International Journal of Applied Dental Sciences 2017; 3(4): 493-498

ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2017; 3(4): 493-498

www.oraljournal.com
Received: 09-08-2017
Accepted: 10-09-2017

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Association of paired box 9 (*PAX9*) *(rs12881240)* and muscle segment homeobox 1(*MSX1*) *(rs12532)* gene polymorphisms in human tooth agenesis

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Abstract
Agenesis of one or more teeth is the most common anomaly observed in human craniofacial development. The aim is to test the association between *PAX9 (rs12881240)* and *MSX1 (rs12532)* polymorphisms and tooth agenesis in local population. DNA samples of 25 subjects with non-syndromic tooth agenesis and 25 unrelated controls, collected from the department were used for the study. The extracted DNA samples were subjected to Polymerase chain reaction and then subjected to DNA sequencing. This study also suggests that the likelihood of Non syndromic tooth agenesis is higher in subjects having CT (p=0.02) genotype of PAX 9 gene variant rs12881240 & AG (p=0.02) genotype for MSX 1 gene variant rs12532. Conclusion is the PAX 9 gene variant rs12881240 and MSX 1 gene variant rs12532 can be considered as genetic markers for Non-syndromic Tooth agenesis in local population.

Keywords: Non-syndromic tooth agenesis, PAX 9 gene variant rs12881240, MSX 1 gene variant rs12532

Introduction
Teeth have a prominent relevance to socio-cultural interactions and at an individual level can represent a bad or good life quality [1]. The development of dentition is a fascinating process that encompasses a complex series of epithelial–mesenchymal interactions involving growth factors, transcription factors, signal receptors and other morphogens. It is not surprising that such a complex process is prone to disturbances and may result in tooth agenesis.

Agenesis refers to the failure of an organ to develop during embryonic growth and development due to the absence of primordial tissue. Agenesis of one or more teeth is the most common anomaly observed in the human craniofacial development [1].

Amongst all non-syndromic (familial or sporadic) agenesis conditions detected in humans, the most common is the absence of third molar followed by upper lateral incisors and second premolars. The Paired Box Gene 9 (PAX9) and Muscle Segment Homeobox 1 (MSX1) genes have been associated with tooth morphogenesis [1].

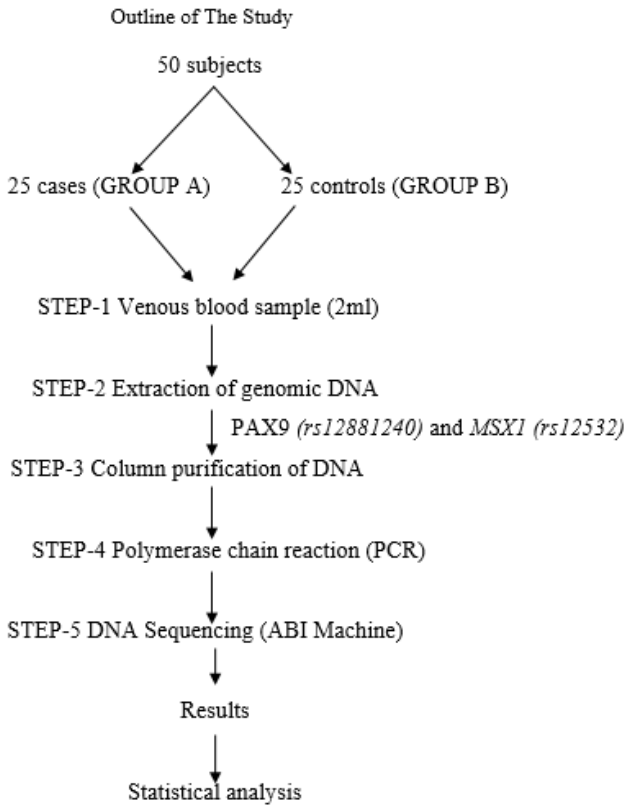
PAX9 is mapped onto chromosome 14q12-q13 and mutations in this gene can lead to non-syndromic tooth agenesis. PAX9 is expressed in dental mesenchyme at initiation, bud, cap and bell stages of odontogenesis. Protein products of this gene serve as transcription factors that are responsible for the crosstalk between epithelial and mesenchymal tissues and are essential for the establishment of the odontogenic potential of the mesenchyme [2].

The MSX1 gene is located on the chromosome 4 and belongs to the homeobox MSX gene family related to the Drosophila msh like gene family. The gene encodes a DNA bonding protein, which is involved in many epithelial mesenchymal interactions during vertebrate embryogenesis, leading to organogenesis. MSX1 expression appears to be most critical during early tooth development [3].

It has been reported that both MSX1 and PAX9 have many polymorphic variants. Therefore, by deciphering the association of the same with tooth agenesis, can give an in depth knowledge, regarding the genetic influences on tooth agenesis. Hence, there is a need to establish the role of PAX9 and MSX1 polymorphisms in tooth agenesis.

Materials and methods

The present study aims to test the association between *PAX9 (rs12881240)* and *MSX1 (rs12532)* polymorphisms and tooth agenesis. The polymorphism in *PAX9* gene variant rs12881240 and *MSX1* gene variant rs12532 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 labeled 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.



Blood samples from 25 cases with non syndromic tooth agenesis and 25 unrelated controls, who visited Department of Orthodontics and Dentofacial Orthopedics, were taken after the written informed consent.

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 subjects:
Patients with sporadic tooth agenesis that is not associated with any known syndrome.

Exclusion criteria for Group-A subjects

Patients with missing tooth due to reasons such as trauma, extraction.

Methodology

The methodology consisted of five steps:
Step 1: Collection and storage of blood samples,
Step 2: Extraction of Genomic DNA,
Step 3: Column purification of Genomic DNA,
Step 4: Polymerase Chain Reaction Test (PCR),
Step 5: DNA sequencing

Statistical methods

Z test has been used to find the significance of association between *PAX9 (rs12881240)* and *MSX1 (rs12532)* polymorphisms and tooth agenesis.

Z-test for proportions formula

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

$$SEDp = \sqrt{\hat{P}(1 - P\hat{})(1/n1 + 1/n2)} \text{ and } P = \frac{X1+X2}{n1+n2}$$

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 $p \leq 0.001$
Significant $p \geq 0.001$ and ≤ 0.05
Not significant $p \geq 0.05$

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 relationship between *PAX9 (rs12881240)* and *MSX1 (rs12532)* gene variants 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 *PAX9 (rs12881240) and MSXI (rs12532) gene* variants

For *PAX9 (rs12881240)* three genotypes can be possible:

T/T or G/G	Homozygous mutant allele
C/G or C/T	Heterozygous mutant allele
C/C	Normal homozygous allele

Later, the results of these fifty patients were tabulated based on the presence or absence of TT, CT and CC genotype of PAX9 rs*12881240* variant (Table 1). The number of cases and controls with difference in their genotype frequencies has been tabulated (Table 2).

In Group A

7 out of 25 cases showed the presence of TT genotype.
14 out of 25 cases showed the presence of CT genotype.
4 out of 25 cases showed the presence of CC genotype.

In Group B

6 out of 25 controls showed the presence of TT genotype.
6 out of 25 controls showed the presence of CT genotype.
13 out of 25 controls showed the presence of CC genotype.
After statistical analysis (Z- test) (Table 3):

- There were statistically significant difference in CT and AA genotype frequencies between cases and controls
- CC genotype was found to be statistically significant with the controls (GROUP B) (p=0.007)

- CT genotype was found to be statistically significant with the cases (Group A) (p=0.02)
- TT genotype was found to be statistically insignificant with the cases (Group A) (p=0.75)

Results for MSX1 rs12532 variants

For MSX1 (rs12532) three genotypes can be possible

G/G Homozygous mutant allele
A/G Heterozygous mutant allele
A/A Normal homozygous allele

Later, the results of these fifty patients were tabulated based on the presence or absence of GG, AG and AA genotype of MSX1 (rs12532) variant (Table 4). The number of cases and controls with difference in their genotype frequencies has been tabulated (Table 5).

In Group A

8 out of 25 cases showed the presence of GG genotype.
13 out of 25 cases showed the presence of AG genotype.
4 out of 25 cases showed the presence of AA genotype.

In Group B

6 out of 25 controls showed the presence of GG genotype.
5 out of 25 controls showed the presence of AG genotype.
14 out of 25 controls showed the presence of AA genotype
After statistical analysis (Z- test) (Table 6):

- There was statistically significant difference in AG genotype with cases. (Group A) (p=0.02)
- GG genotype was found to be statistically insignificant with the cases. (Group A) (p=0.53)
- AA genotype was found to be statistically significant with the controls (Group B) (p=0.003)

Discussion

Tooth agenesis may result from diverse factors, including environmental factors (e.g. trauma), genetic factors, multi reagent chemotherapy, radiotherapy, etc [4]. The important role of genetics has been increasingly recognized in recent years with respect to the understanding of dental anomalies, especially tooth agenesis. Investigations on animals have shown that tooth development is regulated by interactions between epithelial and mesenchymal cells and is dependent on a number of genes. These genes encode transcription factors and signal molecules that exhibit dynamic expression patterns during embryogenesis in a variety of tissues and play an important role in the formation of a number of organs, including teeth.

The identification of genetic risk factors of tooth agenesis has been the subject of intensive research and various candidate genes have been identified in studies conducted on populations of diverse ethnic backgrounds.

PAX 9 gene plays an important role in odontogenesis as it can transactivate the Bmp4 promoter construct. The tooth-agenesis-causing *PAX9* mutations impair DNA binding and Bmp 4 promoter activation. The R28P (arginine to proline) mutation reduces the DNA binding of the *PAX9* paired domain and this loss of DNA binding causes tooth agenesis [5].

MSX1 is also reported to repress transcription from this proximal Bmp4 promoter, and that, in combination with *PAX9*, acts as a potentiator of *PAX9*-induced Bmp4 transactivation. Two substitution mutations, Arg 196 Pro and Met 61 Lys cause only familial non-syndromic tooth agenesis. Frameshift mutations, Ser 202 Stop mutation and Ser 105 Stop mutation, cause complete absence of the *MSX1* homeodomain and are responsible for the most severe phenotype, which includes orofacial clefts with accompanied tooth agenesis [4].

In the present study, the role of *PAX 9 (rs12881240)* and *MSX1 (rs12532)* gene variants with tooth agenesis were assessed in 50 subjects.

PAX9 (*rs12881240)*

PAX9 is considered as one of the most commonly involved gene affecting the odontongenic process. The *PAX9* gene is particularly attractive as a candidate gene for tooth agenesis, which is not only demonstrated by mouse study models but also by genetic studies in humans. In accordance with the various studies quoted earlier, it can be concluded that at present, 14 mutations and one deletion of the *PAX9* gene have been associated with familial, non syndromic tooth agenesis, spreading throughout the entire gene and clustering in the paired DNA-binding domain [6].

In this study done on local population, in group A, 14 out of the 25 cases, tested positive for the presence of CT genotype which was statistically significant (P=0.02). This result is similar as in the case of Peres *et al*. [7] who had reported that two polymorphisms (*rs2073244* and *rs2073246*) of *PAX9* were associated with sporadic tooth agenesis in a Caucasian population. However, Wang *et al*. [8] failed to duplicate the significant association between *rs2073244* and sporadic tooth agenesis as reported by Peres *et al*.

Similarly, 7 out of 25 cases, tested positive for the presence of TT genotype which was statistically not significant (P=0.75) and 4 out of 25 cases, tested positive for the presence of CC genotype which was statistically not significant. (Table 1, Table 2, Table 3, Graph 1). This indicates that the CC and TT genotypes of *PAX9 (rs12881240)* 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 [8].

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 the variant allele (T allele) of *rs2073244* was 35.3%% in the Caucasian population reported by Peres *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 *PAX9* 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 Peres *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 *PAX9* gene may account for third molar agenesis and that other genetic variants may be responsible for mandibular incisor agenesis.

MSX1 (rs12532)

Apart from PAX9, MSX1 gene alone has shown to play a pivotal role in odontogenic process. Although, MSX1 in conjuction with PAX9 gene was reported to show a synergistic effect. Therefore, a deficiency of MSX1 can result in tooth agenesis. In this study done on local population, in

group A, 13 out of the 25 cases, tested positive for the presence of AG genotype which was statistically significant (P=0.02). This is in confirmation to the study done by Mostowska and Biedziak on a Polish family [9]. Similarly, 8 out of 25 cases, tested positive for the presence of GG genotype which was statistically not significant (P=0.53) and 4 out of 25 cases, tested positive for the presence of AA genotype which was statistically not significant (p=0.147) (Table 1, Table 2, Table 3, Graph 1). This indicates that the AA and GG genotype of *MSX1 (rs12532)* gene variants does not contribute to the occurrence of tooth agenesis in local population. This is also in accordance with the study done by Mostowska and Biedziak on a Polish family [9].

These results affirm that the novel heterozygous transition found in *MSX1* might be responsible for tooth agenesis. This mutation resulting in Ala194Val substitution is localized at the beginning of the second helix of the highly conserved homeodomain. To date, mutations identified in the homeodomain containing proteins have been associated with many diseases, including not only developmental abnormalities but also metabolic disorders as reviewed by Chi in 2005. These mutations might affect post-transcriptional modifications of the primary transcript, protein expression level, protein stability, localization, and interactions with other proteins as proposed by Wang and Moult in 2001. The novel Ala194Val substitution of *MSX1* is located only at 2 amino acid residues from the first mutation (Arg 196 Pro) associated with human tooth agenesis as reported by Vastardis *et al*. (1996) [10]. Functional analysis of this mutated protein revealed that its ability to interact with DNA and other transcription factors as well as its transcriptional repression capacity were severely impaired (Hu *et al*. 1998).[11] These observations may suggest that the novel heterozygous c.581C>T transition leads to a similar effect on the gene product, and might be responsible for the loss of function of the encoded protein.

The above findings suggest that *PAX9 (rs12881240)* CT genotype and *MSX1 (rs12532)* AG genotype may be implicated as genetic marker for tooth agenesis in local population. This can be confirmed by further studies with a larger sample size. In contrast *PAX9 (rs12881240) TT and CC* genotype and *MSX1 (rs12532) GG and AA genotype* did not show any significant statistical association with tooth agenesis.

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

Table 1: Tabulated results for fifty subjects showing variation in presence of genotypes of PAX9 (*rs12881240)* gene variant among cases and controls.

Group a (cases)	Genotype TT	Genotype CT	Genotype CC	Group b (controls)	Genotype TT	Genotype CT	Genotype CC
1.	Absent	Absent	Present	1.	Absent	Present	Absent
2.	Absent	Present	Absent	2.	Absent	Absent	Present
3.	Absent	Absent	Present	3.	Absent	Absent	Present
4.	Absent	Present	Absent	4.	Absent	Absent	Present
5.	Absent	Present	Absent	5.	Absent	Absent	Present
6.	Absent	Absent	Present	6.	Absent	Absent	Present
7.	Present	Absent	Absent	7.	Absent	Present	Absent
8.	Absent	Present	Absent	8.	Present	Absent	Absent
9.	Absent	Absent	Present	9.	Absent	Absent	Present
10.	Present	Absent	Absent	10.	Absent	Present	Absent
11.	Present	Absent	Absent	11.	Present	Absent	Absent
12.	Absent	Present	Absent	12.	Absent	Absent	Present
13.	Absent	Present	Absent	13.	Absent	Present	Absent
14.	Absent	Present	Absent	14.	Absent	Absent	Present
15.	Present	Absent	Absent	15.	Present	Absent	Absent
16.	Present	Absent	Absent	16.	Absent	Absent	Present
17.	Absent	Present	Absent	17.	Absent	Absent	Present
18.	Absent	Present	Absent	18.	Absent	Present	Absent
19.	Absent	Present	Absent	19.	Absent	Absent	Present
20.	Present	Absent	Absent	20.	Present	Absent	Absent
21.	Absent	Present	Absent	21.	Present	Absent	Absent
22.	Absent	Present	Absent	22.	Absent	Absent	Present
23.	Absent	Present	Absent	23.	Present	Absent	Absent
24	Absent	Present	Absent	24	Absent	Absent	Present
25.	Present	Absent	Absent	25.	Absent	Present	Absent

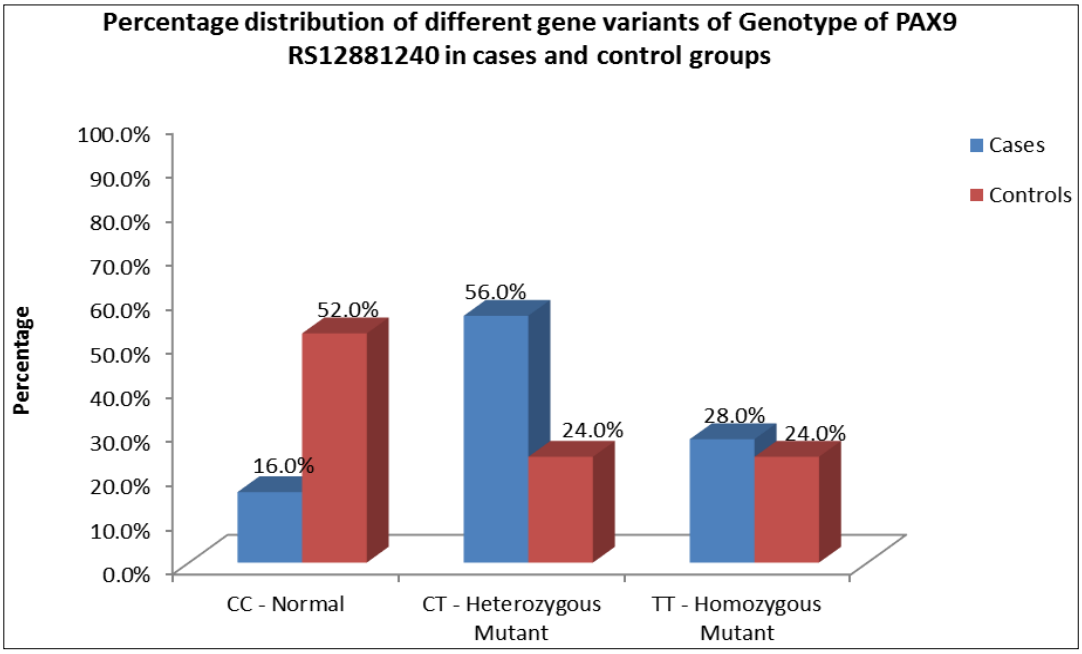
Table 2: The presence of tt, ct, cc genotype of pax9 (*rs12881240)* gene variants among cases and controls

Genotype of PAX9 (*rs12881240)* Gene variant	Group a (cases)	Group b (controls)	Total
TT	7	6	13
CT	14	6	20
CC	4	13	17
Total	25	25	50

Table 3: The table denotes the statistical significance of the genotype when cases and controls are compared using z-test.

Genotype of PAX9 RS12881240 Gene Variant	Cases		Controls		Difference in Proportions	Z	P-Value
	n	%	n	%			
CC	4	16	13	52	-0.36	-2.687	0.007*
CT	14	56	6	24	0.32	2.357	0.02*
TT	7	28	6	24	0.04	0.322	0.75

* - Statistically Significant



Graph 1

Table 4: Tabulated results for fifty subjects showing variation in presence of genotypes of MSX1 (rs12532) gene variant among cases and controls

Group a Cases	Genotype GG	Genotype AG	Genotype AA	Group b controls	Genotype GG	Genotype AG	Genotype AA
1.	Absent	Absent	Present	1.	Present	Absent	Absent
2.	Absent	Absent	Present	2.	Absent	Absent	Present
3.	Present	Absent	Absent	3.	Absent	Present	Absent
4.	Absent	Present	Absent	4.	Present	Absent	Absent
5.	Absent	Present	Absent	5.	Absent	Absent	Present
6.	Absent	Present	Absent	6.	Absent	Absent	Present
7.	Present	Absent	Absent	7.	Present	Absent	Absent
8.	Present	Absent	Absent	8.	Absent	Absent	Present
9.	Present	Absent	Absent	9.	Absent	Absent	Present
10.	Absent	Present	Absent	10.	Present	Absent	Absent
11.	Absent	Present	Absent	11.	Absent	Absent	Present
12.	Present	Absent	Absent	12.	Absent	Absent	Present
13.	Absent	Absent	Present	13.	Absent	Absent	Present
14.	Absent	Present	Absent	14.	Absent	Present	Absent
15.	Absent	Present	Absent	15.	Absent	Absent	Present
16.	Absent	Present	Absent	16.	Absent	Present	Absent
17.	Absent	Present	Absent	17.	Absent	Absent	Present
18.	Present	Absent	Absent	18.	Present	Absent	Absent
19.	Absent	Present	Absent	19.	Absent	Absent	Present
20.	Present	Absent	Absent	20.	Absent	Absent	Present
21.	Absent	Present	Absent	21.	Absent	Present	Absent
22.	Absent	Present	Absent	22.	Absent	Present	Absent
23.	Present	Absent	Absent	23.	Present	Absent	Absent
24	Absent	Present	Absent	24	Absent	Absent	Present
25.	Absent	Absent	Present	25.	Absent	Absent	Present

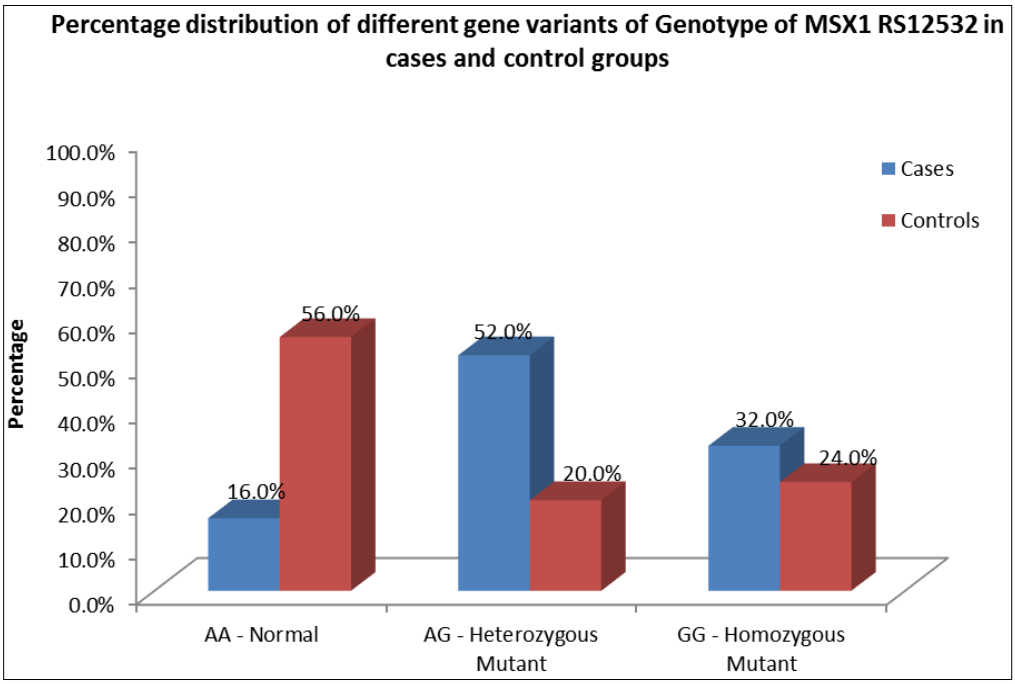
Table 5: The Presence of GG, AG, AA genotype of MSX1 (rs12532) gene variant among cases and controls

Genotype of MSX1 (rs12532)Gene variant	Group A (Cases)	Group B (Controls)	Total
GG	8	6	14
AG	13	5	18
AA	4	14	18
Total	25	25	50

Table 6: The table denotes the statistical significance of the genotype when cases and controls are compared using Z-test

Genotype of MSX1 RS12532 Gene Variant	Cases		Controls		Difference in Proportions	Z	P-Value
	n	%	n	%			
AA - Normal	4	16	14	56	-0.40	-2.946	0.003*
AG - Heterozygous Mutant	13	52	5	20	0.32	2.357	0.02*
GG - Homozygous Mutant	8	32	6	24	0.08	0.630	0.53

* - Statistically Significant



Graph 2

Conclusion

The conclusions drawn from this study are:-

1. This study indicates that there is a significant association between the presence of PAX9 gene variant rs*12881240* and MSX1 gene variant rs12532 with the incidence of Non syndromic Tooth Agenesis.
2. This study suggests that the possibility of Non syndromic Tooth Agenesis is higher in subjects having CT (p=0.02) genotype for PAX9 gene variant rs12881240 and AG (p=0.02) genotype for MSX1 gene variant rs12532.
3. This study suggests that the incidence of Non syndromic Tooth Agenesis is lesser in subjects having TT (p=0.75) & CC (P=0.007) genotype of PAX9 gene variant rs12881240 and GG (p=0.53) & AA (p=0.003) genotype of MSX1 gene variant rs12532.
4. The findings of this study suggest that PAX9 gene variant rs12881240 and MSX1 gene variant rs12532 can be considered as genetic markers for Non syndromic Tooth Agenesis in local population.

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