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Genetic Insights into Oligodontia: A Comprehensive Review of Mutations in Key Genes and Their Implications for Tooth Development

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ABSTRACT:
Introduction: Tooth agenesis is one of the most frequent congenital abnormalities found in the maxillofacial region. Oligodontia, a severe form of tooth agenesis, occurs as an isolated anomaly or as a syndromic feature.
Objectives: To identify the molecular genetic etiology of multiple missing permanent teeth (oligodontia).
Discussion: Disruptions in tooth development arise from mutations in genes like WNT10A and PAX9, where PAX9 plays a crucial role in dental epithelial cell differentiation. Additional genes, such as MSX1, AXIN2, EDA, EDAR, and EDARADD, play diverse roles in tooth agenesis. The WNT pathway, particularly the WNT/β-catenin signaling, is crucial in tooth development. Mutations in LRP6 compromise the activation of this pathway, indicating its functional significance in tooth development. Biallelic variants in POLR3GL have been associated with oligodontia, expanding the spectrum of POLR3-related disorders. Disruption of Pol III function may affect the transcription of essential RNAs involved in tooth development.
Conclusions: Oligodontia is a genetically heterogeneous condition with a complex genetic basis involving multiple genes and pathways. Molecular analysis and genetic testing are essential for accurate diagnosis and management, contributing to our evolving understanding of the genetic causes of oligodontia.

KEYWORDS: Genetic Mutations, Oligodontia, Tooth Agenesis

INTRODUCTION

Tooth agenesis is defined as the absence of teeth from the normal series due to a failure to develop and encompasses hypodontia, oligodontia, and anodontia.[1] The absence of up to five teeth is classified as hypodontia, the congenital absence of six or more teeth is defined as oligodontia, and anodontia refers to the complete absence of all teeth from the normal series.[1] Tooth development is regulated by a series of signaling pathways, and genetic mutations in specific genes have been described as the causes of such defects.[2] Moreover, environmental factors such as trauma, infections, toxins, and dietary deficiencies have been implicated and could interact with the genetic factors as a complex and multifactorial disease.[3] The prevalence of oligodontia is rare with an estimated incidence of 0.08% to 0.14% worldwide.[4]

The occurrence of oligodontia can be observed as an isolated trait (non-syndromic oligodontia) or accompanying other features as part of a syndrome.[5] In cases of non-syndromic oligodontia, the congenital absence of teeth stands as the sole discernible clinical characteristic.[6] Nevertheless, the intricate interplay between oligodontia and syndromes has increasingly captured attention. The association of oligodontia with over 60 different syndromes, including but not limited to hypohidrotic ectodermal dysplasia (HED), Rieger's syndrome, Down's syndrome, and Van der Woude's syndrome, underscores its significance as a phenotypic marker and a consequence of intricate genetic interactions.[7]

Patients with oligodontia present serious deficiencies in their quality of life due to decreased masticatory function, phonetic ability, and maxillofacial aesthetics.[4] In addition to genetic factors, studies have suggested that tooth agenesis can also be influenced by many environmental and/or host factors, such as radiotherapy, chemotherapy, disease/infection of the preceding deciduous teeth, viral infection during pregnancy, and metabolic imbalances, etc.[8] In this study, we focus only on oligodontia caused by genetic factors.

AIMS

The aim of this library study is to comprehensively understand the genetic basis of oligodontia, focusing on the mutations in specific genes associated with this condition. The study aims to elucidate the molecular pathways and genetic factors contributing to the development of oligodontia, providing a foundation for improved diagnosis and management of patients with this condition.

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The information for this library study is derived from multiple scientific studies and research papers. The search was conducted using PubMed, Scopus, Wiley Online Library, and supplemented by a gray literature search on Google Scholar. The literature reviewed spans from 2013 to 2021, encompassing studies and research articles that investigate the genetic underpinnings of oligodontia. This period ensures the inclusion of recent findings and advancements in genomic technologies, such as next-generation sequencing, which have contributed to the identification of novel genes and variants associated with tooth agenesis.

DISCUSSION

Mutations in specific genes have been associated with oligodontia. The study from (Ruf, et al., 2013) identified seven genes that are known to have the potential to cause nonsyndromic oligodontia: PAX9, EDA, MSX1, AXIN2, EDARADD, NEMO, and KRT17. These genes exhibit variability in terms of the number of identified mutations and documented patients. PAX9, for example, has 33 mutations and 93 patients on record, while EDARADD, NEMO, and KRT17 each have only one mutation documented in one patient.[9]

Mutations in WNT10A disrupt the WNT signaling pathway, which is crucial for tooth development, leading to the absence of multiple teeth. Another gene frequently implicated in the genetic etiology of isolated oligodontia is PAX9. Mutations in PAX9 have been shown to cause tooth agenesis, and they are often associated with the absence of specific teeth, such as premolars and third molars. PAX9 is involved in dental epithelial cell differentiation and tooth development, and its disruption can result in the failure of tooth formation. In addition to WNT10A and PAX9, several other genes have been linked to oligodontia. MSX1, AXIN2, EDA, EDAR, and EDARADD are examples of genes that, when mutated, can lead to tooth agenesis. These genes are involved in various developmental processes during tooth morphogenesis, including dental placode formation, signaling pathways regulation, and ectodermal- mesenchymal interactions.[10]

The mode of inheritance of oligodontia can vary depending on the specific gene involved. X-linked, autosomal dominant, and autosomal recessive patterns of inheritance have been reported. For instance, X-linked hypohidrotic ectodermal dysplasia (HED) caused by mutations in the EDA gene is associated with oligodontia. On the other hand, mutations in PAX9 and MSX1 are typically inherited in an autosomal dominant manner. It is important to note that the genetic causes of oligodontia are highly heterogeneous, and different genetic mutations can result in a similar clinical phenotype.[10]

The study from (Sun, et al., 2021), have identified different types of PAX9 variants in patients with non-syndromic oligodontia NSO, including frameshift variants and missense variants. Frameshift variants result from the insertion or deletion of nucleotides within the gene sequence, leading to a shift in the reading frame and ultimately producing a non-functional or truncated PAX9 protein. Missense variants, on the other hand, involve a single nucleotide change that results in the substitution of one amino acid with another in the PAX9 protein sequence. These variants can disrupt the normal structure and function of the protein. The PAX9 gene contains a paired domain (PD) that is critical for its function. The PD consists of two helix-turn-helix motifs connected by a linker and is responsible for binding to specific DNA sequences. Structural impairment of the PD, caused by PAX9 variants, can affect the ability of the protein to bind to its target DNA sequences and activate downstream genes involved in tooth development, such as the bone morphogenetic protein 4 (BMP4) gene. Furthermore, functional analyses have revealed that PAX9 variants can exhibit a dominant-negative effect. This means that even in the presence of one normal copy of the PAX9 gene, the mutated variant can interfere with the function of the normal protein, leading to impaired tooth development and the manifestation of NSO.[11]

The study from (Yang, et al., 2020), two novel mutations in MSX1 were identified in unrelated individuals with non-syndromic oligodontia. The mutations, a missense mutation (c.572 T>C) and a frameshift mutation (c.590_594 dup TGTCC), were located in the homeodomain of the MSX1 protein. The homeodomain is a conserved region that plays a crucial role in DNA binding and transcriptional regulation. Structural modeling and bioinformatics analysis were performed to predict the conformational changes caused by these mutations, particularly in terms of hydrogen bond formation and protein binding. The findings of this study, combined with previous structural analyses of MSX1 mutations, suggest a correlation between the observed phenotypes (oligodontia) and alterations in hydrogen bond formation. Disruption of hydrogen bond interactions within the homeodomain can potentially affect the binding of MSX1 to its target DNA sequences and interfere with its transcriptional regulatory functions. These disruptions in gene regulation during tooth development can lead to the absence of multiple teeth seen in oligodontia. It is important to note that oligodontia is a genetically heterogeneous condition, and mutations in other genes, such as PAX9, AXIN2, WNT10A, EDA, and LRP6, have also been associated with NSTA. These genes are involved in various signaling pathways and molecular interactions

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critical for tooth development. The identification of mutations in these genes has provided further insights into the genetic basis of oligodontia and expanded our understanding of the complex regulatory networks involved in tooth development.[12]

The research from (Zhou, et al., 2021) identified a total of 20 causative genes associated with oligodontia based on the analysis of 393 cases. Among these genes, WNT10A, EDAR, and LRP6 were found to be particularly relevant. A novel mutation in WNT10A (c.99_105dup) and eight previously reported mutations in WNT10A (c.433 G > A; c.682 T > A; c.318 C > G; c.511.C > T; c.321 C > A), EDAR (c.581 C > T), and LRP6 (c.1003 C > T, c.2747 G > T) were identified. The study also examined the correlation between specific gene mutations and the clinical features of oligodontia patients. The analysis revealed that molars agenesis is more likely linked to PAX9 mutations, while mandibular first premolar agenesis is least associated with PAX9 mutations. Mandibular incisors and maxillary lateral incisor agenesis were found to be most closely linked to EDA mutations.[13]

The researchers from (Park, et al., 2019) conducted whole-exome sequencing on two Korean families with oligodontia to identify potential genetic mutations. In family 1, the proband was missing 14 permanent teeth, and compound heterozygous WNT10A mutations (c.364A > T and c.511C > T) were identified. In family 2, two affected individuals were missing 20 and 12 permanent teeth, respectively, and compound heterozygous WNT10A mutations (c.364A > T and c.637G > A) were found. The findings of this study highlight the role of WNT10A gene mutations in the pathogenesis of non-syndromic oligodontia. The Wnt signaling pathway, in which WNT10A is involved, plays a critical role in tooth development (odontogenesis). Mutations in genes related to odontogenesis can disrupt the normal formation and eruption of teeth, leading to dental agenesis. The use of whole-exome sequencing in this study allowed for the efficient identification of compound heterozygous mutations in the WNT10A gene, which may have been challenging through candidate gene sequencing alone. This approach provides a comprehensive analysis of the entire exome, enabling the detection of potential genetic variants associated with oligodontia.[14]

The WNT pathway, particularly the WNT/β-catenin signaling, is of significant importance in regulating cell differentiation, proliferation, and migration during dental and orofacial development. One gene associated with the WNT pathway that has been implicated in oligodontia is the low-density lipoprotein receptor-related protein 6 (LRP6). LRP6 is a transmembrane receptor and a coreceptor for WNT ligands. It has been found to have crucial functions in WNT signal transduction. Mutations in LRP6 have been identified in patients with oligodontia. In the study mentioned in the document, four novel LRP6 mutations were discovered in a subset of oligodontia patients. These mutations included two nonsense mutations (c.2292G>A and c.1681C>T) and two frameshift mutations (c.195dup and c.1095dup). The presence of these mutations compromised the activation of WNT/β-catenin signaling, indicating the functional significance of LRP6 in tooth development.[15]

The identification of the LRP6 variant in the Japanese family provides further evidence of the involvement of the Wnt/β-catenin signaling pathway in tooth development and the genetic causes of oligodontia. The truncated LRP6 protein resulting from the mutation is likely to disrupt the normal Wnt signaling cascade, affecting tooth development and leading to the absence of multiple permanent teeth.[16]

The study from (Zhang, et al., 2020), the researchers investigated the role of the ectodysplasin A receptor (EDAR) gene in nonsyndromic oligodontia. EDAR is a key component of the ectodysplasin A (EDA)/EDAR/nuclear factor-κB (NF-κB) signaling pathway, which plays a critical role in the development of teeth and other ectodermal organs. Mutations in genes associated with this pathway, such as EDA, EDAR, and EDAR-associated death domain (EDARADD), have been linked to hypohidrotic ectodermal dysplasia (HED)-related tooth agenesis. The researchers performed mutation screening using whole-exome sequencing in a cohort of 112 unrelated patients with nonsyndromic oligodontia. They identified seven heterozygous mutations in the EDAR gene, including five novel mutations (c.404G>A, c.871G>A, c.43G>A, c.1072C>T, and c.1109T>C) and two known mutations (c.319A>G and c.1138A>C). These findings suggest that EDAR mutations are present in approximately 10.7% of nonsyndromic oligodontia cases.[17]

To assess the potential pathogenic effects of the identified mutations, the researchers conducted evolutionary conservation and conformational analyses. The results indicated that the mutations might lead to conformational changes in the EDAR protein, which could impair its function in the NF-κB signaling pathway. This provides evidence for the involvement of EDAR haploinsufficiency in nonsyndromic tooth agenesis. Furthermore, the researchers compared the tooth agenesis patterns between EDAR-related and EDA-related oligodontia. They found that the mandibular second premolars were most frequently missing in patients with EDAR mutations. This pattern differed from the tooth agenesis pattern associated with EDA mutations. These findings suggest that EDAR and EDA mutations result in distinct phenotypic manifestations of tooth agenesis, indicating the need for different mutation screening approaches in clinical genetic diagnosis.[17]

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The identification of EDAR as a candidate gene for nonsyndromic oligodontia expands our understanding of the genetic causes underlying this condition. Although previous studies have primarily focused on genes such as PAX9, MSX1, and WNT10A, which are frequently associated with nonsyndromic oligodontia, this study highlights the importance of considering the role of EDAR in the pathogenesis of tooth agenesis. The findings also emphasize the phenotypic variability and genotype-phenotype correlations in oligodontia, which can guide mutation screening and improve clinical diagnosis.[17]

Previous research has shown that variants in genes encoding other subunits of Pol III, such as POLR3A, POLR3B, POLR1C, and POLR3K, can cause a spectrum of phenotypes termed POLR3-related disorders. These disorders are characterized by various neurological and developmental abnormalities, including oligodontia. The identification of biallelic variants in POLR3GL expands the spectrum of POLR3-related disorders and suggests that POLR3GL should be included in genetic testing for suspected cases. The specific mechanisms by which variants in POLR3GL lead to oligodontia are not fully understood. However, it is likely that disruption of Pol III function affects the transcription of essential RNAs involved in tooth development. The loss of full-length POLR3GL RNA transcripts may result in abnormal expression of genes that are crucial for tooth development, leading to the absence of multiple permanent teeth.[18]

Molecular analysis plays a crucial role in understanding the genetic basis of oligodontia. Genetic testing and screening for specific gene mutations can aid in the diagnosis and management of patients with oligodontia. Additionally, advances in genomic technologies, such as next-generation sequencing, have facilitated the identification of novel genes and variants associated with tooth agenesis, further expanding our understanding of the genetic causes of oligodontia.

CONCLUSION

Oligodontia, a condition characterized by the absence of multiple teeth, is caused genetically heterogeneous condition with a complex genetic basis involving multiple genes and pathways such as WNT10A, PAX9, MSX1, and others. Several studies also highlight the role of the Wnt/β-catenin signaling pathway, especially through the LRP6 gene, in regulating tooth development and causing oligodontia. EDAR-related oligodontia may exhibit distinct phenotypic manifestations compared to EDA-related cases. Additionally, variations in Pol III subunit genes, such as POLR3GL, may also contribute to this condition. Although understanding is continually evolving, further research is needed to enhance the diagnosis and management of oligodontia.

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REFERENCES

1. de La Dure-Molla, M., Fournier, B.P., Manzanares, M.C., Acevedo, A.C., Hennekam, R.C., Friedlander, L., Boy-Lefèvre, M.L., Kerner, S., Toupenay, S., Garrec, P. and Vi-Fane, B., 2019. Elements of morphology: Standard terminology for the teeth and classifying genetic dental disorders. American Journal of Medical Genetics Part A, 179(10), pp.1913-1981.
2. Zhu, X., Shen, Y. and Zheng, J., 2021. Progress in genetic research on tooth agenesis associated with Wnt/beta-catenin signaling pathway. Zhonghua yi xue yi Chuan xue za zhi= Zhonghua Yixue Yichuanxue Zazhi= Chinese Journal of Medical Genetics, 38(5), pp.506-509.
3. Al-Ani, A.H., Antoun, J.S., Thomson, W.M., Merriman, T.R. and Farella, M., 2017. Hypodontia: an update on its etiology, classification, and clinical management. BioMed Research International, 2017.
4. Dhamo, B., Kuijpers, M.A.R., Balk-Leurs, I., Boxum, C., Wolvius, E.B. and Ongkosuwito, E.M., 2018. Disturbances of dental development distinguish patients with oligodontia-ectodermal dysplasia from isolated oligodontia. Orthodontics & craniofacial research, 21(1), pp.48-56.
5. Baba, R., Sato, A. and Arai, K., 2022. Consecutive tooth agenesis patterns in non-syndromic oligodontia. Odontology, 110, pp.183-192.

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www.ijcsrr.org

6. Ritwik, P. and Patterson, K.K., 2018. Diagnosis of tooth agenesis in childhood and risk for neoplasms in adulthood. Ochsner Journal, 18(4), pp.345-350.
7. Klein, O.D., Oberoi, S., Huysseune, A., Hovorakova, M., Peterka, M. and Peterkova, R., 2013, November. Developmental disorders of the dentition: an update. In American Journal of Medical Genetics Part C: Seminars in Medical Genetics (Vol. 163, No. 4, pp. 318-332).
8. Bural, C., Oztas, E., Ozturk, S. and Bayraktar, G., 2012. Multidisciplinary treatment of non-syndromic oligodontia. European journal of dentistry, 6(02), pp.218-226.
9. Ruf, S., Klimas, D., Hönemann, M. and Jabir, S., 2013. Genetic background of nonsyndromic oligodontia: a systematic review and meta-analysis. Journal of Orofacial Orthopedics/Fortschritte der Kieferorthopadie, 74(4).
10. Castilho, N.L., Resende, K.K.M., Santos, J.A.D., Machado, R.A., Coletta, R.D., Guerra, E.N.S., Acevedo, A.C. and Martelli-Junior, H., 2023. Oligodontia in the Clinical Spectrum of Syndromes: A Systematic Review. Dentistry Journal, 11(12), p.279.
11. Sun, K., Yu, M., Yeh, I., Zhang, L., Liu, H., Cai, T., Feng, H., Liu, Y. and Han, D., 2021. Functional study of novel PAX9 variants: The paired domain and non-syndromic oligodontia. Oral diseases, 27(6), pp.1468-1477.
12. Yang, L., Liang, J., Yue, H. and Bian, Z., 2020. Two novel mutations in MSX1 causing oligodontia. PLoS One, 15(1), p.e0227287.
13. Zhou, M., Zhang, H., Camhi, H., Seymen, F., Koruyucu, M., Kasimoglu, Y., Kim, J.W., Kim-Berman, H., Yuson, N.M., Benke, P.J. and Wu, Y., 2021. Analyses of oligodontia phenotypes and genetic etiologies. International journal of oral science, 13(1), p.32.
14. Park, H., Song, J.S., Shin, T.J., Hyun, H.K., Kim, Y.J. and Kim, J.W., 2019. WNT10A mutations causing oligodontia. Archives of Oral Biology, 103, pp.8-11.
15. Yu, M., Fan, Z., Wong, S.W., Sun, K., Zhang, L., Liu, H., Feng, H., Liu, Y. and Han, D., 2021. Lrp6 dynamic expression in tooth development and mutations in oligodontia. Journal of Dental Research, 100(4), pp.415-422.
16. Goto, H., Kimura, M., Machida, J., Ota, A., Nakashima, M., Tsuchida, N., Adachi, J., Aoki, Y., Tatematsu, T., Takahashi, K. and Sana, M., 2021. A novel LRP6 variant in a Japanese family with oligodontia. Human Genome Variation, 8(1), p.30.
17. Zhang, L., Yu, M., Wong, S.W., Qu, H., Cai, T., Liu, Y., Liu, H., Fan, Z., Zheng, J., Zhou, Y. and Feng, H., 2020. Comparative analysis of rare EDAR mutations and tooth agenesis pattern in EDAR-and EDA-associated nonsyndromic oligodontia. Human mutation, 41(11), pp.1957-1966.
18. Terhal, P.A., Vlaar, J.M., Middelkamp, S., Nievelstein, R.A., Nikkels, P.G., Ross, J., Créton, M., Bos, J.W., Voskuil-Kerkhof, E.S., Cuppen, E. and Knoers, N., 2020. Biallelic variants in POLR3GL cause endosteal hyperostosis and oligodontia. European Journal of Human Genetics, 28(1), pp.31-39.

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