***https://doi.org/ 10.33472/AFJBS.6.9.2024.613-619***

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

**REVIEW ARTICLE**

# USAG gene 1 "A blessing for the healthcare field" A narrative review

**[1]Dr. Avineet Kaur, [2]Dr. Jasjit Kaur Sahota, [3]Dr. Anupama Vithalkumar Betigeri, [4]Dr. Reshma Dodwad, [5]Dr. Sahib Sharma, [6]Dr. Pragati Rohila**

[1]Reader, [2]Professor and Head, [6]PG Student, Department of Periodontology and Oral Implantology, Swami Devi Dyal Hospital and Dental College, Golpura, Panchkula, Haryana, India

[3]Professor and Head, Department of Physiology, Manav Rachna Dental College, SDS, MRIIS, Faridabad, Haryana, India

[4]Reader, Department of Pedodontics and Preventive Dentistry, Krishna Devarya College of Dental Sciences, Banglore, Karnataka, India

[5]Junior Resident, Department of Pediatrics, Gian Sagar Medical College and Hospital, Banur, Rajpura, Punjab, India

**Corresponding author:** Dr. Avineet Kaur, Reader, Department of Periodontology and Oral Implantology, Swami Devi Dyal Hospital and Dental College, Golpura, Panchkula, Haryana, India

**Email:** kauravineet85@gmail.com

Article History

Volume 6,Issue 9, 2024

Received:22 Mar 2024

Accepted : 27 Apr 2024

doi: 10.33472/AFJBS.6.9.2024.613-619

**ABSTRACT**

The function of secretory signaling molecules in mediating links between the oral epithelium and mesenchyme makes tooth development an area of study. The growth of additional teeth depends on Wnt signaling, while bone morphogenetic protein (BMP) signaling is required for the formation of more teeth. For mice to regenerate teeth, USAG-1—a BMP antagonist and Wnt signaling modulator—is essential. This implies that in addition to permanent dentition, "third dentition" may also result in the emergence of new teeth. It is believed that genetic factors contribute to the full or partial activation of the third dentition in humans. Supernumerary teeth are the result of enhanced BMP signaling, and in the USAG-1 defective mouse model, Wnt signaling modulates BMP signaling. Dementia and cognitive impairment are separately linked to tooth loss, and prompt prosthodontic therapy with dentures may slow the rate at which tooth loss-related cognitive decline advances. USAG-1 plays essential functions in kidney disease progression, impacting acute and chronic kidney damage and recovery of allograft kidney function by modulating BMP and Wnt signaling pathways. Bone morphogenetic proteins (BMPs) play a crucial role in kidney development and injury. According to a study, uterine sensitization-associated gene-1 (USAG-1) binds to and inhibits the biological activity of BMP-7, acting as a kidney-specific BMP antagonist. USAG-1-deficient animals are the primary negative regulators of BMP function in the adult kidney and are resistant to renal damage. The isolation and characterization of a new gene, uterine sensitization-associated gene-1 (UASG-1), suggested that it plays a role in endometrial receptivity for implantation and sensitization for the decidual cell reaction.

**Keywords:** USAG gene 1, Dementia, Kidney Diseases, BMP Signalling

## INTRODUCTION

The tooth is one of the vertebrate organs whose molecular development is being studied. It is already known that secretory signaling molecules mediate the sequential and reciprocal inductive connections that form between the mouth epithelium and mesenchyme. Ultimately, the dental enamel knot was shown to contain a signaling or organizing center that appears to constrain tooth form and conveys the same signals as other organizing centers in the embryo. Molecular signals that govern organogenesis include those derived from the bone morphogenetic protein (BMP) and Wnt molecules, which govern the morphogenesis of a single tooth. While Wnt signaling is essential for the creation of extra teeth , BMP signaling is required for the morphogenesis of extra teeth . However, whether BMP or Wnt signaling is required to count the teeth is unknown. USAG-1 (uterine sensitization associated gene-1) is a Wnt signaling modulator and BMP antagonist that is mostly expressed in the kidneys. It inhibits BMP7 bioactivity, which is essential for tooth development . Bone morphogenetic protein-7, a homodimeric 35-kDa protein, regulates apoptosis in a range of developmental processes and is crucial for the specification and patterning of the early embryo .Usag1 inhibition is important for mouse tooth regeneration, as shown by a single-gene knockout (KO) mouse model for Usag-1, also known as Sclerostin domain containing 1 (SOSTDC1), ectodin, Wnt modulator in surface ectoderm (WISE), CCAAT/enhancer-binding protein beta (CEBPB), Sprouty homolog 2 (SPRY2), Sprouty homolog 3 (SPRY3), or Epiprofin (EPFN). [1]

## SUPERNUMERAY TEETH AND USAG DEFICIENCY ARE RELATED

When BMP signaling is blocked, supernumerary teeth do not grow in the E15 incisor. Using KO mice models, a number of genes, including Msx1, Runx2, Ectodysplasin A (EDA), and Pax9, have been linked to oral agenesis. Studies have shown that in Runx2/USAG-1/ animals, a supernumerary mouse model, tooth development that had been stopped in Runx2/mice, a mouse model for congenital tooth agenesis, may be reversed. Targeted molecular treatment can be used to treat more teeth in order to promote tooth regeneration. Scientists from outside India have also worked on the anti-Usag1 technique. When applied to damaged teeth, dienteglusib increases WNT signaling by blocking GSK-3, which leads to teeth repair. Sugenami et al. suggested USAG-1 as a potential drug target for teeth regeneration; however, their anti-USAG-1 method has been linked to numerous adverse effects. [1]

## CATEGORIZATION OF DENTAL AGENESIS

Tooth agenesis is categorized as hypodontia, oligodontia, or anodontia based on the quantity of congenital teeth absent . Based on the concomitant symptoms of tooth loss, syndromic and non-syndromic forms of tooth agenesis are another group. Numerous systemic diseases and syndromes are linked to the syndromic form of the disease . Anomalies such enamel hypoplasia, canine transposition, and delayed tooth production and eruption are possible in patients with syndromic dental agenesis. Ectodermal dysplasia, cleft lip, cleft palate, Down syndrome, and Van der Woude syndrome are other potential clinical markers of tooth agenesis . Non-syndromic tooth agenesis is more prevalent than the syndromic type . The sole noticeable sign in patients with this type of dental agenesis is congenitally absent teeth. Furthermore, non-syndromic tooth agenesis may be inherited or occur sporadically . Hypoodontia (less than six missing teeth, typically one to three missing teeth) can occasionally be brought on by hereditary or environmental reasons. In individuals without other concomitant symptoms, this condition may indicate tooth agenesis . In situations involving family members

Hypodontia may be the sole clinical sign of tooth agenesis or it may be a component of a related condition that is inherited autosomally dominantly. Rubella virus infection and tooth

agenesis brought on by orofacial trauma during odontogenesis are additional variables that cause tooth agenesis in addition to congenital, acquired, and environmental causes . Numerous investigations have measured craniofacial abnormalities in those who have dental agenesis syndromic. Several underlying reasons have been identified as a result of developments in molecular, next-generation sequencing, and imaging technologies. About how genetics and genomic variations affect tooth agenesis and related medical issues, and how they play a role in nonsyndromic tooth agenesis.[2]

## TOOTH AGENESIS GENETICS

Examining and determining the genetic variables that control the interactions between epithelial and mesenchymal cells requires an understanding of tooth development. The structure and function of teeth within the dentition typically determines and has evolved to conserve the number of teeth in all animals. Nevertheless, by showing how USAG-1 deletion causes primitive incisor teeth to survive and grow as supernumerary teeth, researchers have made significant progress. Despite the fact that it was a mouse study, there is still hope for comparable outcomes in people. The idea that "third dentition," when activated, can develop new teeth and occur in addition to permanent dentition, would be supported if similar results were established in humans. Unlike non-congenital causes, congenitally absent permanent teeth are uncommon. There are frequent clinical and scientific reports on anomalies such as syndromic tooth agenesis. Teeth agenesis is mainly due to genetic factors, which are important for tooth formation. Dental implant surgeries and tooth transplantation have become more commonplace during the past few decades. possibilities for dental agenesis treatment. Almost 200 genes that are expressed in several pathways throughout the various phases and locations of tooth growth . In order to clarify the function of particular functional mutants and offer insights into the underlying biological and molecular mechanisms that result in the creation of supernumerary teeth, a number of animal models—mice in particular—are used as model organisms. Based on the present understanding of the biology of extra teeth, genetic factors are assumed to be involved in the partial or complete activation of the human third dentition. It is anticipated that candidate genes will be involved in regulating the quantity and kind of regenerated teeth or in promoting teeth throughout embryonic development. Therefore, investigating the biological function of potential genes when they are active or deregulated offers a great chance to advance and create tools for successfully growing new teeth.[2]

## IN MICE LACKING USAG-1, INCREASED BMP SIGNALING LEADS TO THE PRODUCTION OF EXTRA TEETH

Uterine sensitization associated gene-1 (USAG-1) is a BMP antagonist, and also modulates Wnt signaling. As we previously documented, mice lacking USAG-1 have an excess of teeth. The rudimentary upper incisor appears to develop sequentially to give rise to the supernumerary maxillary incisor. The apoptotic elimination of odontogenic mesenchymal cells was prevented by USAG-1 abrogation. We confirmed that BMPs were expressed in both the epithelium and mesenchyme of the rudimentary incisor at E14 and E15. BMP signaling in the rudimentary maxillary incisor, measured by expressions of Msx1 and Dlx2 and the phosphorylation of Smad protein, was dramatically elevated. Additionally, there was an upregulation of Wnt signaling, as seen by the nuclear localization of β-catenin. Inhibition of BMP signaling recovers supernumerary tooth development in E15 incisor explants culture. These findings lead us to the conclusion that increased BMP signaling causes more teeth, and in the USAG-1 defective mouse model, Wnt signaling modulates BMP signaling.[3]

## ANALYSIS OF RESEARCH

The dose-response relationships between tooth loss and the chance of dementia and cognitive impairment were assessed by **Xiang Qi, et al.**[4] This analysis includes longitudinal studies that looked at the relationship between cognitive function and tooth loss. From March 1, 2020, a comprehensive search was conducted across six databases. The study followed the reporting criteria set forth by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Random-effects models were used to pool the risk estimates. Generalized least squares spine models were utilized to evaluate the dose-response correlations. Adults from the community, institutions, outpatient clinics, and hospitals were among the participants in the meta-analysis. As a result, assessments for dementia and cognitive impairment were based on neuropsychological examinations, diagnostic standards, or medical documentation. Clinical examinations or self-reporting were used to measure tooth loss. The meta-analysis included 14 trials with 34,074 participants and 4,689 cases of reduced cognitive function, according to the results. Individuals who experienced greater tooth loss were 1.48 times more likely to experience cognitive impairment (95% CI = 1.18–1.87) and 1.28 times more likely to receive a dementia diagnosis (95% CI = 1.09–1.49). For those who wore dentures, the correlation was not statistically significant (RR = 1.10, 95% CI = 0.90–1.11). The dose-response analysis comprised eight investigations, and the data were consistent with the application of linear models. A 0.014 increase in the relative risk of cognitive impairment and a 0.011 increase in the relative risk of dementia were linked to each additional tooth loss. Individuals who were born without a chromosome had a 1.40 times higher chance of developing dementia and a 1.54 times higher risk of cognitive impairment. In light of this, it was determined that there was a moderate degree of evidence linking tooth loss to dementia and cognitive impairment on its own, and that the likelihood of cognitive decline rose as more teeth were lost. Additionally, prompt denture-based prosthodontic treatment may slow the rate at which cognitive decline associated with tooth loss advances.

## THE PROGRESSION OF KIDNEY DISEASES ASSOCIATED WITH UTERINE SENSITIZATION-ASSOCIATED GENE-1

It has been shown that uterine sensitization-associated gene-1 (USAG-1), which was first discovered to be a secretary protein that was selectively produced in the endometrium of sensitized rats, regulates the expression of Wnt and bone morphogenetic protein (BMP) and is crucial in kidney disease. The course of both acute and chronic kidney impairment, as well as the recuperation of via controlling the Wnt and BMP signaling pathways, allograft kidney function. Furthermore, it has been discovered that USAG-1 plays a role in the T cell immune response. Its potential to suppress humoral immunity and impede germinal center activity is crucial for managing autoimmune nephropathy and antibody-mediated rejection (AMR) following renal transplantation, because of drug toxicity, ischemic reperfusion, sepsis, etc. When the kidneys are injured, the distal tubules secrete more USAG-1, which causes the level to rise. This, in turn, causes a decrease in BMP 7, TGF-β, and Wnt, which in turn causes a decrease in Smad 1/5/8 and β Catenin, which in turn causes an increase in epithelial injury, an increase in inflammatory cell infiltration, and an increase in interstitial fibrosis.[5]

## EXPRESSION OF BMP-7 AND USAG-1, AN ANTAGONIST OF BMP, IN THE DEVELOPMENT AND DAMAGE OF THE KIDNEY

The transforming growth factor-b superfamily includes bone morphogenetic proteins (BMPs), which are phylogenetically conserved signaling molecules. BMP-7 is a 35-kDa homodimeric protein, and the kidney is the primary site of BMP-7 synthesis during embryogenesis and in postnatal development. BMP-7-deficient mice die soon after birth due

to severe renal hypoplasia. We have discovered that the uterine sensitization-associated gene-1 (USAG-1) product functions as a BMP antagonist that is unique to the kidneys. USAG-1 binds to and inhibits the biological activity of BMP-7.We also showed that USAG-1 is the primary negative regulator of BMP function in the adult kidney and that animals lacking USAG-1 are resistant to renal damage.[6]

**PARALLEL RESEARCH**

**David G. et al.** discovered that in the current investigation, we used the suppressive subtraction hybridization technique to try and find genes related to the initiation of receptivity. The unique gene uterine sensitization-associated gene-1 (UASG-1) that is predominantly expressed within the most sensitized/receptive rat endometrium is reported to have been isolated, cloned, and characterized here. A putative 206 amino acid protein with a potential N-terminal secretion signal and a C-terminal cystine knot like motif is encoded by the USAG-1 mRNA. The induction of USAG-1 mRNA was limited to the Day 5 pregnant or pseudopregnant uterus, according to Northern blot analysis. Experiments using in situ hybridization showed that this induction was limited to the uterine glandular epithelial cells. USAG-1 may be implicated in the initiation of endometrial receptivity for implantation/sensitization for the decidual cell reaction due to the incredibly tight restriction of its expression.[7]

**Mishima S et al** described that Runt-related transcription factor 2 (Runx2)-deficient mice can be utilized to replicate congenital tooth agenesis in humans. In contrast, mice lacking the uterine sensitization-associated gene-1 (Usag-1) have an excess of teeth growing in their mouths. Arrested tooth development can be restored by crossing both knockout-mouse strains; however, it remains unclear whether topical suppression of Usag-1 expression can permit the recovery of tooth creation in Runx2-deficient mice. Here, we explored whether blocking the topical expression of Usag-1 can correct halted tooth development after Runx2 abrogation. The results demonstrated that local application of Usag-1 Stealth small interfering RNA (siRNA) improved tooth development following Runx2 siRNA-induced agenesis. Cationized gelatin has also been shown to be a useful drug-delivery mechanism via renal capsule transplantation of siRNA-loaded cationized, gelatin-treated mouse mandibles. We subsequently performed renal capsule transplantation of wild-type and Runx2-knockout (KO) mice mandibles, treated with Usag-1 siRNA, indicating that impeded tooth development was recovered by Usag-1 knockdown. Furthermore, topically applied Usag-1 siRNA partially recovered halted tooth development in Runx2-KO mice, suggesting its potential for rebuilding teeth in Runx2-deficient animals. The development of topical therapies for congenital tooth agenesis is affected by our findings.[8]

**Maeda K** demonstrated that Runt-related transcription factor 2 (Runx2)-deficient mice can be utilized to replicate congenital tooth agenesis in humans. In contrast, mice lacking the uterine sensitization-associated gene-1 (Usag-1) have an excess of teeth growing in their mouths. Arrested tooth development can be restored by crossing both knockout-mouse strains; however, it remains unclear whether topical suppression of Usag-1 expression can permit the recovery of tooth creation in Runx2-deficient mice. Here, we explored whether blocking the topical expression of Usag-1 can correct halted tooth development after Runx2 abrogation. The results demonstrated that local application of Usag-1 Stealth small interfering RNA (siRNA) improved tooth development following Runx2 siRNA-induced agenesis. Cationized gelatin has also been shown to be a useful drug-delivery mechanism via renal capsule transplantation of siRNA-loaded cationized, gelatin-treated mouse mandibles. We subsequently performed renal capsule transplantation of wild-type and Runx2-knockout (KO) mice mandibles, treated with Usag-1 siRNA, indicating that impeded tooth development was recovered by Usag-1 knockdown. Furthermore, topically applied Usag-1 siRNA partially recovered halted tooth development in Runx2-KO mice,

suggesting its potential for rebuilding teeth in Runx2-deficient animals. The development of topical therapies for congenital tooth agenesis is affected by our findings.[9]

## ANTI-USAG GENE 1 TREATMENT FOR IMPROVED BMP SIGNALING-MEDIATED TOOTH REGENERATION

A deficit in uterine sensitization-associated gene-1 (USAG-1) results in increased bone morphogenetic protein (BMP) signaling, which in turn causes the creation of extra teeth. Moreover, tooth development is accelerated by antibodies that block USAG-1's binding to BMP but not lipoprotein receptor-related protein 5/6 (LRP5/6). We postulated that USAG-1 plays important regulatory roles in inhibiting tooth development since it directly binds to the Wnt and BMP coreceptors, LRP5/6, and inhibits these vital signals. It is unknown, nevertheless, if USAG-1 plays a role in the different forms of congenital tooth agenesis. Here, we show that limiting USAG-1 function through USAG-1 deletion or anti–USAG-1 antibody injection reduces congenital tooth agenesis induced by diverse genetic disorders in mice. Our data reveal that USAG-1 limits the number of teeth by suppressing growth of prospective tooth germs in wild-type or mutant mice deficientteeth. Anti–USAG-1 antibody injection is, thus, a viable strategy for tooth regeneration therapy.[10]

## CONCLUSION

Tooth formation is controlled by secretory signaling molecules, including bone morphogenetic protein (BMP) and Wnt signaling. USAG-1, a BMP antagonist and Wnt signaling modulator, is critical for tooth regeneration in mice. Tooth agenesis, a disorder characterized by hypodontia, oligodontia, or anodontia, can be syndromic or non-syndromic. Understanding tooth development helps discover genetic factors affecting epithelial and mesenchymal cell interactions.

## REFERENCES

1. Poorani R, Elakkiya E, Gupta KK. USAG1 protein: An important drug target in teeth regeneration [Internet]. Cold Spring Harbor Laboratory; 2022 Aug [cited 2024 Mar 29]. Available from: http://dx.doi.org/10.1101/2022.08.01.502414
2. Ravi V, Murashima-Suginami A, Kiso H, Tokita Y, Huang CL, Bessho K, et al. Advances in tooth agenesis and tooth regeneration. Regenerative Therapy. 2023 Mar;22:160–8.
3. Murashima-Suginami A, Takahashi K, Sakata T, Tsukamoto H, Sugai M, Yanagita M, et al. Enhanced BMP signaling results in supernumerary tooth formation in USAG-1 deficient mouse. Biochemical and Biophysical Research Communications. 2008 May;369(4):1012–6.
4. Qi X, Zhu Z, Plassman BL, Wu B. Dose-Response Meta-Analysis on Tooth Loss With the Risk of Cognitive Impairment and Dementia. Journal of the American Medical Directors Association. 2021 Oct;22(10):2039–45.
5. Li X, Yue W, Feng G, Li J. Uterine Sensitization-Associated Gene-1 in the Progression of Kidney Diseases. Journal of Immunology Research. 2021 Aug 7;2021:1–6.
6. Tanaka M, Endo S, Okuda T, Economides AN, Valenzuela DM, Murphy AJ, et al. Expression of BMP-7 and USAG-1 (a BMP antagonist) in kidney development and injury. Kidney International. 2008 Jan;73(2):181–91.
7. Simmons DG, Kennedy TG. Uterine Sensitization-Associated Gene-1: A Novel Gene Induced Within the Rat Endometrium at the Time of Uterine Receptivity/Sensitization for the Decidual Cell Reaction1. Biology of Reproduction. 2002 Nov 1;67(5):1638–45.

8. Mishima S, Takahashi K, Kiso H, Murashima-Suginami A, Tokita Y, Jo JI, et al. Local application of Usag-1 siRNA can promote tooth regeneration in Runx2-deficient mice. Scientific Reports. 2021 Jul 1;11(1).
9. Maeda K, LEE D S, Yanagimoto U, Suzuki H . Expression of Uterine Sessitization Associated Gene 1 (USAG-1) in the mouse uterus During the Peri Implantation Period. J Reprod. Dev. :931-936,2007 :53.
10. Murashima-Suginami A, Kiso H, Tokita Y, Mihara E, Nambu Y, Uozumi R, et al. Anti–USAG-1 therapy for tooth regeneration through enhanced BMP signaling. Science Advances. 2021 Feb 12;7(7).