

# Hypohidrotic Ectodermal Dysplasia: Genetic aspects and clinical implications of hypodontia.



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## ABSTRACT

Hypohidrotic Ectodermal Dysplasia (HED) is a rare genetic disorder, characterised by a distinctive facies, hypotrichosis and hypohidrosis. Hypodontia/oligodontia is a significant component of the condition, contributes to aesthetic and functional problems and may require special dental management. Furthermore, specific dental changes may alert the practitioner to the possible diagnosis of HED. Contemporary investigations to elucidate the molecular pathogenesis of HEDS have drawn attention to the disorder. For this reason, we have reviewed the genetic basis of HED and in particular hypodontia/oligodontia in the light of our own experiences and provided a literature search. Different approaches to the dental management and treatment options in hypodontia/oligodontia in HED are also included.

The Ectodermal dysplasias (OMIM 305100) are a group of more than 150 hereditary disorders that affect tissues and organs derived from the ectodermal germ layer. The most common variants of ED are the hidrotic and hypohidrotic (anhidrotic) forms. The distinguishing feature between the two types is the presence or absence of sweat glands. Persons affected by Hypohidrotic Ectodermal Dysplasia (Christ-Siemens-Touraine syndrome) have characteristic facies, including frontal bossing, a depressed nasal bridge / saddle-shaped nose and hyperkeratosis.<sup>1</sup> The congenital absence of teeth results in excessive resorption of the alveolar bone, a reduction in the height of the face and full lips. Fine, pigmented, linear wrinkles around the eyes are frequently seen. Symptoms arising from impaired mucous production are common, including upper respiratory infections, otitis, dysphagia and bronchitis.<sup>2</sup> Specialised radiographic techniques can be used to detect the reduced sizes of all craniofacial bones. Apart from the otolaryngeal changes, general health is usually good, and the intellect is unimpaired.

The inheritance of HED is by either an autosomal, dominant, autosomal recessive or X-linked patterns. Four gene mutations are linked to the pathogenesis of HED. The EDA<sup>1</sup> gene mutation is associated with the X-linked variant and EDAR, and EDARADD mutations are associated with the autosomal dominant and autosomal recessive forms.<sup>3</sup> WNT10A mutations have been linked to HED patients who have distinct phenotypic expressions including striking dental changes without facial changes.

## ACRONYMS

Hypohidrotic Ectodermal Dysplasia (HED)

## KEY WORDS

Dental, Genetic, Hypodontia

HED is uncommon. Nguyen-Nielsen et al. reported the frequency of HED in the Danish population to be 1.6 per 100,000 in molecularly confirmed affected persons.<sup>4</sup>

The primary dental feature, hypodontia/oligodontia, occurs in both dentitions and may lead to mastication problems, impaired speech and poor aesthetics. Xerostomia as a result of hypoplastic salivary glands may predispose the existing teeth to dental caries. For these reasons, dental management is an essential aspect of the well-being of affected persons.

## CASE REPORT

A South African male of mixed ancestry was referred to the Faculty of Dentistry, University of the Western Cape, Cape Town in 2017. At the time of his assessment, he was 20 years old. A diagnosis of HED was based on his phenotypic manifestations. He had two affected siblings with similar abnormalities.

### Extraoral examination

The affected individual had sparse silky hair, scant eyebrows, the tip of his nose was narrow, and the nasal bridge was flattened. The skin covering his forehead, cheeks and chin was dry. He had prominent, pigmented wrinkles under the eyes. Thick lips were evident and the helices of his ears were flattened [Figure 1]. His facial profile was straight [Figure 2].

### Intraoral examination

The size of his oral cavity was normal relative to the size of the face. His palate was within normal limits, but several teeth were missing in both the maxillary and mandibular dental arches [Figure 3].

Caries and gingival recession were present in both the maxillary and mandibular first molars and second premolar teeth. Both the sizes and shapes of teeth were normal. The remaining atrophic alveolar ridges were edentulous. The mucous membranes lining the soft tissues were dry. No history of previous extractions was elucidated and the patient wore maxillary and mandibular partial dentures which had been made by an unqualified technician [Figure 4]. Both partial dentures lacked clasps and had under-extended flanges which contributed to poor retention and instability. There was generalized wear of the prosthetic teeth and the denture had stains and calculus. Radiographic imaging was non-contributory.

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**Figure 1:** 20-year-old male with fine hair and sparse eyebrows, a saddle nose, decreased vertical height of the face and thick lips. The skin over his forehead, cheeks and chin is dry and scaly



**Figure 2:** Low-set ears and mild midface hypoplasia

#### Management options

The treatment objectives were to improve and maintain the oral health, restore carious teeth, replace missing teeth and to restore function and aesthetic profile

The following management options were considered:

#### Option 1

- A root canal treatment on the right maxillary second premolar and submerge the root to preserve the bone for a dental implant in the future
- Restoration of the remaining teeth apart from the left maxillary second premolar, which would be extracted.
- Restoration of function and aesthetics with a removable partial denture

#### Option 2

Similar to treatment option one except that the function and aesthetics would be restored by the placement of dental implants and fixed dental prostheses.

#### Option 3

Similar to option one apart from function and aesthetics would be restored by an overdenture supported by implants.

#### Option 4

Extraction of all remaining teeth which would be replaced by complete upper and lower dentures.

Based on financial constraints, the first management option was chosen.

## DISCUSSION

The most common form of HED is inherited as an X-linked trait, with a spectrum of phenotypic expression. The disorder is associated with a mutation in the *EDA1* gene which is coded for ectodysplasin A, a transmembrane protein belonging to the tumour necrosis group responsible for the development of ectodermal tissues.<sup>5</sup> The *EDA1* gene is located on Xq12-q131.<sup>1</sup> chromosomes and deletions in these loci are responsible for HED. The full spectrum of the disorder is usually expressed in males. Phenotypic expression is variable and less severe in females.

Hypodontia, the most significant dental feature, refers to a hereditary disorder where one or more teeth fail to develop. When six or more teeth are developmentally absent, the condition is referred to as oligodontia. In HED, tooth agenesis affects both the primary and secondary dentition. Hypodontia/oligodontia results in poor articulation, compromised aesthetics and inefficient mastication. Xerostomia may exacerbate the problem and increase the risk of dental caries. A lack of dentition results in atrophy of alveolar bone and a resultant decrease in the height of the face. When present, the erupted teeth are misshaped, and the incisors and canines often appear conical. The cosmetic appearance of the dentition is unsightly and may affect the psychological well-being of the affected person.

Hypodontia/oligodontia may occur as part of a genetic syndrome or as a non-syndromic isolated trait. Several theories have been proposed to explain tooth agenesis. Whilst early investigators viewed the environmental and genetic aspects of hypodontia/oligodontia in isolation, the process is in fact multifaceted, as with so many disorders<sup>6</sup> Environmental influences play a minor role during the initial stages of tooth formation,<sup>7,8</sup> but may be important if they are persistent. Local factors including dental caries may affect the chronological sequence of tooth maturation. During the transition from the primary to the permanent dentition, which usually occurs during puberty, epigenetic influences such as hormonal changes may suppress tooth development.<sup>9</sup>

Hypodontia/oligodontia can occur as a consequence of aberrations during any stage of tooth morphogenesis. Mutations in genes responsible for either tooth formation or maturation can result in changes in the number, shape or structure of one or more teeth in either the primary or secondary dentition or both.<sup>8</sup>

#### Genetics of hypodontia/oligodontia

There are more than 300 genes responsible for tooth formation and maturation. Several researchers have associated mutations



in *MSX1*, *PAX9*, *AXIN2*, *EDA*, *EDAR*, *EDARADD* and *WNT10A* with hypodontia and oligodontia in mice. Moreover, these authors suggested that the regular expression of these genes may be imperative for the formation and development of the normal tooth germ.<sup>3,10-13</sup> Mutations in similar genes expressed during the various stages of odontogenesis have been associated with the agenesis of specific teeth and with patterns of inheritance in humans. Apart from their role in initiating the development and positioning of teeth, these genes belong to signalling pathways that regulate the morphogenesis of other organs. Their mutations therefore affect the development of structures beyond dental morphogenesis resulting in syndromic developmental disorders. Aberrations in the *MSX1* and *AXIN2* genes are associated with tooth agenesis and with systemic features including cleft palate and colorectal cancer.<sup>14</sup>



**Figure 4:** Congenital tooth agenesis with resorbed mandibular ridge, gingival recession and dental caries



**Figure 5:** Ill-fitting dentures

*MSX1* gene provides the instructions for proteins that regulate the activity of other genes. The gene belongs to a group of homeobox genes responsible for cell division and differentiation during embryogenesis. The *MSX1* gene is found at 4p16.3-p16.115 and is expressed in regions of condensing ectomesenchyme in the tooth germ.<sup>16</sup> The gene is responsible for regulating the *Bmp2*, *Bmp4*, and *Lef1* via the Wnt/ $\beta$ -catenin signalling pathway. Underexpression of *MSX1* results in accelerated odontoblastic differentiation, early cessation of tooth development and impaired cell division in mice. Mutations are also responsible for severe forms of hypodontia in humans.<sup>17</sup> *MSX1* mutations have been linked to oligodontia,<sup>18</sup> and autosomal dominant<sup>10,19</sup> and autosomal recessive variants of hypodontia.<sup>20</sup>

*PAX9* is a member of the paired box (*PAX*) family of transcription factors and is found on the long arm of chromosome 14 locus 14q12-q13.<sup>21</sup> The gene is expressed in the mesenchyme of the developing tooth.<sup>22</sup> Although *PAX9* is essential for the formation of the mesenchyme throughout odontogenesis,<sup>23</sup> its levels are highest during the early stages of tooth development.<sup>24</sup> The gene regulates the expression of *MSX1* via *BMP4* and also plays a critical

part in fetal development and in the progression of malignancies.<sup>25</sup> Mutations in both coding and non-coding regions of the gene have been reported involving exons 1, 2, 3 and 4. These have been associated with the termination of tooth development at the bud stage.<sup>26</sup>

Heterozygous mutations in *PAX9*, have been associated with non-syndromic tooth agenesis in humans,<sup>22</sup> mainly autosomal dominant and recessive, non-syndromic, familial oligodontia forms.<sup>27</sup> Aberrations in *PAX9* gene are also associated with peg-shaped laterals<sup>28</sup> and microdontia incisors.<sup>29</sup>

*AXIN2* or axis inhibitor protein 2 is a gene located on the long arm of chromosome 17 (17q23-q24).<sup>30</sup> The gene plays a role in cell growth, proliferation, and differentiation. Axis inhibition protein regulates the Wnt signalling pathway and controls cell-to-cell communications during embryogenesis. Gene mutations have been associated with several forms of hypodontia<sup>25,31,32</sup> discovered an association between mutations in the Wnt, signalling regulator *AXIN2*, oligodontia and increased susceptibility to colorectal cancer in a large Finnish family. The authors proposed that tooth agenesis, and in particular, severe oligodontia could be an indicator of predisposition to cancer. Mostowska et al. demonstrated mutations in *AXIN2* in hypodontia and oligodontia.<sup>11</sup>

*EDA* (ectodysplasin 1) is a gene is situated on Xq12-q13.1 and mutations are involved in isolated, non-syndromic X-linked and sporadic hypodontia.<sup>33</sup> Mutations in this gene also cause X-linked HED, the features which have been extensively described in this manuscript.

The tooth is a complex organ derived from both ectodermal and mesenchymal germ layers. The same genes responsible for tooth development are involved in the growth and development of the other tissues derived from the ectoderm. Hence, factors that disrupt the expression of these genes not only interfere with dental development but may also influence the development of the other ectodermal organs including the hair, nails, skin and glands.

#### Clinical implications of genetic aberrations in hypodontia/oligodontia

The study of the genetic basis of tooth agenesis gave rise to the development of experimental tooth restoration techniques including tissue scaffolding<sup>34</sup> and tooth engineering.<sup>35</sup> Furthermore, the association of genes such as *AXIN2* and *PAX9* with both tooth agenesis and certain types of malignancy indicate that tooth agenesis could serve as a potential genetic marker for the early diagnosis of cancer.<sup>14,36,37</sup>

## CONCLUSION

The dental manifestations of HED may cause functional, aesthetic and psychological problems. Oral rehabilitation is costly and protracted and may influence dental management. Salivary gland aplasia or agenesis may complicate dental changes and precipitate or aggravate caries in the remaining dentition. Hyperthermia, a concomitant finding in HED and AED may compound dental management. Mutations in genes responsible for HED are implicated in tooth agenesis and certain types of malignancy. Oral health professionals may be the first to encounter individuals with HED and therefore require a sound knowledge of the clinical features and genetic basis of the condition.

Permission to reproduce the photographs was granted.

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