CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1490833

Available online at: http://www.iajps.com *Review Article*

MOLECULAR BASES OF ECTODERMAL DYSPLASIA AND HYPOHIDROTIC ECTODERMAL DYSPLASIA IN TEETH MISSING A MINI REVIEW

Sahrish Khan[1], Jahangir Hammad[2], Naeema Anwar[1], Mehwish Durrani[1], Malala Ubaidullah[1], Fozia Karam Khan[1], Nazo Rahim[1], Abdul Rahman[1], and Sheikh Ahmed[1]

[1] Institute of Biochemistry, University of Balochistan, Quetta, Pakistan

[2] Bolan Medical University and Health Sciences, Quetta

Abstract:

Ectodermal dysplasia is large heterogeneous group of genetic disease, that are defined by primary defect in the development of 2 or more tissues derived from embryonic ectoderm .The tissues primarily involved are the skin and skin appendages such as hair, nail, sweat gland and teeth. Ed can be disassociated in to two large classes, Hypohidrotic type(which is X-linked recessive and hidrotic(which is autosomal inherited).Hypodontia is a deficiency of teeth in Ed. The alternation in the gene which causes different type of mutation in different type of gene that are EDA, EDAR, EDARADD,MSX1,WnT10A, NEMO etc which causes missense mutation, Noval mutation Non senese and frame shift mutation etc. These all genes are involved in teeth missing.The purpose of this review paper is to describe these type of mutation involvedin teeth missing or hypontia or Hypohidrotic E.D permanent which is dentition is most common intra oral finding. Ectodermal dysplasia is not only physically devastating to individual but also emotional demoralizing .It is essential that they be treated at an early age to improve their quality of life.

Key words:*Ectodermal dysplasia, hypohidrotic ectodermal dysplasia, gene, teeth missing ,*

Corresponding author:

Sahrish Khan,

Institute of Biochemistry,

University of Balochistan,

Quetta, Pakistan

QR code

Please cite this article in press Sahrish Khan et al., ***Molecular Bases of Ectodermal Dysplasia and Hypohidrotic Ectodermal Dysplasia in Teeth Missing a Mini Review.,*** *Indo Am. J. P. Sci, 2018; 05(11).*

INTRODUCTION:

Ectodermal dysplasia (ED) is reported as the first time by Thurman that is a genetically disorder arising as a result of interference in the ectoderm of the growing embryo.

The triad of Hypotrichosis or Alopecia (rare light hair on eyebrows and scalp),onchodysplasia(nail dystrophy),and palmoplanter hyperkeratosis is generally fellowed by a deficiency of sweat glands (hypohidrosis) and a limited or total lack of permanent or primary dentition.(Bani et al., 2010).ED constitute a great and concerned variety of disorders containing other than 170 dissimilar clinical disorder.(Bani et al., 2010) .ED create a huge heterogeneous.(Freire-Maia, 1977)

Ectodermal dysplasia can be dissociate in to two large classes: the Hypohidrotic type(x-linked recessive) and the Hydrotic type(Autosomal inherited)(Singh and Gauri, 2008).

1 Clouston's syndrome or Hidrotic ectodermal dysplasia
2 Hypohidrotic ectodermal dysplasia or ChristSiemens-Tourine syndrome(X-linked hypohidrotic ED(Vasconcelos Carvalho et al., 2013).

Hidrotic ectodermal dysplasia

Hidrotic ectodermal dysplasia is a unusual case where sure ectodermal arrangements are one of two primitive or under primitive. The case is genetic by a one autosomal dominant gene, lethal which homozygous modes are Clinically the disorder is distinguish by hyperkeratosis of the soles and palms ,defect of dystrophic nails and hair(Verma and Singh, 1973).

Hypohidrotic ectodermal dysplasia

The Hypohidrosis type show the typical traid-hypodontia, hypotrichosis and hypohidrosis generally X-linked recessive legacy is detect .Females show only minor defects while males are afflicted harshly. In the hidrotic type nails, teeth and hair are affected. The sweat glands are normally excess. It is generally heritable as an autosomal dominant triad(Varghese and Sathyan, 2011).HED is universe vast with an approximated rate of 1/100,000(Chassaing et al., 2006).

In human being ,there are three kind of HED with various inheritance, Autosomal dominant HED , autosomal recessive HED and X-link HED , which is was ordinary type of HED(Kuramoto et al., 2011).
Ectodermal dysplasia display genetically heterogeneity and a large degree of clinical(Pinheiro and Freire-Maia, 1994a).

Different degrees of reliability, as follows

Autosomal recessives: 14-23 cases(25-40%);--X-linked semidominant:1 case(2%);-- unknown eitiolog:6—19 case(11—33%);autosomal dominants: 21—22 case (37—39%);--X-linked recessive:1 case (2%);--X-linked dominants :1-4 case (2-7%) (Pinheiro and Freire-Maia, 1994b).

Distinctions among the hypohydrotic and hydrotic type of ectodermal dysplasia

Table 1(Varghese and Sathyan, 2011)

	Hydrotic	**Hypohydrotic**
Mode of inheritance	Most often , Autosomal , Dominant	Most often, autosomal, recessive
Scalp Hair	Soft,dawny, Color is darker	Fine in texture, fair and short
Teeth	Anodontia to hypodontia	Anodontia to Hypodontia
Lips	No Abnormality	Protruding
Sweat glands	Active	Reduced to Absent
Nasal bridge	No Flattening	Underdeveloped
	Dystrophic Nails	No Abnormality
Eyebrows	Frequently Absent	Absent
Eyelashes/ Public/ Axillary hair	Scanty/absent	Variably Affected

Hypohidrotic ectodermal dysplasia (HED) should be uncertain in an individual with Hypotrichosis

Is the deficiency of scalp and body hair .scalp hair is lightly pigmented and has thin \Shafts:Note Hair staff can be twisted and brittle or have further abnormality on microscopic analysis; although these detecting are not enough delicate to be symptomatic help. Secondary sexual Hair (imperial; pubic and axillary hair) can be ordinary.

Hypohidrosis (decreased capacity to sweat).

Decreased capacity to sweat in take to warmth conducts to hyperthermia.

- The role of sweat glands can be determined by conducting the skin toward with an iodine solution and increasing atmosphere temperatures to produce sweating. The iodine mixture changes color when susceptible to sweat and may be given to regulate the quantity and emplacement of sweating.
- The numeral and dispersion of sweat pores may be resolved by covering parts of the body (generally the hypothenar prominences of the palms) with effect substances generally accustomed by dental surgeon.
- Although skin biopsy have been given to regulate the disbursement and structure of sweat glands, congenital methods are uniformly efficient. Alive confocal microscopic photographing is capable visualize the sweat duct on palms.

Hypodontia (Inborn deficiency of teeth):

- A normal of nine permanent teeth commonly the first molars and canines grow in humans with typical HED.
- An altered morphology of teeth are generally smaller than average;the frontal teeth generally have conical crowns.
- Dental radioactivity's are useful for deciding the limit of hypodontia and are helpful in the detection of weakly afflicted persons. Taurodontism (extension of the pulp chamber) is other normal in molar teeth of persons with HED than in un pretended persons(Wright et al., 2017).

Clinical Description

Classic HED

Females and males with autosomal recessive hypohidrotic ectodermal dysplasia (ARHED) and males with X-linked hypohidrotic ectodermal dysplasia (XLHED) which caused by EDARADD or EDAR caustic modification have the typical shape of HED (hypohidrotic ectodermal dysplasia.

Newborns with Hypohidrotic ectodermal dysplasia perhaps analyzed cause of skin peeling, alike that of babies “post mature” and periorbital dark circles. Early childhood, they may be irascible cause of intolerance of heat; raised body temperatures are not unusual. Constantly, determination is retarded up to the teeth fall to normal appear at the age (6-9) or the teeth that appear are shape in conical .By means of this era, affected persons may have periobital skin may appear wrinkled and chronic eczema. The basic characteristics of HED develop into apparent concerning infancy:

- **Hypotrichosis.** Weakly pigmented, slow-growing and thin scalp hair. The probable inactive development of scalp hair can proceed from the extreme delicacy of the shafts, which rupture simply with the normal tear and wear of infancy.
- **Hypohidrosis.** Extremely decreased sweat role controlling to incident of hyperthermia up to the afflicted person or family obtains incident with environmental conversions to regulate temperature.
- **Hypodontia.** In which teeth are abnormally formed, later than average appearance of only a few teeth(Wright et al., 2017).

Treatment of Manifestations

Supervision of affected persons marks the three basic characteristic and is conducted at improving psychosocial development, preventing hyperthermia and establishing optimal oral function.

Hypotrichosis.

Special hair care formulas or wigs and methodology to control spare ,dry hair can be helpful .A child describes by one report with alopecia and HED who was deal with topical minoxidil to the scalp and consequent hair development.

Hypohidrosis.

Pending warm weather, afflicted persons necessary entry to an sufficient amount of water and a chill surrounding, air conditioning which can mean ,a spray bottle of water or a wet T-shirt .A few persons can use taken away “chilling clothes.”

Afflicted persons determine to manage their hazard to heat and consequences its to minimize, but particular condition can derive in which interference by doctors and useful in families. For example ,a doctor can have to determine an air cooler previously conforms by a district school .Either forefathers can have to promoter as kids which use to take liquefied with in demesne site they are interdicted.

Hypodontia.

- Must have initiate at an early age the dental treatment, ranging from simple restoration to dentures. In young afflicted individuals

improves aesthetic and chewing ability by bonding of conical shaped of teeth.
- Dental orthopedics can be compulsory.
- Only in children age seven years and older the dental implants in the anterior section of mandibular arch demonstrate successfully.
- Every 2.5 years the dental prostheses have to need succeed the children with generally HED.
- In adults the artificial teeth can assist esthetic and effective dentition.
- Hyper salivation is appearing in few persons, influencing them to tooth decay and require for caries control and therapeutic conducted at maintaining oral lubrication.
- Those persons who have difficulty chewing and swallowing contempt adequate dental care by dietary counseling can be helpful(Wright et al., 2017).

Table 2:Molecular Genetic Testing Used in Hypohidrotic Ectodermal Dysplasia by the Molecular Genetics information on allelic variants detected in this gene(Wright et al., 2017).

Gene [1]	**MOI**	**Proportion of HED Attributed to Pathogenic Variants in This Gene**	**Proportion of Pathogenic Variants** [2] **Detectable by This Method**	
			Sequence analysis [3, 4, 5]	**Gene-targeted deletion/duplication analysis** [6]
EDA	XL	~65%-75%	~85%-90% [7]	~10%-15% [7]
EDAR	AD, AR	~10%-15%	>99% [8]	See footnote 9
EDARADD	AD, AR	1%-2% [10]	8/8 [11]	None reported [12]
WNT10A	AR	5%-6% [13]	~100%	None reported
Unknown [14]		~10%	NA	

Symptoms of Ectodermal dysplasias

Teeth missing frequency

Agenesis in which the number of teeth missing diverse among 6 as well as 20(median7).111 individuals(68.5%) were missing6 ,7, either8 teeth; and 16(9.9) were missing more than 12 teeth and ninety individuals (55.6%) were 6 to 7 teeth missing .The largest generally teeth missing(Bergendal, 2010).

Ectodermal signs from nail, sweat glands and hair

Reported of ectodermal sings seventeen individuals involving 5 with a syndrome and 114 persons with no syndrome,5 (4.4%) abnormal hair,4 (3.5%) abnormal nails and 12(10.5%) abnormal sweating; few described signs in multiple of these ectodermal structure(Bergendal, 2010).

Laboratory tests

Skin biopsy, Pilocarpine iontophoresis and include sweat pore counts(Goyal et al., 2015).

Ectodermal Displasia Groups Associated Diseases.

1. One group, classical Hypohidrotic is the sex-linked "recessive" mode (CST synany inner aetiological heterogeneousness (Pinheiro and Freire-Maia, 1994b).
2. A category of specific and definitely discriminated disorderes one of them beyond each inner aetiological heterogeneousness one of the kinds is appear a "recessive" X-linked gene along few incorporation in the heterozygotic females(CST syndrome),and more to (Clouston syndrome) an autosomal dominant gene(Pinheiro and Freire-Maia, 1994b).
3. The hidrotic and the anhidrotic forms" main" diseases by a group of two, along few diversity the "anhidrotic form" is CST syndrome;the "hidrotic form" is clouston syndrome(Pinheiro and Freire-Maia, 1994b).
4. A group of a lot of disorders :Eight cases: Marshall's ,Feinmesser's ,CST ,Robinson's ,Enamel hypoplasia, Clouston's and Pilli torti and deafness and curly hair .Hypohidrotic ectodermal dysplasia is also referred as CST and Clouson's expression as Clouston's is misspelled.Ectodermal dysplasia has been given to nominate two well-expressed disorders (Clouston syndromes and CST),it must not irregularly and incorrectly be augmented to wrap each symptoms among a character complicated including origin of ectodermal structures.ED of five syndromes inferior the category which is:Hidrotic ED,i.e, Clouston syndrome (they assume that Robinson syndrome may be a "Variant" of it),Ellis-van Creveld syndrome, EEC (ectrodactyly-ectodermal dysplasia –cleft lip and palate),Congenital ectodermal dysplasia of the face and Hypohidrotic ED(CST)(Pinheiro and Freire-Maia, 1994b).

Dental agenesis Prevalence (Bozga et al., 2014)

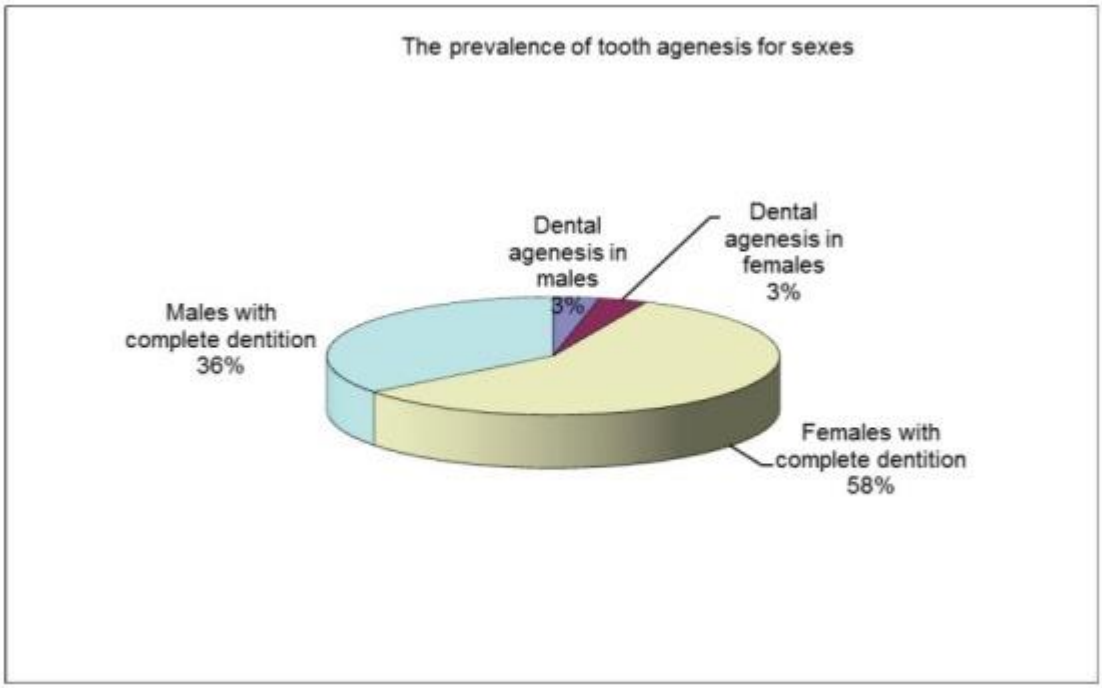

Fig 1:Tooth prevalence of both sexes.(Bozga et al., 2014)

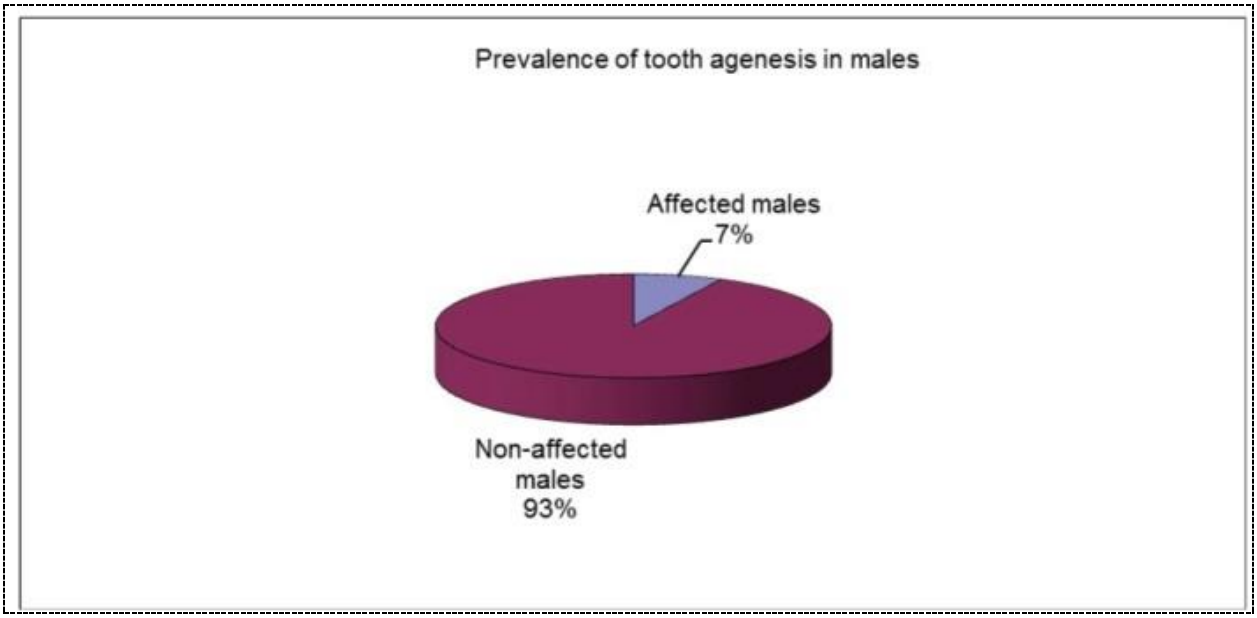

Fig 2:Tooth agenesis prevalence in males(Bozga et al., 2014)

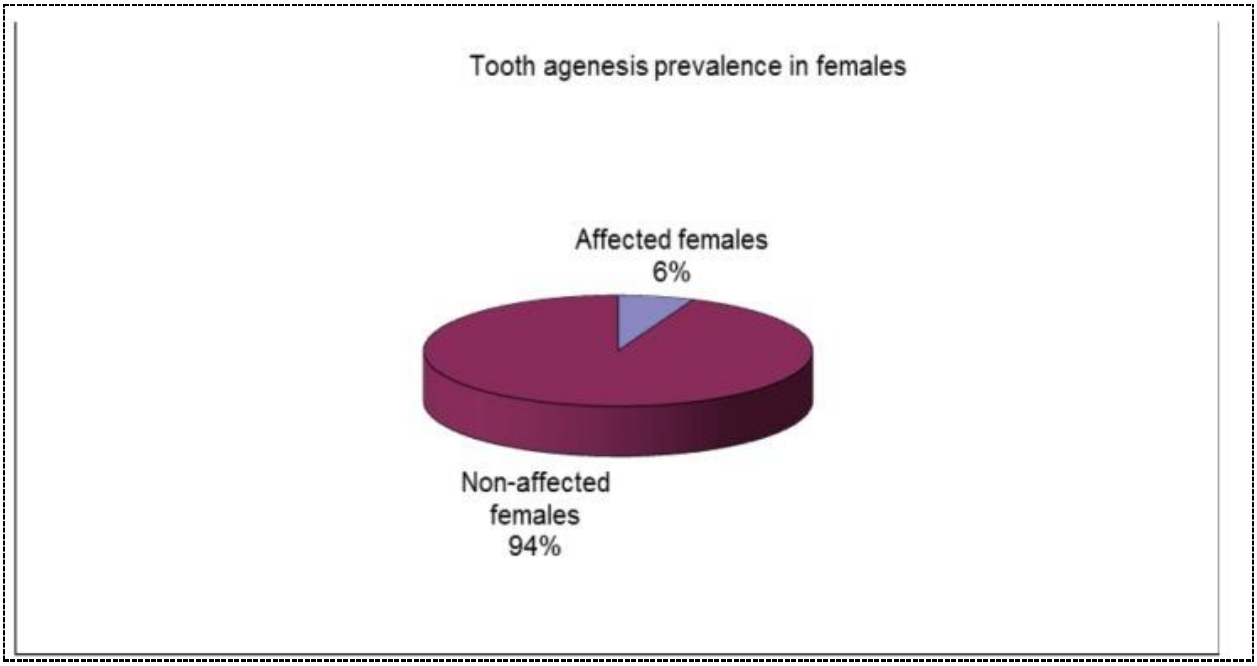

Fig.3:Tooth agenesis prevalence in females(Bozga et al., 2014).

Gene responsible for Mutation

EDA

The protein ectodysplasin-A (EDA) encodes by the EDA gene, which is associate TNF or tumor necrosis factor super family. A type II transmembrane protein is EDA with C-terminal TNF homogeneity domain containing of 10 indicated anti-parallel β-sheets which linked by variable loops.A homotrimer forms by the TNF homology domain. The interaction of EDA with its receptor is affected by TNF domain in which mutation in occure, (EDAR) andectodysplasin-A2 receptor, ectodysplasin-A receptor(EDA) in which observed missense mutation which is (residues 245-391)of ED and locted within TNF domain(Song et al., 2009).

EDAR

Death domain(DD) protein is EDAR which is belong to (TNFR)or tumour necrosis factor receptor family which is necessary for the growth of teeth,hair and further ectodermal derivates. EDAR is a type I transmembrane protein consisting a cysteine-rich domain in the region of extracellular along with DD potential in the region of intracellular.EDA-A1 [9] is activated by EDAR and the nuclear factor (NF)-jB is signaling pathway which is activated by uses of EDARADD as an adapter. Two novel mutations identified in EDAR gene, which present on chromosome 2q11-q13(Naeem et al., 2005).

EDARADD

The mutations of EDARADD gene can be hereditary or more over recessive or autosomal dominant which localization on (1q42.3) Equally the EDAR insufficiency causes autosomal dominant types(Trzeciak and Koczorowski, 2016).

T RAF6

TRAF6 is localized on 11q12 chromosome. Denovo originated the first mutation reported in TRAF6.Conceptually the HED of inheritance pattern as a result mutation in TRAF6 gene,would be autosomal dominant is in patient,hence the HED only mild symptoms were identified in his heterozygotic mother(Trzeciak and Koczorowski, 2016).

MSX1

A transcription factor that regulates the expression of bone morphogenetic protein 4 (BMP4) is encoding by a homeobox gene which is also know MSX1. A component of the modifying development factor-β (TGF-β) is super family ,during the cap and bud phases of the development of tooth the MSX1 gene that regulates the transcription factor which is encoding by homeobox gene (Salvi et al., 2016). Hypodonit associated with Missense mutation caused by MSX1 gene(Reddy et al., 2013).

WNT10A

WNT10A is belongs to Wnt proteins which a large family of secreted signaling proteins, a 46.4-kDa protein with 10 putative α-helices and seven putative β-strands .Wnt10 is express in embryonic limb such as teeth, hair follicles and skin during the development of embryo which performs an essential role in tooth morphogenesis distinction odontoblast.WNT10A gene in which mutation caused for HED,SSPS,OODD a unusual type of ectodermal dysplasia. Ectodermal abnormalities associated character is palmoplantar keratoderm, hypotrichosis ,nail dystrophy and abnormal teeth etc. (He et al., 2013)

NEMO

NEMO alike XEDAR and EDA is located on X chromosome (Xq28) and in this gene mutation are generally heterozygous mothers transmitted. The symptoms of HED ordinary seen only in male's hemizygous.HED symptoms because of in frame mutation in NEMO are usually associated by incontinentia pigmenti (EDA-ID) and immunodeficiency. When mutations precede to truncation of gene product of protein, lymphedema (OL-EDA-ID) and osteopetrosis is accompanied by immunodeficiency. The majority of cases servicer genodermatosis is connected with hypodontia, malformed teeth or peg-shaped teeth and many patients have neurological and ophtalmological problems. (Trzeciak and Koczorowski, 2016)

AXIN2

AXIN2 is gene which cause mutation in colorectal cancer and tooth agenesis .Mutation lack 8-27 permanent teeth carried by the patient.Colorectal cancer is very high level of penetrance .Deficiencies in deciduous dentition were seen only in one patient(Bailleul-Forestier et al., 2008)

PAX9

PAX9 is gene which caused mutation in transcription factor gene is known as PAX9 which preced of absence of permanent molars\ among and lack of hypodontia in primary teeth. Several persons as well have missing mandibular premolar and or maxillary apart from and central mandibular incisors. In affected individual indicate to observed by smaller teeth that PAX9 is involved in morphologenesis of entire dentition and also positioning and development of certain teeth .The phenotype-genotype association occurs PAX9 mutation ,nonsense and frameshift mutant than missense mutation give a milder phenotype(Bailleul-Forestier et al., 2008).

CONCLUSION:

Ectodermal dysplasia is syndrome is unusual genetic disease with the association of different tissue in the body. Various changes in genes coding for proteins like EDA, EDAR, and EDARADD are the causes for the presentation of ectodermal dysplasia. Teeth missing is the major problem in all over the world .So we need particular measure for the identification of such mutated gene necessary for the awareness of people.

REFERENCES:

1. Bailleul-Forestier, I., Molla, M., Verloes, A., Berdal, A., 2008. The genetic basis of inherited anomalies of the teeth: Part 1: Clinical and molecular aspects of non-syndromic dental disorders. European journal of medical genetics 51, 273-291.
2. Bani, M., Tezkirecioglu, A.M., Akal, N., Tuzuner, T., 2010. Ectodermal dysplasia with anodontia: a report of two cases. European journal of dentistry 4, 215.
3. Bergendal, B., 2010. Oligodontia and ectodermal dysplasia: on signs, symptoms, genetics and outcomes of dental treatment. Umeå universitet.
4. Bozga, A., Stanciu, R., Mănuc, D., 2014. A study of prevalence and distribution of tooth agenesis. Journal of medicine and life 7, 551.
5. Chassaing, N., Bourthoumieu, S., Cossee, M., Calvas, P., Vincent, M.C., 2006. Mutations in EDAR account for one-quarter of non-ED1-related hypohidrotic ectodermal dysplasia. Human mutation 27, 255-259.
6. Freire-Maia, N., 1977. Ectodermal dysplasias revisited. Acta geneticae medicae et gemellologiae: twin research 26, 121-131.
7. Goyal, M., Pradhan, G., Gupta, S., Kapoor, S., 2015. Hypohidrotic ectodermal dysplasia with ankylosis of temporomandibular joint and cleft palate: a rare presentation. Contemporary clinical dentistry 6, 110.
8. He, H., Han, D., Feng, H., Qu, H., Song, S., Bai, B., Zhang, Z., 2013. Involvement of and interaction between WNT10A and EDA mutations in tooth agenesis cases in the Chinese population. PloS one 8, e80393.
9. Kuramoto, T., Yokoe, M., Hashimoto, R., Hiai, H., Serikawa, T., 2011. A rat model of hypohidrotic ectodermal dysplasia carries a missense mutation in the Edaradd gene. BMC genetics 12, 91.
10. Naeem, M., Muhammad, D., Ahmad, W., 2005. Novel mutations in the EDAR gene in two Pakistani consanguineous families with autosomal recessive hypohidrotic ectodermal dysplasia. British Journal of Dermatology 153, 46-50.
11. Pinheiro, M., Freire-Maia, N., 1994a. Ectodermal dysplasias: a clinical classification and a causal review. American Journal of Medical Genetics Part A 53, 153-162.
12. Pinheiro, M., Freire-Maia, N., 1994b. Ectodermal dysplasias: a clinical classification and a causal review. American journal of medical genetics 53, 153-162.
13. Reddy, N.A., Adusumilli, G., Devanna, R., Pichai, S., Rohra, M.G., Arjunan, S., 2013. MSX1 gene variant-its presence in tooth absence-a case control genetic study. Journal of international oral health: JIOH 5, 20.
14. Salvi, A., Giacopuzzi, E., Bardellini, E., Amadori, F., Ferrari, L., De Petro, G., Borsani, G., Majorana, A., 2016. Mutation analysis by direct and whole exome sequencing in familial and sporadic tooth agenesis. International journal of molecular medicine 38, 1338-1348.
15. Singh, R., Gauri, S.L., 2008. Hypohidrotic Ectodermal Dysplasia: A Case Report. Journal Of International Dental And Medical Research 1, 11-14.
16. Song, S., Han, D., Qu, H., Gong, Y., Wu, H., Zhang, X., Zhong, N., Feng, H., 2009. EDA gene mutations underlie non-syndromic oligodontia. Journal of dental research 88, 126-131.
17. Trzeciak, W.H., Koczorowski, R., 2016. Molecular basis of hypohidrotic ectodermal dysplasia: an update. Journal of applied genetics 57, 51-61.
18. Varghese, G., Sathyan, P., 2011. Hypohidrotic ectodermal dysplasia—a case study. Oral & Maxillofacial Pathology Journal 2.
19. Vasconcelos Carvalho, M., Romero Souto de Sousa, J., Paiva Correa de Melo, F., Fonseca Faro, T., Nunes Santos, A.C., Carvalho, S., Veras Sobral, A.P., 2013. Hypohidrotic and hidrotic ectodermal dysplasia: a report of two cases. Dermatology online journal 19.
20. Verma, K., Singh, K., 1973. Hidrotic ectodermal dysplasia. Indian journal of pediatrics 40, 227-228.
21. Wright, J.T., Grange, D.K., Fete, M., 2017. Hypohidrotic ectodermal dysplasia.