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Mutations in the WNT10A Gene in Patients with Tooth Agenesis.

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ABSTRACT

Tooth agenesis is the most common congenital dental anomaly in humans. Missing teeth can be found as a result of genetic disorders or environmental factors that influence during the dental development. Mostly, tooth agenesis is a condition that has a genetic predisposition. Mutations in MSX1, PAX9, AXIN2, EDA, IRF6 and WNT10A that were found in patients with tooth agenesis confirm its genetic etiology. The aim of this study was to examine if mutation in WNT10A can be considered as a risk factor for tooth agenesis. For this purpose a genetic examination for possible mutation in WNT10A gene in 11 patients with congenitally missing teeth was made. WNT10A mutations were identified in 4 patients with isolated tooth agenesis. The roll it has in tooth development and high prevalence of mutation in WNT10A gene in patients with tooth agenesis makes this gene an important factor for the occurrence of this congenital anomaly.

Keywords: Tooth agenesis, WNT10A, mutation, genetic disorder

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INTRODUCTION

Tooth agenesis is a condition where the patient lacks one or more teeth due to failure in their development [1]. This is the most common congenital dentofacial anomaly [2-4].

Congenital absence of teeth can be found as a isolated condition (non-syndromic) or as an accompanying symptom of a syndrome disorder (syndromic). Furthermore, non-syndromic tooth agenesis can be familial or isolated. Isolated, or sporadic tooth agenesis is found only in one member of a family, while the family related is found in two or more members of a family [5]. The presence of tooth agenesis in more members of the same family indicates the role of the hereditary factor as a reason for this condition.

The reason for absence of some teeth remains unclear, but it is believed that this condition is associated with both genetic and environmental factors that have their influence during the dental development.

Many studies confirm the genetic hereditary factor as a reason for tooth absence. Researches done on twins and members of the same family points that hereditary factors predominate over the environmental ones [6-10].

With the development of molecular genetics, genetic mutations have been identified in a number of syndromes and severe forms of isolated cases of tooth agenesis. In these mutations different modes of inheritance are confirmed [11].

The mode of inheritance of tooth agenesis may be autosomal dominant [12-17], autosomal recessive [18], X-linked [19-21], and also there is possibility of polygenic inheritance [22-24]. Many genes have their role in the inheritance mode. Mutations in these genes cause phenotypic modifications among which is tooth agenesis. This happens because of wrong transcription of proteins which have a role in the tooth development. However, not always there is an exact way in genes penetration and their expression, which suggests the multifactorial manner of inheritance [25].

Many studies in genes mutations are conducted so far to identify if there is connection between those mutations and congenital absence of teeth. In most of the cases mutations in genes that are identified are those that are causing severe and rare dominant forms of tooth agenesis. However , most of the mutations in genes that are responsible for minor forms of tooth agenesis, which are also more common, are still unknown.

MATHERIALS AND METHODS

The aim of this study was through family history, clinical examination and panoramic radiographs to confirm that tooth agenesis is hereditary disorder. Also our goal was to identife if there are mutations in WNT10A-gene in patients with tooth agenesis.

The examination was conducted in dental office “Pop Acevi” and at the Department of orthodontics at the Faculty of dentistry in Skopje. Clinical examination and panoramic X-ray were made as well as family history was taken from 25 examinees with tooth agenesis along with their closest relatives. This was made in purpose to see if there is any kind of hereditary influence. According to presence or absence of another case or cases with tooth agenesis in the family, they were divided in two groups, first with positive history of familial agenesis and second with negative.

The genetic examination for possible mutation in WNT10A-gene, which is located on the second chromosome, was performed at the Research Centre for Genetic Engineering and Biotechnology at Macedonian academy of sciences and arts in Skopje. Examinees were informed about the purpose and methods of the research and their approval was obtained. Medical and dental history of the examinees was taken and those with suspected or already diagnosed syndrome were excluded from the study. The genetic material for this study was obtained using a buccal swab of the oral mucosa of patients with previously confirmed tooth agenesis. Isolation and DNA-sequencing (Sanger method) by automated genetic analyzer were made on the swab samples to determine if there is possible mutation in the WNT10A-gene.

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DNA isolation from the oral swab was conducted by the standard procedure for isolation with Roche kit (High Pure Viral Nucleic Acid Kit).

RESULTS

Out of 25 examinees with tooth agenesis in 13 of them was confirmed that there is at least one more member of the closest family with the same condition. In the remaining 12 no absence of teeth was confirmed among the closest family.

Genetic examination was made in 11 randomly selected examinees (6 males and 5 females) for possible mutations in the WNT10A-gene. One of the samples was made among members of the same family (brother and sister). After the DNA-sequencing four mutations in examined gene were found, one intronic and three exonic mutations. Results of the DNA-sequencing and amplification of exons are shown in Figure 1 and Table 1.

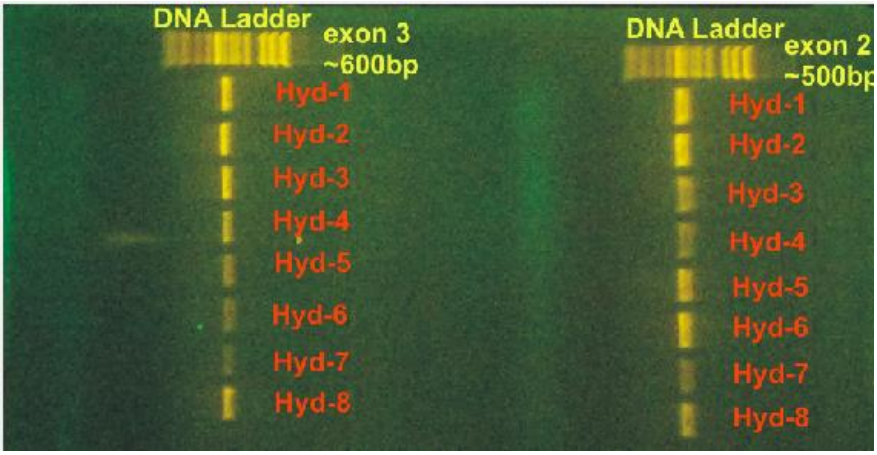

Figure 1: **Agarose gel electrophoresis of the PCR-amplification of exon 2 and 3**

Table 1: Results of the DNA-sequencing

Examinee	WNT10A exon 1	WNT10A exon 2	WNT10A exon 3	WNT10A exon 4
Hyd 1	Ok	Ok	c.511C>T	Ok
Hyd 2	Ok	Ok	Ok	Ok
Hyd 2_S	Oк	Ok	Ok	Ok
Hyd 3	Oк	Ok	Ok	Ok
Hyd 4	Ok	Ok	c.493G>A	Ok
Hyd 5	Ok	Ok	Ok	Ok
Hyd 6	Ok	Ok	Ok	Ok
Hyd 7	Ok	Ok	Ok	Ok
Hyd 8	Ok	Ok	Ok	Ok
Hyd 9	Ok	Ok	c.682T>A	Ok
Hyd 10	Ok	c.114-56T>C	Ok	Ok

DISCUSSION

Genetic role is often associated with tooth agenesis. In everyday practice more and more genetic studies are made in order to find out more about the mode of inheritance and which genes are responsible for which diseases or disorders.

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Knowing the process of teeth development and genes that allows it to go smoothly, we can identify any reasons that are responsible for specific dental anomalies.

In most of the cases tooth agenesis has genetic predisposition. It is more common in patients that already have a relative having this condition.

In addition to this goes the result of our research where more than half of the examinees have at least one more member in their family with the same disorder. Even in those examinees with no positive family history from the closest family, there could be some distant relative that had the same condition (grandmother, grandfather, great grandmother, great grandfather…).

Similar results were confirmed by Brook et al. where one third of the respondents with tooth agenesis had a relative of their closest family with the same anomaly [26].

Tests made on twins also point the role of genetic influence as a risk factor for tooth agenesis. Tooth agenesis is more common in identical twins than in non-identical [27, 28].

Mutations in genes which regulate the development of teeth are interfering the process of transcription of proteins and prevent the normal process between the mediators in odontogenesis. There are so many complex epithelio-mesenchymal processes which are responsible for normal teeth development. Any irregularities in those processes can cause a tooth absence. Up to date four families of genes are identified that have integral part in teeth development (Shh, FGF, BMP, Wnt) [29]. Mutations in some of the genes which are responsible for proper expression on these mediators can prevent the activation of the signal path, which will cause some defects in epithelial placodes from which teeth develop.

These genotypic changes often correlate with phenotypic changes, in our case congenital absence of the tooth [30]. However, as already mentioned, not always there is an exact way in genes penetration and their phenotypic expression, which suggests the multifactorial manner of inheritance.

Genes which are most commonly studied as responsible for tooth agenesis are MSX1 (fourth chromosome), PAX9 (14 chromosome), AXIN2 (17 chromosome), EDA (10 chromosome) and WNT10A (second chromosome).

Mutations in these genes are frequently identified in more severe cases of tooth agenesis [31], although mutations are noted in the mild cases as well. In addition to this are results in our research, where we got mutation in WNT10A-gene in patients with absence with only one or two teeth.

Cytogenetic location of the WNT10A-gene is 2q35.

Molecular location is on the second chromosome from the base pairs 218, 880, 532 to the base pairs 218, 893, 928 (Figure 2).

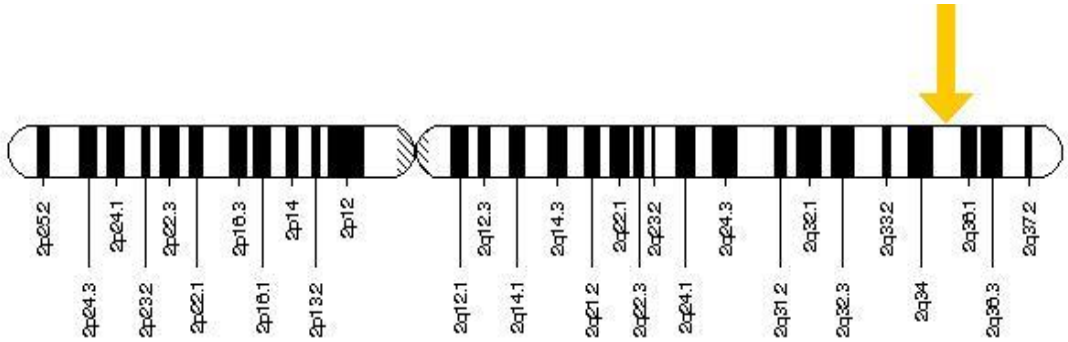


Figure 2: WNT10A-gene is locates on the long arm (q) of the second chromosome on position 35.

The integral role of WNT10A-gene in epithelio-mesenchymal interactions which take place during the teeth development process is pointed by Dassule et al. and Sarkar et al. respectively in their studies [32, 33]. Mutations in this gene cause wrong transcription of proteins which results in phenotypic changes among which is tooth agenesis.

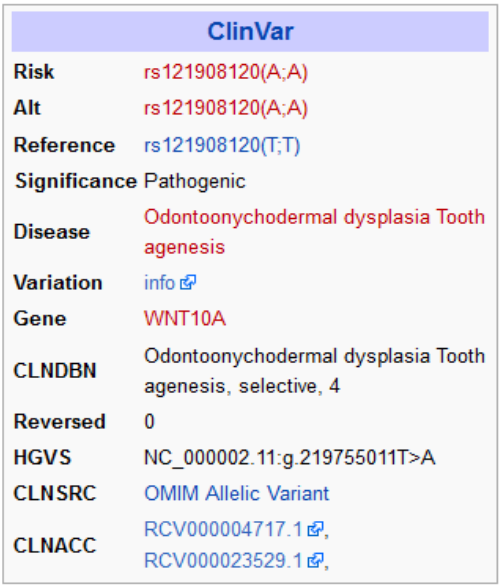
Results from the examination show four mutations in WNT10A-gene among 10 different samples with tooth agenesis. All of them are heterozygotes. Three of these mutations are in the exonic part of the gene (c.511C>T, c.493G>A и c.682T>A) and the last one is in its intronic part (c.114-56T>C). All of the three exonic mutations are found in the third exon of the WNT10A-gene. WNT10A has four exons.

These mutations are checked if they are already known as pathogenic in NCBI (National Center for Biotechnology Information) and results are shown in table 2.

Table 2: Verified mutations in NCBI

Mutation	Protein	SNP	NCBI	MAF
c.511C>T	p.R171C	rs116998555	Not Available	T=0.0032/16
c.493G>A	p.G165R	rs77583146	Not Available	A=0.0022/11
c.682T>A	p.Phe228Ile	rs121908120	With Pathogenic allele	A=0.0060/30
c.114-56T>C	/	rs10180544	Not Available	C=0.1418/710

Pathogenic mutation c.682T> A (p.Phe228Ile) in exon 3 was confirmed by the NCBI database and it correlates with odonto-oniho-dermal dysplasia, ectodermal dysplasia and congenital absence of teeth (Figure 3). This mutation causes a change in the nucleotide thymine with adenine. This results in replacing amino acid phenyl alanine at position 228 with isoleucine and changes the conformation of the protein.



ClinVar	
Risk	rs121908120(A;A)
Alt	rs121908120(A;A)
Reference	rs121908120(T;T)
Significance	Pathogenic
Disease	Odontoonychodermal dysplasia Tooth agenesis
Variation	info
Gene	WNT10A
CLNDBN	Odontoonychodermal dysplasia Tooth agenesis, selective, 4
Reversed	0
HGVS	NC_000002.11:g.219755011T>A
CLNSRC	OMIM Allelic Variant
CLNACC	RCV000004717.1, RCV000023529.1,

Figure 3: Map of clinical significance of the mutation c.682T> A

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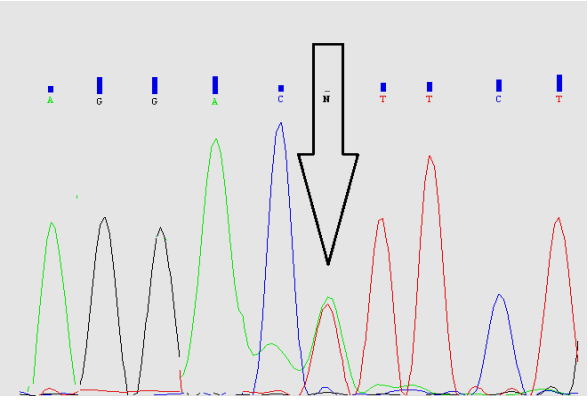

Figure 4: The electropherogram for mutation c.682T> A

The presence of this mutation is detected by Bohring et al. [34], Van den Boogaard et al. [35], Sirpa et al. [36], Plaisancié et al. [37] and Cluzeau et al. [38] in their studies in patients with congenital absence of teeth. According to Sirpa et al. this mutation is obtained in the most cases and is usually inherited as an autosomal recessive [36]. In our study this mutation is found in Hyd-9. The electropherogram for mutation c.682T> A is shown in the figure 4.

The other mutations that we got in our study were not found in NCBI database. Therefore, using bioinformatic tools, in silico analyses were made. The results of PolyPhen, PROVEAN, SIFT, Mutation Taster and HSF (Human splicing finder) are shown in Table 3.

Table 3: Results of PolyPhen, PROVEAN, SIFT, Mutation Taster and HSF analyses

Mutation	Exon	PolyPhen	PROVEAN	SIFT	Mutation Taster	HSF
c.511C>T	3	Probably Damaging	Deleterious	Damaging	Disease causing	No
c.493G>A	3	Benign	Neutral	Damaging	Disease causing	Potential alteration of splicing.
c.682T>A	3	Probably Damaging	Deleterious	Damaging	Disease causing	No
c.114-56T>C	2	/	/	/	polymorphism	Potential alteration of splicing.

Mutation c.511C> T (p.R171C) in exon 3 was not found as a pathogenic mutation in NCBI database. Therefore in silico analyses with bioinformatic tools such as SIFT, PROVEAN, PolyPhen Mutation Taster and HSF were made. All of them, except HSF, pointed that this mutation causes abnormal protein function. Changing of the nucleotide cytosine with thymine on protein level results in replacement of amino acid arginine at position 171 with cysteine. The fact that cysteine is a hydrophilic amino acid and has different conformation than the amino acid arginine, could cause distorted electrostatic interactions with other amino acids.

This mutation is described in the paper of Huiying et al. "Involvement of and Interaction between WNT10A and EDA Mutations in Tooth Agenesis Cases in the Chinese Population" published in PLOS ONE, November 27, 2013, where the mutation correlates with mutation in the EDA-gene and phenotypically is present tooth agenesis [39]. Out of six cases with mutations in WNT10A and EDA-genes respectively (2 with isolated non-syndromic tooth agenesis and 4 with agenesis of teeth as part of a syndrome) in four of them mutation c.511C> T in WNT10A-gene was obtained. This mutation is actually the same mutation that we received from one of the patients in our study (Hyd-1). The electropherogram of the mutation is shown in

Figure 5. This indicates frequent presence of this mutation among those with congenital absence of teeth, no matter if it is a mild or severe form of this anomaly.

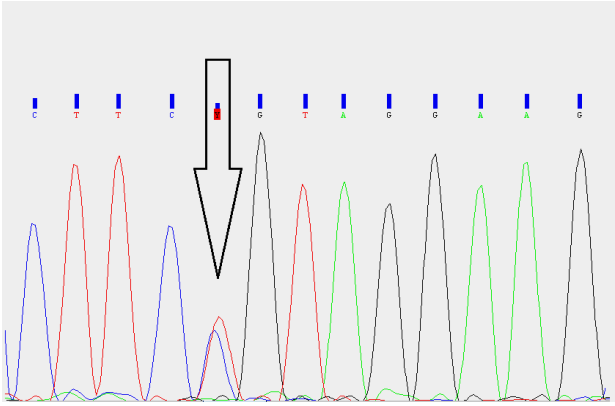

Figure 5: Electropherogram of mutation c.511C>T

Mutation c.493G> A (p.G165R) in exon 3 was not found as a pathogenic mutation in NCBI database. Following the in silico analyses, SIFT and Mutation taster point that this mutation is pathogenic. On the other way by PROVEAN and Polyphen this mutation is neutral. The change of nucleotide guanine to adenine on protein level results in replacement of the amino acid glycine at position 165 with arginine.

This mutation is explained in the study of Sirpa et al. "Candidate Gene Analysis of Tooth Agenesis Identifies Novel Mutations in Six Genes and Suggests Significant Role for WNT and EDA Signaling and Allele Combinations" published in PLOS ONE, August 22, 2013, where despite the recommendation of the in silico analysis, the paper points that this change causes a change in the RGD-motif which is a binding-site [36].

Bohring et al. in their study "WNT10A Mutations Are a Frequent Cause of a Broad Spectrum of Ectodermal Dysplasias with Sex-Biased Manifestation Pattern in Heterozygotes, points that this mutation is found in patients that do not have tooth agenesis [34]. He describes the mutation c.493G> A as a rare form of polymorphism which is found in the trans-position with already proven pathogenic mutation c.682T> A. In our study this mutation is found in patient Hyd-4. Its electropherogram is shown in figure 6.

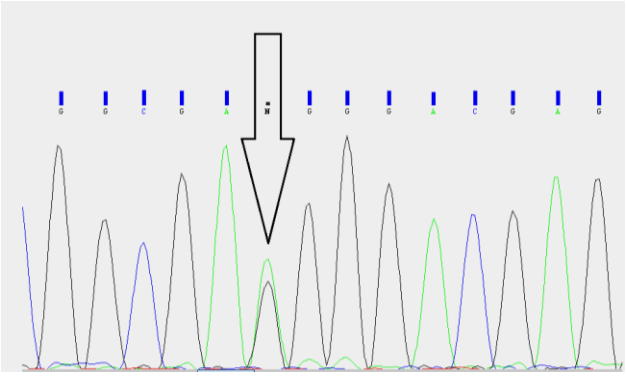

Figure 6: Electropherogram of mutation c.493G> A

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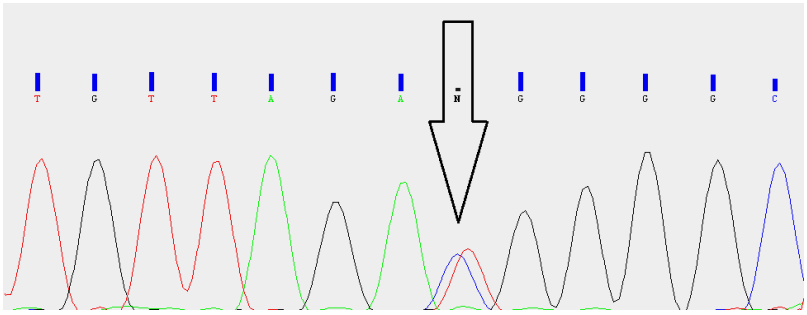

Figure 7: Electropherogram of mutation c.114-56T> C

Mutation c.114-56T> C does not have any clinical effect according the NCBI database. We should have into the consideration that intronic changes do not or hardly ever results with phenotypic modifications because these parts of the DNA are not prescribed during its transcription. This mutation comes with a replacement of nucleotide cytosine with thymine. In our research this mutation is found in Hyd-10 (Figure 7).

Following the results from the patients with mutation in the exonic part of the WNT10A-gene all teeth that are missing are in the anterior segment of the upper jaw, upper lateral incisors and canines (Table 4).

Table 4: Mutations and teeth which are missing

Sex	Location	Mutation	Number of missing teeth	Jaw	Uni/Bilateral affection	Affectted teeth
M	exon 3	c.511C>T	2	Upper	Bilateral	13, 23
M	exon 3	c.493G>A	1	Upper	Unilateral	12
F	exon 3	c.682T>A	2	Upper	Bilateral	12, 22
F	exon 2	c.114-56T>C	1	Lower	Unilateral	43

Mutation c.682T>A is confirmed as pathogenic mutation according NCBI database as well as by in silico analyses. Bohring et al, van den Boogaard et al and Sirpa et al in their studies have respectively confirmed the absence of upper lateral incisor in patients having this mutation in WNT10a-gene [34-36]. That is the case in our study too. This opens a question if this mutation always gives tooth agenesis of upper lateral incisors.

According to the results mutations in WNT10A-gene are present in 40% of the cases. Two, out of four mutations are already proven as pathogenic (c.682T>A and c.511C>T). More examination are needed for the third mutation (c.493G>A) to be decided if it is pathogenic mutation or neutral. Mutation in the intronic part of the WNT10A-gene (c.114-56T>C) does not show any phenotypic modifications, so it is considered as polymorphism.

Results show high prevalence of mutations in WNT10A-gene in patients with tooth agenesis, which makes it a significant factor that causes this condition. The mechanism of inheritance is very complex, therefore it requires additional and extensive tests to show us when a mutation of a given gene will be expressed and does it correlate with the environmental factors.

CONCLUSION

Wnt signaling pathaway initiates formation of dental as well as other epithelial placodes [33, 40-42]. Wnt10A-gene is one among the genes that initiate this pathaway [43-46]. Mutations in this gene disables this

pathaway and prevent formation of dental placodes. Therefore mutations in WNT10A-gene are risk factor for tooth agenesis, which is confirmed by our study, too.

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