Ectodermal dysplasia: a case report and molecular review

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ABSTRACT

The term 'Ectodermal dysplasia' refers to a group of heterogenous hereditary disorders characterized by abnormalities in ectodermal derivatives. Given its varied presentation, there have been a number of classifications for ectodermal dysplasia over time. However, the recent clinical-functional classification by Priolo has given due cognizance to the bio-pathogenic mechanisms of this disorder. This paper presents a case of hypohidrotic ectodermal dysplasia and focuses on various genes and their pathways identified in the past decade.

KEYWORDS: Ectodermal dysplasia, ectodysplasin receptor, NF-κB, taurodontism

Citation: Sood A and Mishra D. Ectodermal dysplasia: Case report and molecular review. Polymorphism 2020; 6: 26-32.

INTRODUCTION

Ectodermal dysplasias (EDs) comprises of a heterogenous group disorders which share the anomalies of the classical ectodermal structures (hair, teeth, nail and sweat glands). The EDs are also known to involve epidermal appendages, organs and other systems. First described by Thurnam in 1848 (Thurnam 1848), the umbrella term now comprises of more than 180 types of EDs. Numerous classifications of ED are seen in the literature given the wide variety of phenotypic presentations. Freire-Maia's clinical classification based on the phenotype segregates ED into two types based on the involvement of classical ectodermal structures. This numerical system (1-2-3-4) allows focusing on distinctive features of ED and facilitates diagnosis (Visinoni et al. 2009). However, it did not consider variability of gene expression and thus included anomalies which represented different phenotypes of the same entity. Priolo and Lagana's clinical-genetic classification in 2001 attempted to bridge the gap between clinical and molecular findings (Priolo and Laganà 2001). Priolo's 2009 classification furthered this concept and was based on clinical and molecular-functional mechanisms. The classification considered the evidence of involvement of mesodermal structures and altered ectodermal-mesenchymal signaling in the development of ED (Manuela Priolo 2009).

In 2017, an international advisory meet at the National Institutes of Health in Bethesda, Maryland proposed a classification based on the mode of inheritance, genotype, phenotype and the molecular pathways. The authors explored the inter-relationships between the involved genes and their pathways (primarily: EDA associated genes, WNT associated genes and TP63 genes) and categorized ED conditions based on their molecular pathways. The authors believed that the classification system would be beneficial to both diagnostic as well as a genetics experts (Jt et al. 2019). It is quite pellucid that the classification systems and the molecular pathways hold the key to identify the association between genotype and its ensuing phenotype. The molecular pathways also hold the key to forming the treatment strategies. This article aims at highlighting the genes associated with EDs.

CASE REPORT

A 16-year-old female reported to the outpatient department of a tertiary referral institute with a complaint of multiple missing teeth. Extra orally, variegated hyperpigmented and hypopigmented regions were noted in the peri-oral, peri-ocular and nasal regions along with thin sparse hair, sparse/ partial eyebrows, dry skin, widened forehead and protruded lips (Figure 1A). Normal nails were present. Intra-oral examination revealed multiple missing teeth in the maxillary arch, edentulous mandible and a flattened shallow palate (Figure 1B, 1C). Orthopantomogram (OPG) revealed the absence of any impacted teeth with multiple missing teeth (Figure D). In addition, unilateral underdevelopment of breast was reported by the patient. Diagnosis of hypohidrotic ectodermal dysplasia was formed on the basis of clinical features according to Freire-Maia's clinical classification.

MOLECULAR REVIEW

Priolo's 2009 classification divided ED into two groups on the basis of pathogenic mechanisms: Group I comprise of conditions with defects in epithelial mesenchymal interaction. Two regulatory mechanisms have been identified in group I:

1. Involvement of NF-κB (nuclear factor κ beta) viaEDA/EDAR/EDARADD (ectodysplasin/ectodysplasin receptor/ EDAR-associated death domain) pathway and NEMO (NF-κB essential modulator) pathway.

2. Involvement of regulators of transcription and/or expression of genes, such as *p63*, *DLX3*, *MSX1*, *EVC2*, and *EVC*.

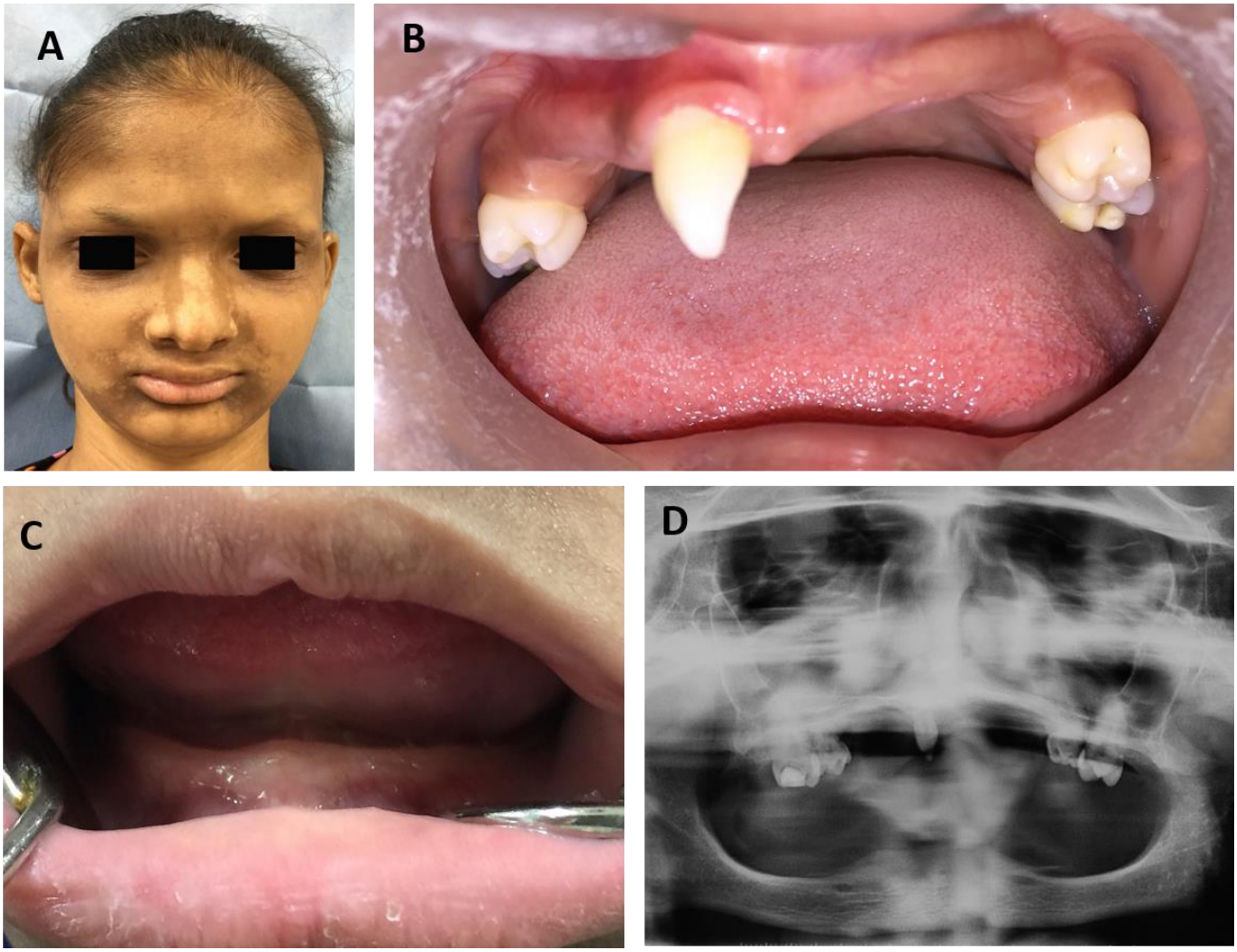

Figure 1. (A) Extra-oral presentation of the patient showing pigmented skin, thin sparse hair, sparse eyebrows, dry skin, widened forehead and protruded lips, (B) Intra-oral examination revealed multiple missing teeth in the maxillary arch, edentulous mandible, (C) Edentulous mandibular arch of the patient, (D) Radiology revealed complete absence of multiple teeth.

The targeted molecules in this group are involved in differentiation, apoptosis and cell survival. Group II comprises of disorders which exhibit anomalous function of structural proteins (e.g nectin, connexin, plakophilin); they are associated with dermatological abnormalities with or without the involvement of highly differentiated epithelia (Manuela Priolo 2009).

EDA associated genes and their molecular pathways have been included by Wright et al (Jt et al. 2019) in the recent 2017 classification due to its action in crucial developmental processes during the formation of epidermal appendages. *EDA1*, *EDAR*, *EDARADD* and *WNT10A* (wingless 10A) have been implicated with Hypohidrotic ED in Spanish, Turkish and Chinese populations (Cluzeau et al. 2011; Mc et al. 2019; G. Y et al. 2019; H. Y et al. 2020). *EDA1* is located on the X chromosome (locus Xq13.1) (Bayes et al. 1998) and is associated with X-linked hypohidrotic ED (Mc et al. 2019; X et al. 2020). Animal studies have revealed that deficient EDA1 signaling is associated with the failure of development of glands of nasopharynx and

auditory tube (A et al. 2016). *WNT10A* is located on chromosome 2q35 and belongs to the WNT family which are responsible for cell patterning during embryogenesis. *WNT10A* mutations have been associated with non-syndromic tooth agenesis (Mj et al. 2012) and Odonto-onycho-dermal dysplasia: rare form of ED (Krøigård et al. 2016). Classically, at least two of the classical ectodermal structures should be involved for clinical diagnosis of ED.
Amongst the other molecules of the WNT pathway: Heterozygous mutations in *KREMEN1* gene have been identified as the cause of ectodermal dysplasia (Issa et al. 2016; Intarak et al. 2018). In particular, Dickkopf-Kremen-LRP6 complex: a highly conserved domain considered to be regulator of WNT signaling has been implicated in ED in a Palestinian family. However, this remains a single case reporting in 4 consanguineous families of Palestinian origin, hence further data and reporting might be needed for its final corroboration.

TP63 gene belongs to the p53 transcription family which are known for their tumor suppressor roles (Morasso and Radoja 2005). *p63* is critical for epidermal development and mutations in this gene can result in the absence of salivary, mammary and lacrimal glands; failure of secondary palate fusion; lack of ectodermal appendage formation and deficient craniofacial morphogenesis (Yang et al. 1999). Heterozygous missense *TP63* mutation has been identified in the ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC) syndrome (Gonzalez, Loidi, and Abalo-Lojo 2017). OMIM database revealed its location on chromosome 3q28. Its mutation has also been associated with ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3) (OMIM # 604292). This disorder has been reported in consanguineous families or as a result of spontaneous post-zygotic mutations (Sripathomsawat et al. 2011; Kosaki et al. 2008).

Recently *KDF1* (keratinocyte differentiating factor 1) has been identified in a multigenerational Saudi family to cause hypohidrotic ED (Table 1) (Shamseldin et al. 2017). KDF1 molecule inhibits cellular proliferation and promotes keratinocyte differentiation in epidermis. It regulates the p63 indirectly via the Notch pathway (Lee, Kong, and Weatherbee 2013). Another regulatory molecule of P63 pathway: IBKL S32 has been implicated in causing ectodermal dysplasia with immunodeficiency and systemic inflammation (Moriya et al. 2018). Mutations in *PVRL4* (Poliovirus receptor like-4) / Nectin 4 which is required for cell-cell adhesion have also been described in ectodermal dysplasia-syndactyly syndrome (Brancati et al. 2010; Florian, Gruber, and Volc-Platzer 2018). Timothy et al illustrated it to be a part of the TP63 pathway in the recent 2017 classification (Jt et al. 2019).

CURRENT DISCOVERIES

ORAI proteins form core structural units of Ca^{2+} release-activated Ca^{2+} (CRAC) channels and are essential for t-cell mediated immunity ("ORAI2 Modulates Store-Operated Calcium Entry and T Cell-Mediated Immunity" n.d.). Recently, *ORAI1* gene mutation has been associated in anhidrotic ectodermal dysplasia with severe immunodeficiency (Table 1) (Lian et al. 2018). The disorder has been previously identified due to mutations in the *IKBKG* and *NFκBIA* genes.

Table 1. Genes and their associated Ectodermal dysplasia presentations

OMIM Number	Gene	Location	Protein	Syndrome/ disease	Inheritance
609607	*NECTIN 4*	1q23.3	Nectin 4	Ectodermal dysplasia-syndactyly syndrome 1 (OMIM# 613573)	AR
616758	*KDF1*	1p36.11	Keratinocyte differentiation factor	Ectodermal dysplasia 12, hypohidrotic/hair/tooth/nail type (OMIM#617337)	AD
610277	*ORAI1*	12q24.31	Calcium release-activated calcium modulator	Anhidrotic ectodermal dysplasia with immunodeficiency(28)	AR
609898	*KREMEN1*	22q12.1	Kringle domain containing transmembrane protein.	Ectodermal dysplasia 13, hair/tooth type (OMIM# 617392)	AR
+153245	*LEF1*	4q25	Lymphoid enhancer binding factor-1	Hypohidrotic ectodermal dysplasia(29)	unknown

CONCLUSION

The wide variety of genes, molecular pathways, phenotypes associated with ectodermal dysplasia is astounding and requires thorough knowledge and understanding of the literature in order to plan treatment strategies for these patients. Various gene and the protein therapies have been corroborated by various investigators in this discipline (Gaide 2009; Novelli et al. 2016). An example of the same is the recent successful use of recombinant ectodysplasin in X-linked hypohidrotic ED in canine models.

Acknowledgments

The authors are thankful to the patients for participation in the study.

Conflict of interest statement

The authors have declared to have no conflict of interest.

Authors' contributions

Conception and design: Sood , Mishra. Acquisition of data: Sood , Mishra. Analysis and interpretation of data: Mishra, Sood. Drafting the article: Mishra, Sood. Critically revising the article: Mishra. Reviewed submitted version of manuscript: Mishra, Sood Approved the final version of the manuscript on behalf of all authors: Mishra. Study supervision: Mishra.

Source of Funding

The authors declare that this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of originality

The authors have declared that the data/text presented in this manuscript is original and no text,

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