskeleton of epithelium cell and foregather into transitional filament. Nail formation can be disturbed by the mutations in the resultant genes as these are cytoskeleton key component of distinguished nail plate. As the process of development starts spinous layer is prepared by the cells nearby nail matrix, division end, new set of fundamental proteins and enzymes characteristic of nail plate begins to synthesize. Krt33, Krt39 (MIM616678), Krt34 (MIM602763), Krt6A (MIM148041), Krt17 (MIM148069), Krt81 (MIM602153) Krt86 and Krt85 (MIM601928), are the further more Krts in nail matrix expression. For the development of nail detailed molecular initials and timing are uncertain, ectodermal projections are somewhat implicit and are dependent on several signaling pathways (Cui *et al*., 2013).

Tooth signaling

Resembling other ectodermal organs, series of interaction takes place meant for the development of tooth, these interactions occur between early ectodermal and mesodermal layers in mammalian embryo. Mesenchyme cell negotiation with epithelium includes ligand-receptor interactions which initiate transcriptional reprogramming essential for tooth growth. About 7th week thickening of oral epithelium occur that is first sign of embryonic tooth development.

This epithelium thickening introversion inlays key (NEURALCREST) mesenchyme. Invagination of epithelium is condensed around by this mesenchyme to form tooth bud about 13th day. Epithelium wraps itself around condensing mesenchyme by extending afar in mesenchyme for cap formation at E14 and at E16 bell-stage tooth germ. Signaling center formed at the tip of late bud identified as enamel knot controls the process. Finally in late-bell stage mesenchyme is entirely surrounded by epithelium invagination at E18. Cell differentiation occurs in the bell phases of tooth growth. Through epithelial cell adjoining to dental mesenchyme distinguishing by way of enamel fabricating ameloblasts, the neighboring mesenchyme cells differentiates as dentin-producing odontoblasts (Tucker and Sharpe, 2004).

Conclusion

Abnormalities in genes or chromosomes cause genetic disorders, many heritable disorders in humans and mutations causing diseases have been recognized in many genes by the discovery of the molecular genetic techniques applications and model organism, consanguinity has provided us opportunity to classify ectodermal dysplasia at molecular or clinical level. Ectodermal dysplasia is a rare disorder affecting one person in every thousands or millions. The different kinds of hereditary Ectodermal dysplasia includes X-linked recessive, autosomal dominant and autosomal recessive.

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