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Research Article

WNT10A (rs 1054630) GENE POLYMORPHISM AND ITS ASSOCIATION WITH HUMAN TOOTH AGENESIS IN SOUTH INDIAN POPULATION - USING DNA SEQUENCING

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Key words:

Non-syndromic Tooth Agenesis; WNT 10A gene variant rs1054630; Genetic polymorphism; Hypodontia.

A B S T R A C T

Context: Non-syndromic tooth agenesis is a congenital defect without any other structural or developmental abnormalities.
Aims and Objectives: To evaluate the relationship, degree of association of WNT10A gene with Non syndromic tooth agenesis in in South Indian population.
Methods: DNA samples of 25 subjects with non-syndromic tooth agenesis and 25 unrelated controls, collected from the department were used for the study.
Group A: - DNA samples of 25 subjects with Non -syndromic tooth agenesis (T1 - T25)
Group B :- DNA samples of 25 unrelated controls (C1 - C25).
The extracted DNA samples were subjected to Polymerase chain reaction in which amplification of the selected gene segments was carried out; later these amplified products were subjected to DNA sequencing. Results were documented in the form of electropherograms.
Results: The results indicated that there is no association between the presence of WNT10A gene variant rs id 1054630 with the incidence of non syndromic tooth agenesis. This study also suggests that the likelihood of Non syndromic tooth agenesis is lower in subjects having AA (p=1.00) genotype.
Conclusion: This study indicates that there is an insignificant association between the presence of WNT10 A (rs 1054630) with the incidence of Non syndromic Tooth Agenesis in South Indian population.

INTRODUCTION

Tooth agenesis is a common developmental anomaly seen in human populations. It is often associated with the permanent dentition, has a female preponderance and overall prevalence ranging from 1% to 10%. Significant variation in patterns of tooth agenesis is seen, with the third molar most commonly absent in up to 30% of subjects, followed by mandibular second premolars in 1%-6% and maxillary lateral incisors in 1%- 4%. The mandibular anterior teeth are absent in around 1 per cent, whilst the absence of the maxillary central incisors, canines and first permanent molars is rare. Tooth agenesis is often associated with other dental developmental anomalies, including microdontia, delayed tooth formation, primary tooth retention and delayed eruption.

Hypodontia is often used as the generic term to describe tooth agenesis affecting less than six permanent teeth, excluding third molars, whilst oligodontia describes an absence of more than six permanent teeth (excluding third molars). Tooth agenesis can have consequences for facial morphology, particularly associated with the upper and lower jaws. Although some research has reported only limited affects, other work has found associations with reduced cranial base angle and length, mandibular and maxillary incisor retroclination, greater interincisal angle, protrusive mandible and reduced lower anterior facial height.[50]

Among several genes involved in tooth development, mutations in MSX1, PAX9, AXIN2, WNT10A, EDA and KDF1 have been reported to play a role in tooth agenesis. MSX1 is the first gene detected to have an association with this anomaly . The mutations of these genes can induce severe hypodontia and non-syndromic tooth agenesis.[54]

WNT10A gene is strongly expressed in embryonic limb, skin, hair follicle, and dental epithelium at the dental lamina and bud stages. During cap stage, its expression in the enamel knot is marked.[39] The only consistent feature of patients with WNT10A mutations in hypodontia.[54] Recent studies revealed that heterozygous WNT10A variants are causative candidates of autosomal-dominant selective tooth agenesis (STHAG4) including maxillary lateral incisor agenesis, as well as other autosomal recessive ectodermal dysplasia syndromes.[44]

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However, little is known about the mechanism underlying the broad spectrum in phenotypes of haploinsufficiency in WNT10A. Here we report allelic frequency of WNT10A variants in South Indian tooth agenesis patients, and describe phenotypic features peculiar to tooth agenesis related to WNT10A gene variants.

Objectives of the study were

- To test the association between WNT10 A (rs 1054630) polymorphisms and tooth agenesis in local population.
- To determine whether WNT10 A (rs 1054630) gene can act as genetic markers for tooth agenesis in local population.

METHODS

The polymorphism in WNT10 A (rs 1054630) were detected using the Polymerase Chain Reaction (PCR) test followed by DNA Sequencing. Automated DNA sequencing procedure was selected for the sequencing of DNA where each nucleotide was labelled with fluorescent dyes. The DNA sequence was detected more precisely and accurately on an electropherogram, by placing the DNA fragments on electrophoresis gel and passed through a laser beam.

Saliva samples from 25 cases with non syndromic tooth agenesis and 25 unrelated controls, who visited Department of Orthodontics and Dentofacial Orthopedics, D.A.P.M.R.V. Dental College, were taken after the written informed consent. Local population is defined as the population set by the investigator.

These were divided into two groups:

Group A: Twenty five cases with Non syndromic tooth agenesis (T1- T25)

Group B: Twenty five controls (C1- C25)

Inclusion criteria for Group-A and B subjects

- Cases-
  Individuals above 18 years of age with the presence of Non Syndromic Tooth agenesis on
- Clinical and Radiographic examination of South Indian origin.
- Controls-

Individuals above 18 years of age with all the complement of teeth including third molars on clinical and radiographic examination of South Indian origin.

Exclusion criteria for Group-A subjects

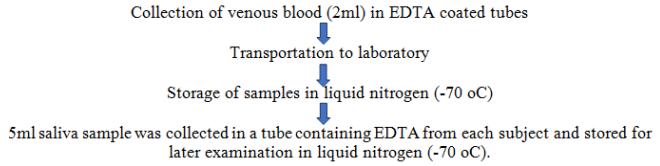
Patients with missing tooth due to reasons such as trauma, extraction and **non- South Indian origin** will be excluded for both cases and controls.

METHODOLOGY

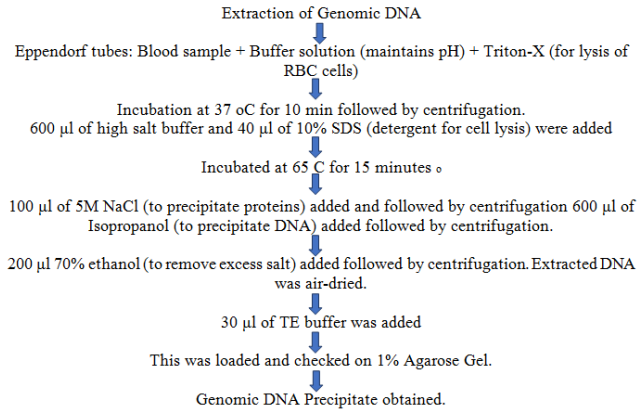
The method was divided into four steps

1. ***Step 1:*** Collection and storage of saliva samples,
2. ***Step 2:*** Isolation of Genomic DNA,
3. ***Step 3:*** Polymerase Chain Reaction Test (PCR),
4. ***Step 4:*** DNA sequencing

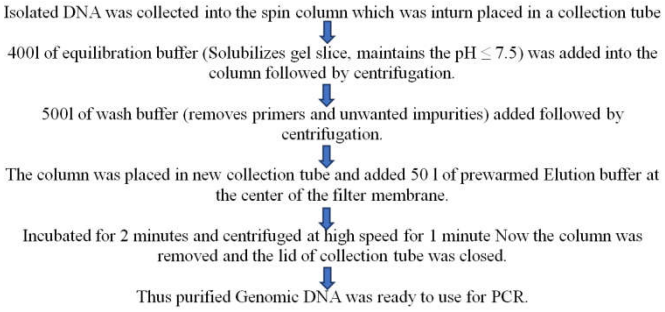
Step 1: Collection and Storage of Blood Samples (Flowchart 1):



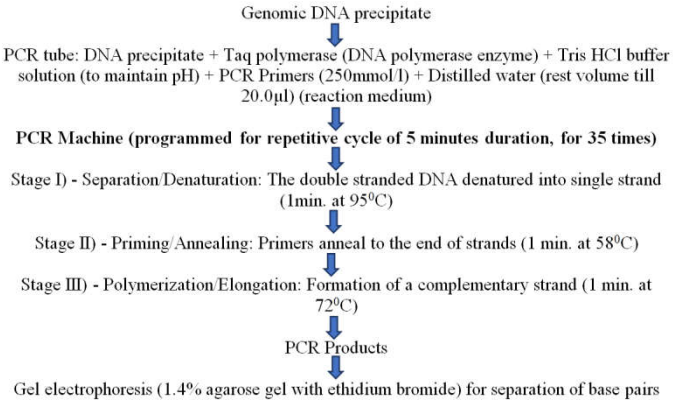
Step 2: Extraction of Genomic DNA (Flowchart 2)



Step 3: Column Purification of DNA (Flowchart 3)

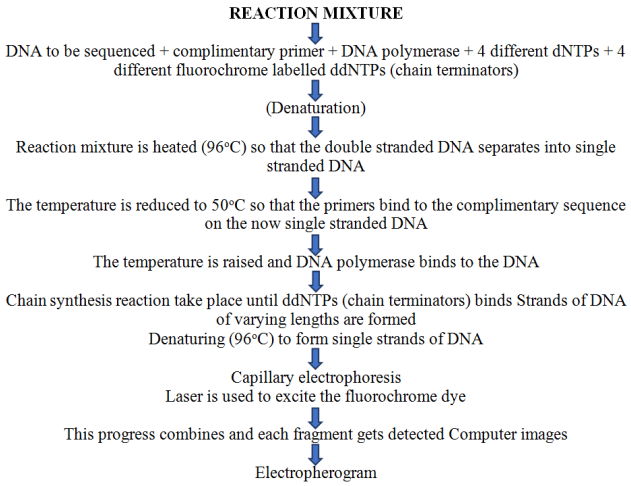


Step 4: Polymerase Chain Reaction (PCR) Test (Flowchart 4)



The Polymerase chain reaction (PCR) is an *in vitro* technique which allows the amplification of a specific deoxyribonucleic acid (DNA).
WNT10 A (RS 1054630)

WNT10AfpN 5'-GTCCTAGAGCCCACAGAAGTG -3'
WNT10ArpN 5'-GAGTGCCGCATCACCGAGTG -3'



Flowchart 5: DNA Sequencing with Capillary electrophoresis

STATISTICAL METHODS

Z test has been used to find the significance of association between WNT10A (RS 1054630) polymorphisms and tooth agenesis.

Z – Test: It can be applied for qualitative as well as quantitative data. Here it was applied to test the difference between two proportions (cases and controls).

Z-test for proportions formula

$$Z = \frac{\hat{P}1 - \hat{P}2}{SEDp}$$

$$SEDp = \sqrt{\hat{P}(1 - P^{\wedge})(1/n1 + 1/n2)}$$ and

$$P = \frac{X1+X2}{n1+n2}$$

p1, proportion1= x1/ n1 p2, proportion2= x2/ n2 x1 =number of cases with the 3 genotypes of each gene.

x2 =number of controls with the 3 genotypes of each gene.
n1 =total number of cases
n2 =total number of controls

Statistical interpretation

Highly significant p<0.001

Significant p≥0.001 and ≤0.05

Not significant p≥0.05

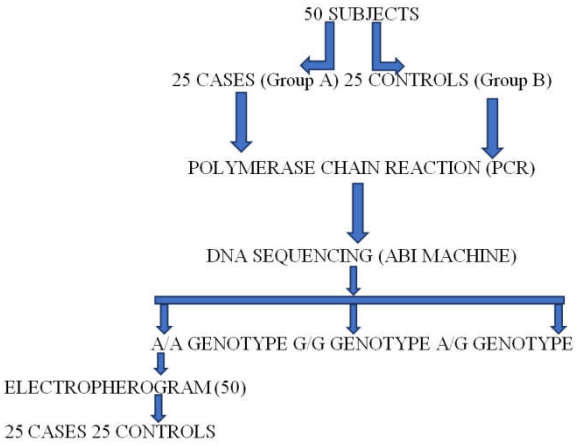
Statistical software: The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

In the present study, the association of WNT10 A (rs 1054630) polymorphisms with non syndromic tooth agenesis was evaluated in 50 subjects consisting of Group A (T1-T25) as cases and Group B(C1-C25) as controls using polymerase chain reaction(PCR) test followed by DNA sequencing.

Results for WNT10 A (rs 1054630) gene variants: For WNT10 A (rs 1054630) two genotypes can be possible:

- A/Aor G/G HOMOZYGOUS MUTANT ALLELE
- A/G HETEROZYGOUS MUTANT ALLELE



Flowchart 1 Results of WNT10 A (rs 1054630)

Later, the results of these fifty patients were tabulated based on the presence or absence of GG, GA and AA genotype of WNT10 A (rs 1054630). The number of cases and controls with difference in their genotype frequencies has been tabulated.

In Group A,1-25 : 25 out of 25 cases showed the presence of AA genotype.

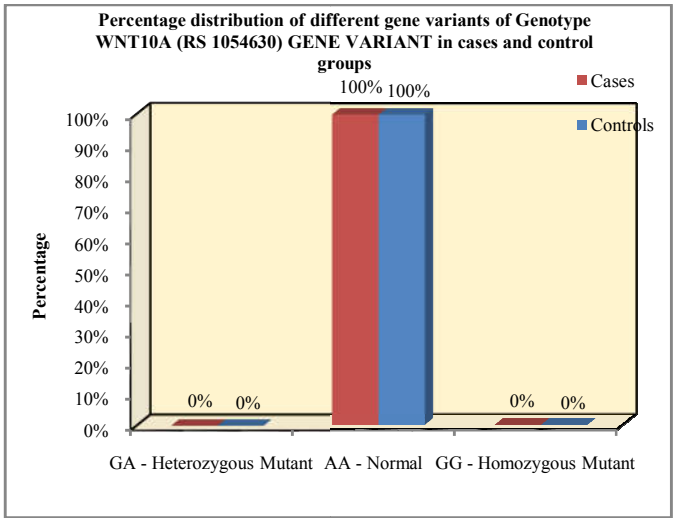
In Group B, C1-C25: 25 out of 25 controls showed the presence of AA genotype.

After statistical analysis (Z- test):

- AA genotype was found to be statistically insignificant with the cases and controls (GROUP A and B) (p=1.00)

Table 1 the Table Denotes the Statistical Significance of the Genotype When Cases and Controls Are Compared Using Z-Test

Genotype of Wnt10Ars 1054630 Gene Variant	Cases		Controls		Difference in Proportions	Z	P-Value
	n	%	n	%			
AA- Normal	25	100%	25	100%	0.0	..	..
AG- Heterozygous Mutant	0	0	0	0	0.0	0.000	1.00
GG- Homozygous Mutant	0	0	0	0	0.0	..	..



DISCUSSION

Identifying a hereditary dental pathology and defining its unique characteristics are the first steps toward the dissection of its genetic basis. A thorough interview of the patient and his or her relatives is the next step to defining the trait as familial; if it proves to be so, it is imperative to define the pattern of inheritance of the anomaly. In this respect, several genes that are pivotal in initiating the development of teeth have been subjected to intense study in the past decade.

Mutations in a number of genes were found to interrupt tooth development in mice. However, there are few genes associated with the nonsyndromic form of human tooth agenesis: AXIN2, Msx1, and Pax9, EDA, EDARADD.[35] Recently, WNT10A was identified as a causal gene of an autosomal recessive ectodermal dysplasia (ED): the odonto-onycho-dermal dysplasia (Adaimy *et al*. 2007) and a broad spectrum of EDs (Bohring *et al*. 2009). Of those reported WNT10A-related syndromic patients, tooth agenesis was the most consistent symptom and showed variable clinical manifestations (Adaimy *et al*. 2007; Bohring *et al*. 2009; Nawaz *et al*. 2009; Van Geel *et al*. 2010; Cluzeau *et al*. 2011; Nagy *et al*. 2010; Wedgeworth *et al*. 2011; Castori *et al*. 2011). Recently, van den Boogaard *et al*., have revealed that WNT10A gene mutations caused severe tooth agenesis (van den Boogaard *et al*. 2012) and Mostowska *et al*., have shown that significant association was found between 2 SNPs in the WNT10A and the risk for tooth agenesis in a relatively small sample size (Mostowska *et al*. 2012).[23]

The importance of the Wnt pathway has been shown in hair-follicle morphogenesis and skin and tooth embryogenesis (Jarvinen *et al*., 2006; Millar *et al*., 1999). In humans, there are 19 members in the WNT family proteins, which are expressed in a spatially restricted and dynamic pattern (Moon, Kohn, De Ferrari, &Kaykas, 2004). These are small secreted cysteine-rich glycoproteins that regulate cell-to-cell interactions during development, by acting as short-range ligands to locally activate receptor-mediated signaling pathways (Peifer&Polakis, 2000). Recently, the reduction of the β-catenin pathway activity and adult epithelial progenitor proliferation has been shown to be caused by the absence of WNT10A (Xu *et al*., 2017) .[53]

Odonto-onycho-dermal dysplasia (OODD) is a rare form of autosomal recessive ED, characterized by oligodontia, nail dysplasia, keratoderma, hyperhidrosis of the palms and soles and hyperkeratosis of the skin (Zirbel, Ruttum, Post, &Esterly, 1995). A homozygous nonsense WNT10A mutation was identified by linkage analysis and candidate gene sequencing in three con- sanguineous Lebanese OODD families (Adaimy *et al*., 2007). Later, it was found that WNT10A mutations can cause a broad spectrum of tooth agenesis, from non-syndromic oligodontia to Schöpf-Schulz-Passarge syndrome (SSPS), a severe form of ED with an additional unique symptom of numerous cysts along the eyelid margins (Bohring *et al*., 2009). Additionally, it was also identified that about half of the heterozygotes exhibited nail and tooth anomalies, such as abnormal shape or agenesis of one or two permanent teeth (Bohring *et al*., 2009). Recent studies demonstrated that WNT10A variants cause about half of the isolated hypodontia cases (Ruiz-Heiland, Lenz, Bock, &Ruf, 2018; Song *et al*., 2014; van den Boogaard *et al*., 2012).

It has been noted that primary dentition is less affected than permanent dentition in a multicentric genotype-phenotype study with 41 patients with WNT10A mutations (Tardieu *et al*., 2017). It has been further suggested that the molecular mechanisms regulating the development of primary and permanent dentition may be different based on the finding that the permanent teeth are missing completely, but only several deciduous teeth (less than 5) are missing in OODD patients caused by biallelic WNT10A mutations (Yu *et al*., 2019). The phenotypic spectrum caused by WNT10A mutations suggests a dosage dependent pattern with variable expression even in the same family members. Biallelic mutations with more harmful effects, such as non- sense or frameshift mutations, cause the rare and severe form of ED, OODD and SSPS. Even these severe mutations cause a limited number of missing primary teeth. Biallelic mutations with less harmful effects, such as missense mutations, cause a mild form of ED or non-syndromic oligodontia/ hypodontia. Individuals with a heterozygous mutation exhibit usually hypodontia with reduced penetrance and variable expressivity.

In the present study, the role of WNT10A (rs 1054630) gene variants with tooth agenesis were assessed in 50 subjects, we sequenced the coding region of the WNT10A gene and investigated the contributions of WNT10A variants to non-syndromic tooth agenesis. Twenty- five non-synonymous variations in the coding region of WNT10A gene were detected. In this study done on local population, in group A, 25 out of the 25 cases, tested positive for the presence of A/A genotype which was statistically insignificant (P=1.00). This result is similar as in the case of Wang *et al*, in which he failed to duplicate the significant association between WNT10A and sporadic tooth agenesis as reported by Peres *et al*. This indicates that the A/A and G/G genotypes of WNT10A (rs 1054630) gene variant does not contribute to the occurrence of tooth agenesis in local population. This is in accordance with the study done by Wang *et al* in Chinese population.

The discrepancy of the results between these two studies and the present study may be explained as follows. Firstly, population diversity may be responsible for the inconsistency. Genetic polymorphisms often show ethnic variation. For example, the frequency of variant allele was 35.3% in the Caucasian population reported by Cluzeau *et al* but 28% in the population of the present study. Therefore, further studies of different ethnic populations are warranted to ascertain the association between genetic polymorphisms of WNT10A and sporadic tooth agenesis.

Secondly the different phenotypic pattern of tooth agenesis may account for the different results obtained between the studies. In the study of Cluzeau *et al*, 70% of the test subjects had third molar agenesis, but in the study done by Wang *et al*, more than half of the test subjects lacked mandibular incisor, and subjects with third molar agenesis were not included because some individuals were too young for this trait to be determined. Therefore, it is possible that genetic variants of the WNT10A gene may account for third molar agenesis and that other genetic variants may be responsible for mandibular incisor agenesis. This is also in accordance with the study done by Mostowska and Biedziak *et al* on a Polish family.

This study could bring about new possibilities of early diagnosis and foresight of orthodontic or prosthetic treatment. Recent advances in tissue and organ engineering and gene

therapy could even allow the implantation of cultured tooth germs or the early repair of genetic defect, leading to normal development. Once these genetic markers have been established they can be used as powerful tools for screening the population. In the near future, with advances in science a correction at molecular level remains a possibility.

Therefore, further studies should focus on (i) genetic study in different populations and a larger sample (ii) identification of functional variants responsible for the identified association signals and (iii) searching for the relationship between the Wnt signalling pathway and increased risk of non-syndromic tooth agenesis.

CONCLUSION

The conclusions drawn from this study are

1. This study indicates that there is an insignificant association between the presence of WNT10 A (rs 1054630) with the incidence of Non syndromic Tooth Agenesis.
2. This study suggests that the likelihood of Non syndromic Tooth Agenesis is lower in subjects having AA (p=1.00) genotype for WNT10 A (rs 1054630).
3. This study suggests that the incidence of Non syndromic Tooth Agenesis is lesser in subjects having AA (p=1.00) in WNT10 A (rs 1054630) genotype.
4. The findings of this study suggest that WNT10 A (rs 1054630) cannot be considered as genetic markers for Non syndromic Tooth Agenesis in South Indian population.

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