

The molecular genetics of selective tooth agenesis

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Abstract

Selective tooth agenesis is a congenital disorder divided into two types based on the number of missing teeth, i.e. hypodontia which is the absence of <6 teeth and oligodontia which is agenesis of >6 permanent teeth excluding the third molars. As the prevalence of tooth agenesis is higher in populations with Arab and Asian descent, it is intriguing to probe deeper into the molecular aspects of this disorder. Selective tooth agenesis inherits as autosomal dominant, autosomal recessive or X-linked dominant mode of inheritance. The 10 loci identified are selective tooth agenesis 1 through 9 and selective tooth agenesis X1. *Genes* for 8 of these loci have been characterised while the causative *genes* for selective tooth agenesis 2 and 5 still remain to be elucidated. The current broad-spectrum review was planned to discuss the molecular genetics of all 10 loci mapped with selective tooth agenesis, their mode of inheritance as well as the proteins encoded by these *genes*, their roles and their interactions.

Keywords: Selective tooth agenesis, STHAG, Hypodontia, Oligodontia.

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Introduction

Odontogenesis is a process of tooth formation from the embryonic cells, their growth and their eruption in the mouth.¹ Tooth agenesis, on the other hand, is the absence of one or more teeth with the exclusion of the third molar. It is one of the most prevalent dental diseases ranging from 3.2% to 13.3% in various human and animal model studies.² After the third molar, mandibular and premolars are the most common teeth missing followed by maxillary lateral incisors and the second premolar teeth, but agenesis of the first permanent molar, canine or maxillary central incisor, has been found to be rather exceptional.² Although many factors, like trauma, heredity, nutrition or infections, can lead to tooth agenesis, it has been found that genetic factors are the major contributors of tooth agenesis.³ At the molecular level, it is caused by the disruption of mechanisms controlling the progression of dental development and dentition pattern, with proven genetic

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involvement.⁴

Different terms have been used to describe the agenesis of teeth and some of which include hypodontia which is the absence of one or few teeth (<6) except the third molar, and oligodontia is the agenesis of >6 teeth with the exclusion of third molars, while anodontia is the complete absence of teeth or any dental structures.⁵

At the genetic level, tooth agenesis can be associated with genetic syndromes or may occur as an isolated genetic disorder, with selective tooth agenesis (STHAG) being the only anomaly present in patients with non-syndromic tooth agenesis. Syndromic tooth agenesis can be associated with syndromes like ectodermal dysplasia, Van Der Woude syndrome, Down's syndrome and Reiger syndrome etc.⁶

Mode of Inheritance

Oligodontia is a congenital disorder inherited mostly as autosomal dominant with variable expression and complete penetrance as in the case of loci STHAG1, STHAG3-4, and STHAG7-9. Loci STHAG2, STHAG4 and STHAG6, however, follow autosomal recessive pattern, whose prevalence is expected to be more in Arab and Asian countries where higher-than-global rates of consanguineous marriages are observed.⁷ STHAGX1, so far, is the only sex-linked locus as it follows the X-linked dominant mode of inheritance. The mode of inheritance for STHAG5 has not yet been elucidated.

Molecular Genetics of Tooth Agenesis

Several recent studies have shown that at least 10 loci are associated with STHAG, and 8 of them have fully characterised *genes* (Table 1). STHAG19 and STHAG X-Linked 1 (STHAGX1) are the 10 loci identified and linked to this disorder which are discussed below (Table 1):

STHAG1

The *gene* for the first locus is Msh Homeobox1 (MSX1) which has only two exons with a genomic size of 4272 bases. MSX1 was first mapped to chromosome 4p16.1 in a family with autosomal dominant agenesis of second and third premolars.⁶ MSX1 protein has 303 amino acids with a molecular mass of 31496 Da.⁸ During embryogenesis, this protein hinders transcription by interacting with components in the core of transcriptional complex and other homeoproteins. It also plays a very important role in

Table-1: Selective Tooth Agenesis (STHAG) loci, Corresponding *Genes*, Chromosomal Location, Mode of Inheritance, Genetic Markers and Subsequent Roles.

Locus	Gene	Cytoband	M.O.D	Genetic Markers	Role/Expression
STHAG1 ^{8,9,10}	<i>MSX1</i>	4p16.2	AD	D4S2703 D4S2615	Formation of limb pattern; tumour growth inhibition; cranio-facial development & odontogenesis
STHAG2 ¹¹	-	16q12.1	AR	D16S3140	Eruption failure causing edentulous state prematurely
STHAG3 ^{4,12,13,15}	<i>PAX9</i>	14q13.3	AD	D14S576 H14A1924	Foetal growth; cancer development
STHAG4 ^{16,17}	<i>WNT10A</i>	2q35	AD/AR	D2S2250 D2S433	Regulation of cell fate and patterning during embryogenesis
STHAG5 ^{18,19}	-	10q11.2-q21	-	D10S196 D10S604 D10S568	Not defined
STHAG6 ^{20,21}	<i>LTBP3</i>	11q13	AR	D11S1910 D11S4109 D11S4191 D11S987	TGF- β signalling pathway; bone and teeth development
STHAG7 ^{22,25}	<i>LRP6</i>	12p13.2	AD	D12S358 D12S77	Canonical Wnt/beta- catenin signaling cascade; regulates cell differentiation, proliferation, development and migration of many kinds of cancer.
STHAG8 ^{26,28}	<i>WNT10B</i>	12q13.12	AD	Not defined	Oncogenesis; cell fate regulation, patterning during embryogenesis.
STHAG9 ^{29,30}	<i>GREM2</i>	1q43	AD	D1S2680 D1S180	Tissue specific differentiation and transformation of cells in early development
STHAGX1 ^{18,31,32}	<i>EDA</i>	Xq13.1	XD	DXS1111 DXS1689 DXS8101	Acts as homo-trimer; responsible for cell-cell signalling; associated with tumour necrosis family

[M.O.D: Mode of Inheritance; AD: Autosomal Dominant; AR: Autosomal Recessive]

limb pattern formation, inhibition of tumour growth, craniofacial development and odontogenesis.⁹ *MSX1*, previously known as homeobox7 (*HOX7*), is related to non-syndromic cleft lip, Wolf Hirscho syndrome, autosomal dominant hypodontia and Witkop syndrome.¹⁰ It has thus been established that *MSX1* should be screened for families with autosomal dominant inheritance patterns of dental anomalies with clefting.^{8,9} This was further proven by transgenic mice homozygous for *MSX1* which rendered facial and dental abnormalities with cleft palate similar to human counterparts.¹⁰

STHAG2

STHAG2 represents the second locus for selective tooth agenesis, first reported in 1998 in a large consanguineous Pakistani family with autosomal recessive hypodontia linked to a 10cM region on chromosome 16q12.1 with maximum 2 point LOD (logarithm of odds) score. Clinical investigations of the affected members of the family indicated that hypodontia was associated with failure of teeth eruption, leading to edentulous state prematurely.¹¹ The *gene* for STHAG2 has not been characterised to date.

STHAG3

Paired box protein 9 (*PAX9*) is the *gene* associated with the third locus of tooth agenesis, or STHAG3. The cytogenetic location of *PAX9* is 14q13.3 and genomic size is 22,148 bases.¹² The *PAX9* encoded by this *gene* is composed of 341 amino acids with 36310 Da molecular mass.¹³ *PAX9* plays a

vital role in foetal exponential growth as well as in cancer development.⁴ A study conducted on *PAX9* of mice clearly indicated that this *gene* is essential for organogenesis and formation of skeletal muscle elements. *PAX9* knockout mice not only had impaired development of teeth, but also had improper growth of organs, musculature and skeleton leading even to neonatal lethality.¹⁴ Another study found that *PAX9* homozygous mice died immediately after birth as they would have while suffering from secondary cleft palate disorder, moreover, craniofacial and visceral skeletogenesis were also disrupted and all teeth were absent.¹⁵

STHAG4

The *gene* associated with STHAG4 is wingless-type mouse mammary tumour virus (MMTV) integration site family member 10A (*WNT10A*) mapped to chromosome 2q35. *WNT10A* spans 25,259 bases and has 4 exons. The protein encoded is *WNT10A* composed of 417 amino acids with 46444 Da molecular mass. Further, 1-35 amino acids of this protein are involved in signal peptide formation and rest of the amino acids (36-417) are involved in the composition of protein chain.¹⁶ This *gene* plays an important role in several developmental processes. During embryogenesis, it is involved in cell fate regulation and patterning. The over-expression of this *gene* has been seen in human cancer cell line HL-60 and SW480 demonstrating the involvement of this *gene* in human carcinogenesis. The moderate levels of *WNT10A* transcripts have also been

observed in adult spleen, placenta and kidney of foetus while low level expression was observed in ovary, prostate, adult kidney and foetal lungs.¹⁶ Null mice having WNT10, a mouse ortholog of WNT10A, were produced by knockout mouse project and had smaller molars with abnormal cusps and pulp calcification. These mice also had supernumerary mandibular fourth molars with an increased risk of re-absorption of root following tooth eruption, as well as molar crown dysmorphologies.¹⁷

STHAG5

STHAG5 represents the fifth locus for tooth agenesis and is mapped to chromosome 10q. The *gene* for this locus has not yet been mapped.¹⁸ STHAG5 was first explained as agenesis of permanent teeth in a large six generation Chinese family, ranging from a few teeth to the complete set of teeth. Penetrance was found to be 0.88 with no other clinical symptoms other than oligodontia. It appeared at 7-8 years of age when primary teeth are replaced by permanent teeth. Most of the affected individuals in this family had first and second molars.¹⁹ Linkage analysis indicated two point and multi-point LOD scores of 13.2 at theta (on marker D10S196) and 18.09 (between markers D10S1772 and D10S1766) respectively. Haplotype analysis has further lessened the 5.5cM interval by markers D10S604 and D10S568 present on chromosome 10q11.2.^{18,19}

STHAG6

Latent transforming growth factor beta binding protein 3 (LTBP3) causes oligodontia associated with sixth locus STHAG6 and is mapped to chromosome 11q13. The results of genome-wide linkage analysis study with microsatellite markers D11S1910, D11S4109, D11S4191 and D11S987 showed that affected individuals shared a 28-Mb autozygous region spanning the centromere of chromosome 11, but this region is absent in normal individuals. It has also been found that this *gene* plays a significant role in transforming growth factor beta (TGF- β) signalling pathway.²⁰ Nonsense, deletion and splice mutations have been identified in LTBP3 *gene* by using homozygosity and whole-exome sequencing. It is actually the first *gene* that is linked with short stature in affected individuals of this disorder inherited in autosomal recessive fashion.²⁰ The expression of this *gene* has been studied in mice. Results of animal modelling revealed that during the developmental stages in mice, LTBP3 *gene* plays a crucial role in tooth development as the LTBP3^{-/-} knockout model demonstrated a minor to absent enamel in incisors and molars.²¹

STHAG7

The *gene* is associated with tooth agenesis locus STHAG7

is low-density lipoprotein receptor-related protein 6 (LRP6). Its cytogenetic location is 12p13.2 with genomic size is 150,988 bases and 24 exons.²² The LRP6 protein is composed of 1613 amino acids with molecular mass of 180429 Da. Also, 1-19 amino acids are involved in signal peptide formation, while the rest of the amino acids (20-1613) are involved in the composition of protein chain.²³ This protein works as receptor or co-receptor for WNT and is involved in the canonical WNT/ β -catenin signalling cascade. WNT signalling has in turn an important role in biological processes during pre-natal and post-natal life of vertebrates and invertebrates.²⁴ In this way, LRP6 regulates cell differentiation, proliferation, development and migration of many kinds of cancer. LRP6 has also been found to be involved in gamma-secretase dependent regulated proteolytic processing (RIP).²³ LRP5 and LRP6 serve as co-receptors for WNT and play a vital role in WNT signalling. Using fluorescent in situ hybridisation (FISH), the map the mouse ortholog LRP6 has been localised to chromosome 6 in mice. A two-base pair duplication was also identified in the mouse LRP6 *gene* that causes a frame shift mutation, resulting in premature termination codon.²⁵

STHAG8

The *gene* associated with STHAG8 is WNT10B and has been mapped to chromosome 12q13.1 by polymerase chain reaction (PCR) typing and FISH. The genomic size of this six exonic *gene* is 6,519 bases and encodes protein WNT10b. The WNT10b is composed of 389 amino acids with 43000 Da molecular mass²⁶ and 1-28 amino acids are involved in signal peptide formation while amino acids 29-389 are involved in the composition of chain of protein. The expression of WNT10B has been observed in 3 out of 50 cases of breast carcinomas with no expression in normal proliferation of human breast tissue. Southern blotting of carcinomas has revealed high level expression of WNT10B.²⁷ Expression patterns of WNT10B suggest that it is synthesised in many adult skeletal muscles and heart tissues.²⁸ This protein is also involved in different sorts of developmental processes, like cell fate regulation and patterning during embryogenesis. WNT10B is a highly conserved *gene* and the homology shared by human WNT10B and mouse WNT10b *gene* is 95%, while corresponding proteins share 96%, and amino acid sequences share 88% homology respectively.²⁷

STHAG9

Gremlin 2 (GREM2) is the *gene* for the ninth locus of oligodontia STHAG9. The cytogenetic location of GREM2 is 1q43 and its product size is 122,700bp with inheritance pattern as autosomal dominant.²⁹ It encodes protein GREM2 that has 168 amino acids with 19320 Da molecular mass. Its first 21 amino acids (91-210) serve as signal

peptide. This protein is present in quaternary structure in the form of homodimers that interact with both bone morphogenetic protein 2 (BMP2) and BMP4 with higher affinity and displays a lower affinity with BMP7. The role of this *gene* is much highlighted in early development, tissue-specific differentiation and transformation of cells.^{29,30} It plays an important role in the activation of p21 as well as in

the inhibition of neoplastic transformation. The expression of GREM1 has been observed in various other tissues also, but the over-expression of this protein in kidney leads to nephropathy in diabetes.³⁰

STHAGX1

The tenth locus for tooth agenesis is mapped on the X chromosome at Xq13.1. Ectodysplasin A (EDA) is the *gene* associated with STHAGX1 with genomic size 423,406 bases. The protein encoded by this *gene* is EDA which is composed of 391 amino acids with 41294 Da molecular mass. Its amino acids 1 to 391 are involved in the composition of protein chain. This protein plays an important role as a homotrimer being responsible for cell-cell signalling during the growth of ectodermal organs and is associated with tumour necrosis family. Thus, alterations in this *gene* can cause both X-linked ectodermal dysplasia and anhidrotic ectodermal dysplasia.³¹ It has been found that variants in EDA *gene* cause X-Linked hypohidrotic ectodermal dysplasia (XLHED) and become a major cause of ectodermal dysplasia in humans. Further molecular analysis reveals that EDA1 plays a crucial role in sweat gland morphogenesis, tooth and hair development while the role of isoform I still remains unclear.³² It was found that an increased expression of mouse ortholog EDA increased the number of cusps in mice. Not only was the number of teeth increased but the cusp position and shapes were also changed along with formation of longitudinal crests.³³

Oligodontia proteins interactions

Protein-protein-interactions (PPIs) are the physical contacts between two or more proteins as a result of electrostatic forces or some biochemical events. Such protein interactions can be established due to the presence a structural domain of proteins which allow the binding of a protein to another protein/s on the basis of their specific sequence.³⁴ Using "Search Tool for the Retrieval of Interacting Genes/Proteins" (STRING) database version 11.0 (©STRING CONSORTIUM 2019), PPI analysis of all eight

Table-2: Various Interactions among Proteins of Selective Tooth Agenesis.³⁵

Protein 1	Protein 2	Homology	Co-expression	Experimentally Determined interaction	Database Annotated	Automated Text-mining	Combined Score
MSX1	PAX9	0	0	0.447	0	0.946	0.969
WNT10B	WNT10A	0.964	0.061	0	0.9	0.813	0.904
WNT10B	LRP6	0	0.054	0.261	0.6	0.692	0.902
LRP6	WNT10A	0	0.054	0.126	0.6	0.656	0.871
PAX9	WNT10A	0	0	0	0	0.647	0.647
MSX1	WNT10A	0	0	0.072	0	0.62	0.632
LTBP3	WNT10A	0	0	0.064	0	0.611	0.62
PAX9	LTBP3	0	0	0	0	0.571	0.571
MSX1	LTBP3	0	0	0	0	0.527	0.527
MSX1	WNT10B	0	0	0.072	0	0.475	0.492

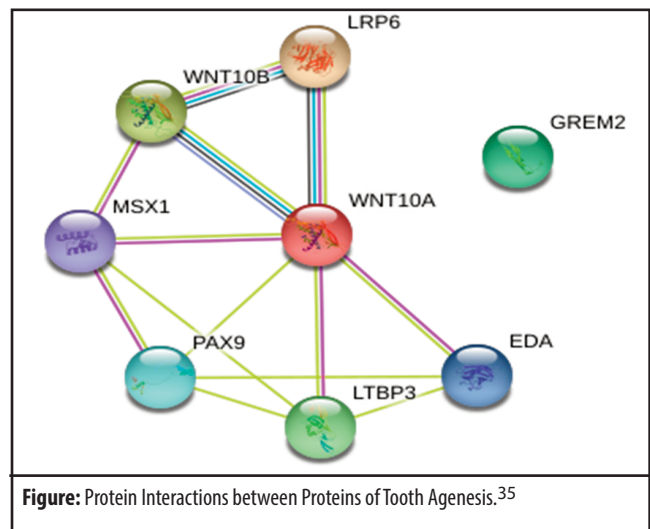


Figure: Protein Interactions between Proteins of Tooth Agenesis.³⁵

characterised oligodontia proteins -- LRP6, WNT10B, MSX1, PAX9, LTBP3, EDA, WNT10A and GREM2 -- was performed in a study.³⁵ No interaction between GREM2 and the other 7 characterised *genes* was found (Figure). However, the other seven had varying degrees of interaction but no interaction based on *gene* neighbourhood, *gene*-fusion or phylogenetic co-occurrence was found between any of these proteins (Table 2).

Conclusion

STHAG is a rare anomaly, but its prevalence experiences a peak in populations exercising consanguineous marriages, including Pakistan. The only way to eradicate this disorder is a proactive approach by understanding the disease mechanism and effective genetic counselling. Since most forms of tooth agenesis adopt dominant mode of inheritance, complete characterisation of the disorder is important to slowly eradicate the disorder from the *gene* pool. Mutation screening of all the affected individuals, followed by carrier screening in cases of recessive mode of inheritance are essential steps towards reducing the

frequency of disease occurrence in our population.

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