A SCOPING REVIEW: GENE MUTATIONS OF NON-SYNDROMIC HYPODONTIA AND ITS PREVALENCE IN GENDER AND TYPE OF TEETH

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Abstract

Non-syndromic hypodontia is a developmental anomaly characterized by the absence of one to six of permanent teeth. The goal of this review was to identify all known gene mutations, prevalence of gender and type of teeth, to review current research and identify knowledge gaps on the topic of non-syndromic hypodontia. Three electronic databases were performed (Science Direct, PubMed, and Scopus) and restricted to English papers published after 2012 until 2019. Search terms were combined as follows: Hypodontia or 'non-syndromic hypodontia' and 'genes' or 'tooth anomaly' and 'mutation' or 'genes' and were checked against the inclusion criteria independently by two investigators. From 16 studies, five genes currently known caused non-syndromic hypodontia: WNT10A (37 variants, 256 patients), MSX1 (9 variants, 112 patients), PAX9 (17 variants, 79 patients), AXIN2 (8 variants, 60 patients) and EDA (2 variants, 11 patients). It was demonstrated that females exhibited a higher prevalence of hypodontia with 89.3% as compared to males with 84.2%. The most commonly missing teeth was a lateral incisor, followed by second premolar and central incisor. Five genes, including WNT10A, PAX9, MSX1, AXIN2 and EDA, are currently considered to have the ability to cause non-syndromic hypodontia. Lateral incisor was found to be commonly missing teeth and there was an increased risk for females to have hypodontia than males.

Keywords**:** Non syndromic hypodontia; Gene mutation; Tooth agenesis

Introduction

In modern society, function of teeth becomes necessary to improve appearance because the facial appearance is important to determine the acceptance of a person into society. Moreover, teeth often play a vital role in speech and communication. However, dental illnesses linked to excruciating pain, anxiety, and poor social functioning can make people lose faith in their own life while also impairing their ability to chew properly, speaking in a different way, and developing aesthetic issues (1). Congenital loss of one or more permanent teeth is the most prevalent developmental anomaly in humans and it affects more females than males. Its prevalence in the general population ranges from 2.6% to 11.3% (2).

Selective tooth agenesis, or congenitally missing teeth (CMT), is also known as tooth agenesis. Hypodontia, oligodontia, and anodontia can be subdivided into three parts. Hypodontia is referred to as the absence of one to six teeth, except the third molar, and is a common dental anomaly in human (3), while oligodontia is referred to as the absence of more than six teeth, excluding the third molar, and anodontia, which lack all teeth which was the most extreme. Hypodontia has been observed either as part of or as a non-syndromic form of the condition. It is more popular to include the number of teeth in varying non-syndromic types. Tooth growth is primarily genetically regulated. There were over 200 genes expressed during the development of the tooth (4, 5).

The key cause of hypodontia and oligodontia is the mutation of the PAX9 and MSX1 genes. These two genes have been known as the paired-box and homeobox transcription factor members that involved in the bud and bell process during the early stage of tooth growth or odontogenesis, respectively (6). In addition to tooth agenesis, an MSX1 gene was correlated with cleft lip and palate (7, 8). Two recent studies have shown that WNT10A may also be susceptible to this dental anomaly mutation. In 56% of the examined patients with non-syndromic hypodontia, Bohring et. al reported that the WNT10A gene was impaired in this gene, making the WNT10A gene a significant gene in the aetiology of this common developmental defect (9). Patients with an AXIN2 gene deficiency are more likely to develop colorectal cancer because this gene codes for axis inhibition protein 2, which regulates the stability of beta-catenin.

Significant inter-individual heterogeneity exists in the pattern of agenesis linked to each of these genes, and some gene mutations can lead to other defects in addition to hypodontia (9). When some disruptions and gene mutations occur during odontogenesis, a gene was believed to be responsible for tooth loss and even dental abnormalities including changes in tooth morphology and size (10).

It would also be of interest to be aware of the all-known gene mutation associated with non-syndromic hypodontia. Therefore, we aimed at summarising the related literature and thoroughly examining the all-known gene mutation associated with it for the first time to review current research and identify knowledge gaps on the topic of non-syndromic hypodontia.

Materials and Methods

We followed the PRISMA-ScR guidelines when conducting this scoping review. In order to find applicable studies with no time limit, the reference and description list for the entire text papers was also looked for.

Type of Publication

It included only research related to non-syndromic hypodontia. The analysis was restricted to papers published after 2012 until 2019. We suggested taking the data from the English abstract wherever possible for papers that were not written in English. The following form of publication was ruled out; letters; editorials; thesis; reviews.

Literature Search

The electronic literature search on the non-syndromic hypodontia was carried out using internet search engines which were Science Direct, PubMed and Google Scholar (Figure 1). Hypodontia or 'non-syndromic hypodontia' and 'genes' or 'tooth anomaly' and 'mutation' or 'genes' were the keywords used for the search. The Boolean operator was used to combine the search terms. The quest was also limited to human studies alone. The duplicate entries were eliminated and a subset of the findings from each database were pooled. Additionally, a manual search of the references list in the chosen papers was done. Only publications with English language abstracts were included and whenever possible, information from English language abstracts was used to supplement entire articles that were not published in English.

The Inclusion Criteria

The inclusion criteria were:

- The patient must be dealing with non-syndromic hypodontia.
- Described the number of congenitally missing teeth in detail.
- Genetic analysis
- The availability of English abstracts major article components (tables, etc) or the ability to carefully translate important content utilising online translators.
- A radiographic examination was required for the "dental agenesis" diagnosis.
- The study designs were unrestricted (e.g., epidemiological studies or research on dental patients).
- In order to include diverse aspects of quantifying treatment burden, quantitative, qualitative, and mixed-method studies were included. Papers were rejected if they did not fit within the study's conceptual framework, which focused on non-syndromic hypodontia and gene mutation.

Selection Process

Prior to starting the review's screening process, to increase uniformity, all reviewers screened the same 54 papers, reviewed the findings, and modified the screening and data extraction process. The entire texts, titles, and abstracts of all the papers uncovered during our searches for potentially pertinent publications were examined by two reviewers working in pairs. By reaching a consensus and, if necessary, talking to other reviewers, we were able to settle disagreements on study selection and data extraction.

Data Collection Process

Using a specially designed data extraction form, information was extracted from all of the chosen research. The initial author, the year of publication, the research nation, the study's design, the features of the study's population, the number of participants, gender, age, and the distribution of missing teeth are all included in the data. In an iterative procedure, the two reviewers separately plotted the data, reviewed the results, and continuously modified the data-charting form.

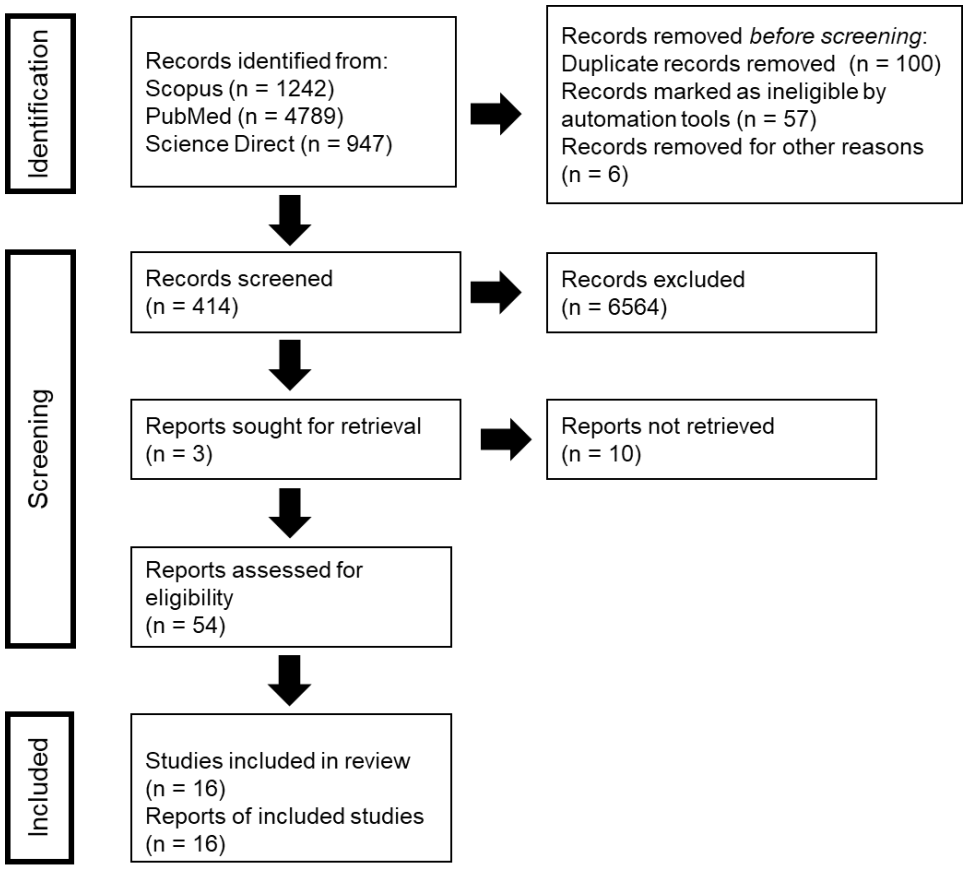


Figure 1: Search results: Scopus, PubMed, Science Direct

Results

Scoping review to identify gene mutations

The electronic screening yielded 6978 articles, including 1242 from Scopus, 4789 from PubMed, and 947 from the Science Direct database. After deleting duplicate research, Endnote identified 414 articles. After the writers screened the titles and abstracts, the complete text of 54 papers was read. 38 of them were eliminated because either no full texts in English were accessible and their abstracts were insufficient, or the entire texts were deemed irrelevant. Finally, 16 studies were chosen for qualitative examination based on reported inclusion criteria as listed in Table 1.

Table 1: Results of the systematic literature review for gene mutation associated with non-syndromic hypodontia

Identified genes	Mutations (n)	Patients (n)	References
WNT10A	37	256	1, 2, 12, 18, 35, 41
PAX9	17	79	3, 15, 41
MSX1	9	112	15, 17, 29, 31
AXIN2	8	60	12
EDA	2	11	7, 38

The selection procedure is outlined in a flowchart (Figure 1). Studies involving patients who were deemed syndromic because they displayed symptoms and indicators unrelated to hypodontia, had more than six congenitally missing teeth, with the exception of the third molar, and exhibited behaviours unrelated to non-syndromic hypodontia were excluded.

A total of 54 posts were included in the review. Of these, some met all-inclusive requirements, but were not evaluated either because they did not exhibit gene mutations in patients or because all cases of hypodontia and oligodontia were included (2, 4, 5, 9, 13, 22, 24, 27, 28, 33-37, 39, 42).

Five genes causing currently known non-syndromic hypodontia have been documented in 16 articles: WNT10A, MSX1 (homeobox 10 muscle segment), PAX9 (pair box 9), AXIN2 (axis inhibitor protein 2) and EDA (Ectodysplasin A). The details of these genes, along with the number of mutations and patients registered, are given in Table 1. There is a wide difference in the number of mutations registered for each gene and the number of patients registered.

By referring the Table 1, WNT10A gene has a higher mutation rate with 37 identified gene variants and extensive data on 256 patients with hypodontia, according to all reported cases. There were 17 gene variants and 79 patients in the PAX9 and MSX1 genes, with 9 variants and 112 hypodontia patients, respectively. They were accompanied by AXIN2 genes with 8 gene variants and 60 patients with hypodontia cases. For EDA, with 2 gene variants and 11 hypodontia patients, substantially fewer mutations have been identified.

Prevalence of non-syndromic hypodontia

The participation rate was recorded in only 14 out of the 16 studies examined. Two studies were omitted because they did not include adequate details on type of teeth and gender. As the publications focused more on gene mutations, the majority of research offered incomplete data for males and females.

Prevalence by gender

In a retrospective analysis of 328 hypodontic patients, 320 cases showed that one or more teeth were missing (Table 2). Females were found to have a combined odds ratio (OR) of 1.06 for non-syndromic hypodontia compared to males (CI: 1.14–1.30). For patients with non-syndromic hypodontia, hypodontia was prevalent in 86.95 percent of cases. Congenitally missing teeth were discovered in 176 female patients (89.3%) and 144 male patients (84.2%). As a result, it shows that females were more prevalent than males.

Table 2: Distribution of subject and OR

Gender	Number of patients		Prevalence (%)	OR
	Affected	**Examined**		
Female	176	197	89.3	0.893
Male	144	171	84.2	0.842
Total	320	368	86.95	1.06

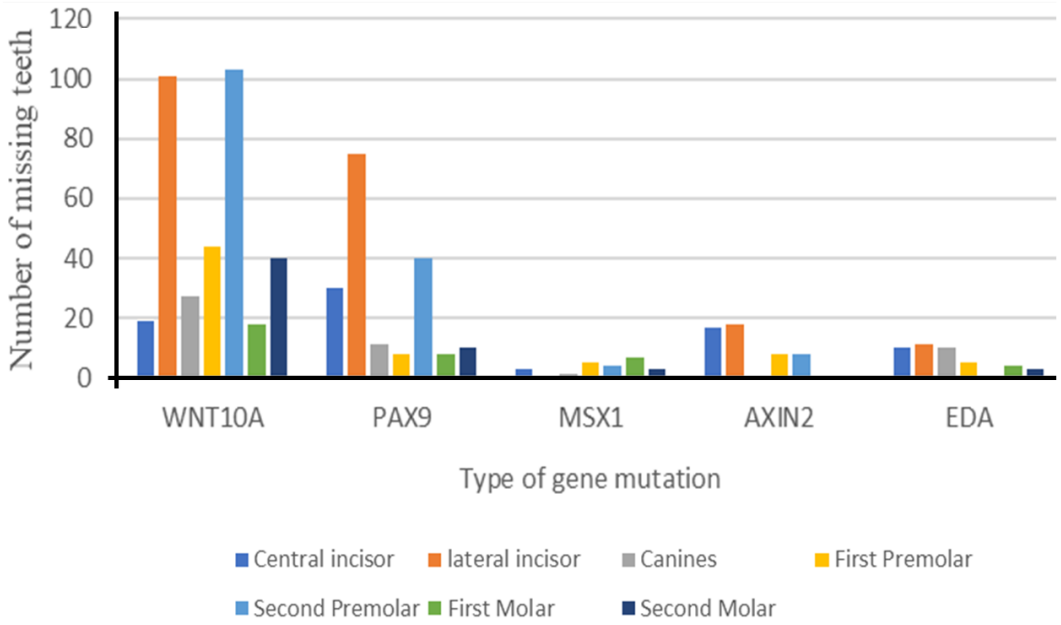
Prevalence by type of teeth

The most often missing tooth among the 320 patients with non-syndromic hypodontia was a lateral incisor, followed by a second premolar and a central incisor (Table 3). Canines and molar agenesis in the maxilla and mandible are extremely uncommon. According to the type of gene mutation, missing teeth were distributed differently in Figure 2.

Table 3: Distribution and statistical comparisons of missing teeth according to type of gene mutation

Type of teeth	Type of gene mutation					Total
	WNT10A	**PAX9**	**MSX1**	**AXIN2**	**EDA**	
Central incisor	19	30	3	17	10	79
lateral incisor	101	75	0	18	11	205
Canines	27	11	1	0	10	49
First Premolar	44	8	5	8	5	66
Second Premolar	103	40	4	8	0	155
First Molar	18	8	7	0	4	37
Second Molar	40	10	3	0	3	56

Figure 2: Distribution of missing teeth by type of gene mutation



In this study, we reported that 16 out of 49 case studies were associated with the inclusion process of genetic analysis in non-syndromic hypodontia. It has been found that both genetic and environmental factors contribute to the aetiology of dental agenesis, and many theories have been suggested to explain its effects especially before in-depth genetic studies have been conducted in recent years (11). The aetiology of dental agenesis is also not entirely clear although several theories have been submitted. An important role in dental agenesis is played by poly diversity. Dental agenesis and the human genome are linked and differences in tooth genesis are caused by human genetics (12).

Mutation of genes affects the sequence of genes in many ways. Recent studies have shown that genes such as PAX9, AXIN2, EDA, SPRY2, TGFA, SPRY4, WNT10A, FGF3, FGF10, FGFR2, and BMP4, are expressed in the odontogenesis process (13). PAX9, MSX1, AXIN2, and EDA are most commonly identified as non-syndromic hypodontia-related genes (14). The WNT10A gene is a significant candidate gene for non-syndromic hypodontia, according to some recent studies. This gene was discovered in non-syndromic hypodontia and may be the cause of permanent dental dysplasia (15).

Only five genes—WNT10A, PAX9, MSX1, AXIN2, and EDA—were found to be candidate genes throughout all searches. These genes are crucial for the growth of the odontogenesis. The expression of PAX9 and MSX1, which are both exclusively expressed in dental mesenchyme, is crucial for sustaining odontogenic potential during this change (16, 17).

The MSX1 and PAX9 genes are also involved in tooth development. Lestari et. al stated that all affected patients had an MSX1 mutation except one patient, whereas PAX9 was present in all patients. In tooth growth, both the PAX9 and MSX1 genes are important. The PAX9 mutation is present in MSX1 activation, which involves transferring the teeth from the bud to the cap stage (18). Reddy has discovered a novel mutation in the MSX1 gene, 671T> C, which causes non-syndromic tooth agenesis in Raichur patients (19). The origin of several forms of congenital teeth has been linked to the MSX1 gene, according to the most recent literature. The MSX1 gene has so far been associated with four instances.

The presence of PAX9 was specifically discovered in the potential conditions of all teeth before any morphological indications of odontogenesis, and it was identified as a key regulating component during the odontogenic process. In the Jordanian population, polymorphisms of the PAX9, c.1031G>A, and c.-912T>C gene promoters were found to be closely related to the development of tooth agenesis (20). This is due to the role of PAX9 during odontogenesis. The PAX9 protein interacts with MSX1 homeoprotein in the dental mesenchyme to regulate BMP4, which has an effect in the downstream signalling cascade. The point mutation on exon 2 was identified from another study (21). In hypodontia mutations, a heterogeneous mutation was observed. This mutation has been reduced to an improved PAX9 transcript level and a lower BMP4 transcript level. Proper regulation of the PAX9 signalling pathway is therefore important for mesenchymal odontogenesis and normal tooth growth

capability (22).

WNT10A mutations have been discovered to occur with non-syndromic hypodontia and be the cause of permanent tooth dysplasia in up to 56% of instances. The WNT10A gene is mostly linked to severe ectodermal dysplasia (23, 35). The WNT10A gene has a high mutation rate and is an important candidate gene for non-syndromic hypodontia. Motowska et. al reported three non-synonymous variants out of 60 samples in the study (24). The variants may represent potential variants of non-syndromic hypodontia inducing disorders (5). He noted a nonsense heterogeneous change in exon 2 of WNT10A in another study (25). Another study recognized novel heterozygous mutations inherited in an autosomal dominant manner close to the study (26). Isolated hypodontia is documented in an American family with two WNT10A mutations, which suggests that this gene has a higher mutation rate (27).

EDA mutations, including 2 gene variants and 11 patients with hypodontia, appeared the least frequently in our study. Intermittent hypodontia has been seen in several investigations in families with EDA and EDA receptor gene abnormalities (28, 37, 41). Additionally, it has been demonstrated that EDA contributes to incomplete maxillary lateral incisor instances. The majority of EDA gene mutations are thought to cause X-linked hypohidrotic ectodermal dysplasia (29, 39). They also stated that mutation is very rare in the same underlying and isolated hypodontia. Missense mutations were then recognized in the EDA gene resulting in differential hypodontia. Another study noted another discovery of a new EDA missense mutation in the Chinese family. Mutations result in EDA protein substitution in the TNF homology domain (30).

The gender-based prevalence of hypodontia was 84.2% for males and that of females 89.3%. CI was similar to 1.0 and the gender difference in the prevalence of hypodontia was not clinically significant. Females were more likely than males to contribute to the study, although there was no significant difference. This suggests that since the interval was not short, there may be a more prevalent tendency for hypodontia prevalence in females. We may agree with the results of some surveys, although other studies have documented females prominence over males (31).

In common cases of hypodontia, the most affected teeth are normally lateral incisors and second premolars. In this study, lacking lateral incisors, except for the MSX1 gene, can be found in all gene mutations while central incisors are most affected teeth. Compared to our observations, some of them show that the second premolar mandibular, followed by the maxillary second premolar, the maxillary lateral incisor, and the mandibular middle incisor are the most often absent teeth (32, 38). Prevalence findings suggest that canine and first molar defects are rare (33, 39). There is no detectable mutation in several individuals with hypodontia in any of the genes mentioned. The frequency of first molar associated agenesis is low. There might be an undisclosed causative cause that requires further study.

Teeth are a weak model in the subject of evolutionary development biology (34, 40). This may be due to advancements in dental patterning, which have demonstrated how intricate tooth formation is. Any gene alterations may be related to the changes in the control of tooth budding morphogenesis (35, 41). Polymorphic genetic loci have been particularly linked to phenotypic diversity in non-vertebrate species. Therefore, it is important to research the connection between genetic polymorphism and tooth agenesis (36, 42).

Conclusion

Sixteen final articles were screened in this systematic review, and methodological characteristics were analyzed. Five genes, including WNT10A, PAX9, MSX1, AXIN2 and EDA, are currently considered to have the ability to cause non-syndromic hypodontia. The most commonly affected teeth were found to be lateral incisor, followed by second premolar and central incisor. The first premolar, canine, second molar, and first molar were determined to be the least damaged teeth. In comparison to males, females were discovered to have a higher prevalence. The study of the genes involved in the development of hypodontia is crucial for understanding the genetic basis of the condition and may also aid in its treatment. Early detection of tooth loss can lead to the preparation and execution of alternative treatment modalities, which will help to develop cosmetic and functional dentistry in the future and lessen the difficulties of hypodontia.

Acknowledgement

We warmly thank Dr Lau Nyok Sean from Centre for Chemical Biology, USM for the linguistic revision of the manuscript and the staff nurse from Advance Medical and Dental Institute. This research is funded by Ministry of Higher Education Malaysia for Fundamental Research Grant Scheme with Project Code: FRGS/1/2018/SKK14/USM/03/2.

Competing interests

The authors claim to have no conflicts of interest.

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