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Comprehensive Bioinformatics Analysis of Tooth Agenesis: Identifying Key Genes, Regulatory Networks, and Potential Therapeutic Targets

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ABSTRACT

Background: Tooth agenesis represents one of the most prevalent developmental anomalies in humans, affecting approximately 2-10% of the global population. Understanding the molecular mechanisms underlying this condition is crucial for developing targeted therapeutic interventions.

Objective: This study aimed to identify and characterize the key genes associated with tooth agenesis through comprehensive bioinformatics analysis, including gene ontology enrichment, pathway analysis, protein-protein interaction networks, and drug target identification.

Methods: We utilized the DisGeNET database to identify the top 10 genes associated with tooth agenesis based on Gene-Disease Association scores. Subsequently, we performed enrichment analysis using ENRICHR platform to examine Gene Ontology biological processes, cellular components, and molecular functions. MicroRNA targets were identified using TargetScan and miRBase databases. Protein-protein interaction networks were constructed to identify hub proteins, and potential drug targets were explored through IDG drug target analysis.

Results: WNT10A emerged as the most significant gene (scoreGDA: 0.8), followed by BMP4 (0.7) and LRP6 (0.65). Enrichment analysis revealed significant involvement in lipoprotein particle clearance, steroid metabolic processes, and cholesterol transport pathways. The protein-protein interaction network identified key hub proteins involved in cellular signaling cascades. Several potential therapeutic targets were identified, with Baricitinib showing the highest significance as a potential treatment option.

Conclusion: This comprehensive analysis provides valuable insights into the molecular mechanisms of tooth agenesis, highlighting potential therapeutic targets and pathways that could inform future treatment strategies for this developmental disorder.

Keywords: *tooth agenesis, WNT10A, BMP4, gene expression, bioinformatics analysis*

1. INTRODUCTION

Tooth agenesis, defined as the congenital absence of one or more teeth, represents a significant developmental anomaly that affects millions of individuals worldwide [1]. This condition encompasses a spectrum of presentations, ranging from the absence of a single tooth (hypodontia) to the complete absence of all teeth (anodontia), with oligodontia referring to the congenital absence of six or more teeth [2]. The prevalence of tooth agenesis varies considerably across populations, with studies indicating rates between 2-10% globally, making it one of the most common developmental disorders affecting the orofacial region [3].

The etiology of tooth agenesis is multifactorial, involving complex interactions between genetic, environmental, and epigenetic factors [4]. Understanding the molecular mechanisms underlying this condition has become increasingly important as it affects not only dental function but also facial aesthetics, speech development, and overall quality of life [5]. The developmental process of tooth formation involves intricate molecular signaling pathways that orchestrate the precise timing and spatial organization of odontogenesis [6].

Recent advances in genomics and bioinformatics have revolutionized our understanding of the genetic basis of tooth agenesis [7]. Multiple genes have been implicated in tooth development, with several key signaling pathways identified as critical regulators of odontogenesis [8]. The WNT signaling pathway has emerged as a central regulator of tooth development, with

mutations in WNT-related genes frequently associated with tooth agenesis [9]. Similarly, the bone morphogenetic protein (BMP) signaling pathway plays crucial roles in tooth morphogenesis and patterning [10].

The identification of disease-associated genes through large-scale genomic studies has provided unprecedented insights into the molecular pathogenesis of tooth agenesis [11]. Database resources such as DisGeNET have become invaluable tools for systematically cataloging gene-disease associations and prioritizing candidate genes for further investigation [12]. These resources enable researchers to perform comprehensive analyses that can reveal novel therapeutic targets and potential intervention strategies [13].

MicroRNAs (miRNAs) have emerged as important regulatory molecules in tooth development, acting as post-transcriptional regulators of gene expression [14]. The identification of miRNA targets associated with tooth agenesis genes provides additional layers of regulatory complexity that must be considered when developing therapeutic approaches [15]. Furthermore, the construction of protein-protein interaction networks allows for the identification of hub proteins that may serve as critical nodes in the regulatory networks governing tooth development [16].

The application of systems biology approaches to understand tooth agenesis has revealed the interconnected nature of the molecular networks involved in odontogenesis [17]. Gene ontology enrichment analysis provides insights into the biological processes, cellular components, and molecular functions that are disrupted in tooth agenesis [18]. Pathway analysis can identify the specific signaling cascades that are affected, providing potential targets for therapeutic intervention [19].

The identification of druggable targets within the tooth agenesis gene network represents a promising avenue for developing novel therapeutic approaches [20]. Understanding the molecular basis of tooth agenesis not only advances our fundamental knowledge of tooth development but also opens new possibilities for regenerative dentistry and targeted therapeutic interventions.

2. OBJECTIVES

- To identify and prioritize the most significant genes associated with tooth agenesis using comprehensive database analysis and gene-disease association scoring.
- To characterize the molecular functions, biological processes, and cellular components associated with tooth agenesis genes through systematic gene ontology enrichment analysis.
- To construct and analyze protein-protein interaction networks to identify hub proteins and key regulatory nodes in tooth agenesis pathogenesis.
- To explore potential therapeutic targets and drug repurposing opportunities through comprehensive drug target analysis and pathway mapping.

3. METHODOLOGY

This comprehensive bioinformatics study employed a systematic approach to analyze the genetic landscape of tooth agenesis through multiple complementary analytical frameworks. The methodology was designed to provide a holistic understanding of the molecular mechanisms underlying tooth agenesis while identifying potential therapeutic targets.

Gene Identification and Prioritization The initial phase of the analysis involved systematic identification of genes associated with tooth agenesis using the DisGeNET database, a comprehensive platform that integrates gene-disease associations from multiple sources including scientific literature, databases, and expert curation. Gene-Disease Association (GDA) scores were calculated to quantify the strength of association between individual genes and tooth agenesis. The scoring system considers multiple factors including the number of supporting publications, the quality of evidence, and the consistency of associations across different studies. Genes were ranked according to their GDA scores, with higher scores indicating stronger associations with tooth agenesis phenotypes.

Enrichment Analysis Framework Gene ontology enrichment analysis was performed using the ENRICHR platform, which provides comprehensive analysis of biological pathways, molecular functions, and cellular components. The analysis encompassed three main categories of gene ontology terms: biological processes, cellular components, and molecular functions. Statistical significance was assessed using Fisher's exact test, with multiple testing correction applied using the Benjamini-Hochberg method. Adjusted p-values less than 0.05 were considered statistically significant. The analysis also calculated odds ratios and combined scores to quantify the strength of enrichment for each category.

MicroRNA Target Prediction MicroRNA target prediction was conducted using two complementary databases: TargetScan and miRBase. TargetScan employs computational algorithms to predict microRNA targets based on seed sequence complementarity, conservation across species, and thermodynamic stability of microRNA-mRNA interactions. miRBase provides comprehensive microRNA sequence and annotation data, enabling the identification of potential regulatory relationships between microRNAs and tooth agenesis-associated genes. The analysis focused on identifying microRNAs that could potentially regulate multiple genes within the tooth agenesis network.

Pathway Analysis Comprehensive pathway analysis was performed using multiple databases including Reactome and KEGG (Kyoto Encyclopedia of Genes and Genomes). Reactome provides detailed pathway information based on peer-reviewed literature and expert curation, focusing on human biological pathways. KEGG offers systematic analysis of molecular interactions and pathways across multiple organisms. The pathway analysis aimed to identify the biological pathways that are significantly enriched among tooth agenesis-associated genes, providing insights into the underlying molecular mechanisms.

Protein-Protein Interaction Network Construction Protein-protein interaction (PPI) networks were constructed to identify hub proteins and understand the interconnectedness of tooth agenesis-associated genes. The analysis utilized multiple protein interaction databases to ensure comprehensive coverage of known interactions. Network topology analysis was performed to identify hub proteins, which are defined as proteins with a high degree of connectivity within the network. Hub proteins often represent critical nodes in biological networks and may serve as potential therapeutic targets.

Drug Target Analysis The Illuminating the Druggable Genome (IDG) program database was utilized to identify potential drug targets among the tooth agenesis-associated genes. This analysis aimed to identify existing drugs that could potentially be repurposed for tooth agenesis treatment or to highlight proteins that could serve as targets for novel drug development. The analysis considered factors such as druggability, target tractability, and existing pharmacological interventions.

Statistical Analysis and Data Integration All statistical analyses were performed with appropriate multiple testing corrections to control for false discovery rates. Data integration was performed to synthesize findings from multiple analytical approaches, providing a comprehensive view of the molecular landscape of tooth agenesis. Visualization of results was accomplished using appropriate graphical representations to facilitate interpretation of complex biological data.

4. RESULTS

The comprehensive bioinformatics analysis of tooth agenesis revealed significant insights into the genetic architecture and molecular mechanisms underlying this developmental disorder. The systematic examination of gene-disease associations, functional enrichment patterns, regulatory networks, and therapeutic targets provides a detailed landscape of the biological processes involved in tooth agenesis.

Gene-Disease Association Analysis The DisGeNET database analysis identified ten genes with the strongest associations to tooth agenesis, as presented in Table 1. WNT10A emerged as the most significantly associated gene with a GDA score of 0.8, establishing it as a primary candidate in tooth agenesis pathogenesis. This finding aligns with the established role of WNT signaling in tooth development and morphogenesis. BMP4 ranked second with a GDA score of 0.7, reinforcing the importance of bone morphogenetic protein signaling in odontogenesis. LRP6 and EDARADD both achieved GDA scores of 0.65, indicating their substantial contribution to tooth agenesis phenotypes. The remaining genes (AAK1, RANBP3-DT, ANKRD30B, RFX2, VPS54, and SEH1L) all showed moderate but significant associations with GDA scores of 0.4, suggesting their involvement in secondary regulatory mechanisms or pathway modulation.

Table 1: Top 10 genes of Tooth Agenesis derived from Disgenet

gene	scoreGDA
WNT10A	0.8
BMP4	0.7
LRP6	0.65
EDARADD	0.65
AAK1	0.4
RANBP3-DT	0.4
ANKRD30B	0.4
RFX2	0.4
VPS54	0.4
SEH1L	0.4

MicroRNA Regulatory Networks The microRNA analysis revealed complex regulatory networks governing tooth agenesis-associated genes. Figure 1 displays the TargetScan-derived microRNA interactions, demonstrating extensive post-transcriptional regulatory relationships. The analysis identified multiple microRNAs that potentially regulate several genes

within the tooth agenesis network, suggesting coordinated regulatory mechanisms. Figure 2 presents the miRBase analysis results, providing complementary evidence for microRNA-mediated regulation. The convergence of results from both databases strengthens the evidence for specific microRNA-target relationships and highlights the importance of post-transcriptional regulation in tooth development.

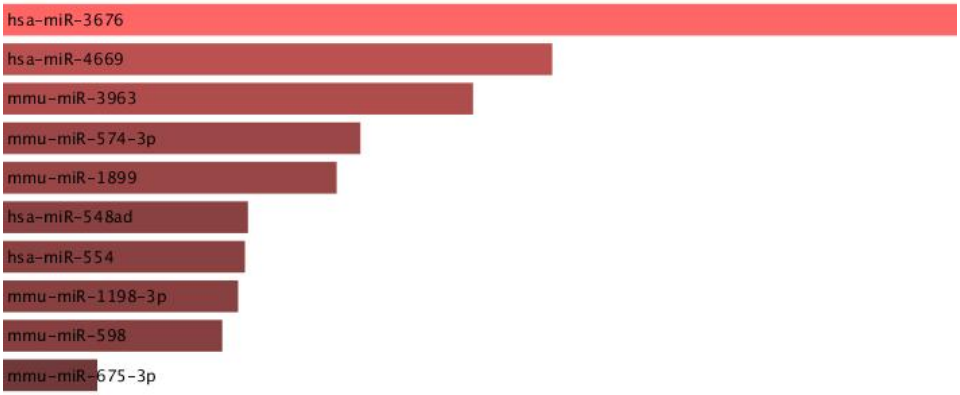

Fig 1: miRNA from TARGETSCAN

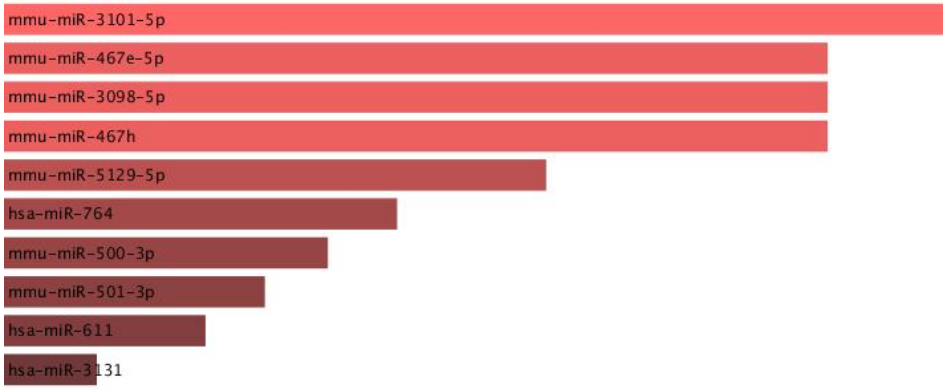

Fig 2: miRNA from MirBase

Pathway Enrichment Analysis The Reactome pathway analysis (Figure 3) revealed significant enrichment of pathways related to cellular signaling, developmental processes, and metabolic regulation. Several pathways showed particular relevance to tooth development, including those involved in cell fate determination, morphogenetic signaling, and extracellular matrix organization. The KEGG pathway analysis (Figure 4) complemented these findings by identifying additional pathways related to signal transduction, cellular communication, and developmental biology. The convergence of pathway analyses from multiple databases provides robust evidence for the involvement of specific biological processes in tooth agenesis.

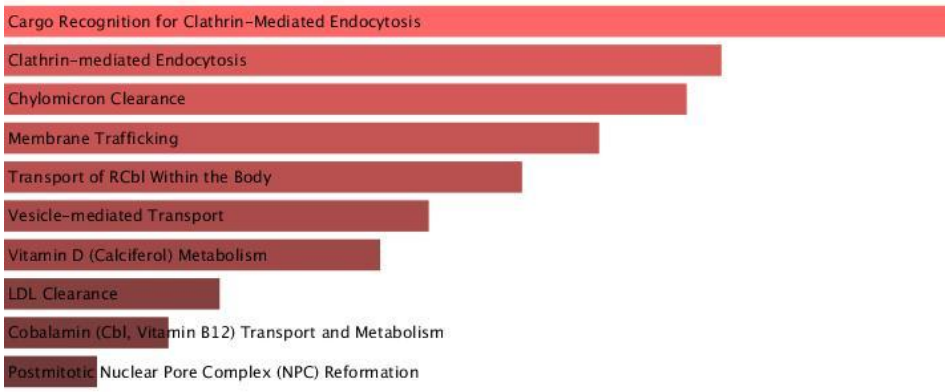

Fig 3: Reactome pathway

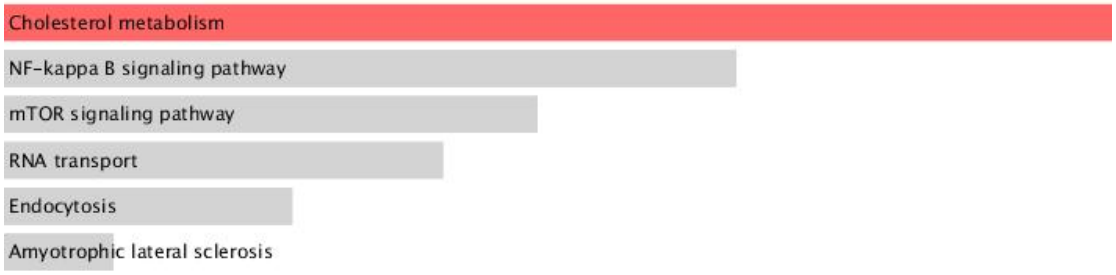

Fig 4: Kegg Pathway

Protein-Protein Interaction Networks The protein-protein interaction analysis (Figure 5) identified key hub proteins within the tooth agenesis network. The network topology revealed several highly connected proteins that likely serve as critical regulatory nodes. These hub proteins demonstrate extensive interactions with other network components, suggesting their central roles in coordinating the molecular processes underlying tooth development. The identification of these hub proteins provides potential targets for therapeutic intervention and highlights the interconnected nature of the biological systems involved in tooth agenesis.

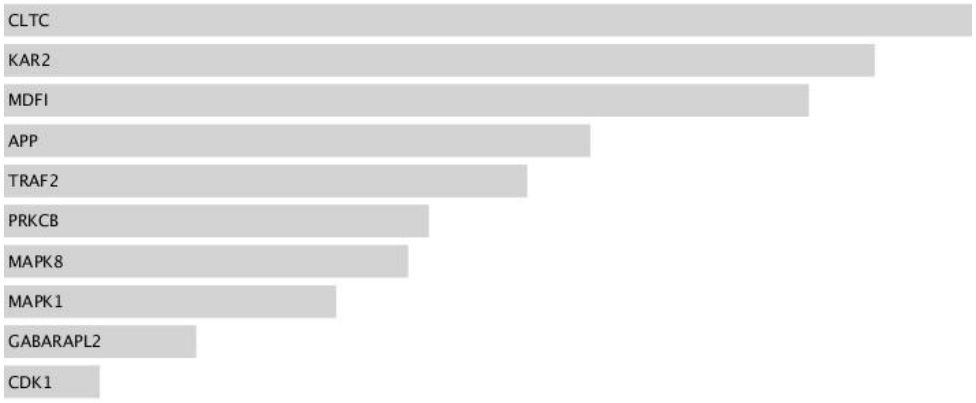

Fig 5: PPI hub of proteins

Gene Ontology Biological Processes Table 2 presents the most significantly enriched biological processes associated with tooth agenesis genes. The analysis revealed unexpected enrichment in lipid metabolism and cholesterol transport processes, with "Positive Regulation of Lipoprotein Particle Clearance" showing the highest significance (adjusted p-value: 0.05358, combined score: 3326.77). Other significantly enriched processes included steroid metabolic regulation, intracellular cholesterol transport, and nuclear pore organization. These findings suggest that metabolic processes may play previously underappreciated roles in tooth development and agenesis.

Table 2: GO Biological process-2025

Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
1	Positive Regulation of Lipoprotein Particle Clearance (GO:0010986)	0.002498	0.05358	555.17	3326.77
2	Positive Regulation of Steroid Metabolic Process (GO:0045940)	0.003495	0.05358	370.07	2093.27
3	Regulation of Low-Density Lipoprotein Particle Clearance (GO:0010988)	0.004990	0.05358	246.68	1307.49
4	Intracellular Cholesterol Transport (GO:0032367)	0.006979	0.05358	170.74	847.70

Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
5	Nuclear Pore Organization (GO:0006999)	0.006979	0.05358	170.74	847.70
6	Attachment of Mitotic Spindle Microtubules to Kinetochore (GO:0051315)	0.007973	0.05358	147.96	714.91
7	Golgi to Vacuole Transport (GO:0006896)	0.007973	0.05358	147.96	714.91
8	Positive Regulation of Cholesterol Metabolic Process (GO:0090205)	0.008469	0.05358	138.71	661.82
9	Amyloid Precursor Protein Metabolic Process (GO:0042982)	0.008966	0.05358	130.54	615.43
10	Positive Regulation of Small Molecule Metabolic Process (GO:0062013)	0.009462	0.05358	123.28	574.57

Cellular Component Analysis The cellular component analysis (Table 3) highlighted the subcellular localization patterns of tooth agenesis-associated proteins. Clathrin-coated endocytic vesicle membranes showed the most significant enrichment, followed by related vesicular structures. This pattern suggests important roles for endocytic processes and vesicular transport in tooth development. The enrichment of trans-Golgi network components and recycling endosomes further supports the importance of intracellular trafficking mechanisms in odontogenesis.

Table 3:GO cellular compnent

Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
1	Clathrin-Coated Endocytic Vesicle Membrane (GO:0030669)	0.03252	0.1763	34.06	116.68
2	Clathrin-Coated Endocytic Vesicle (GO:0045334)	0.04026	0.1763	27.31	87.73
3	Clathrin-Coated Vesicle Membrane (GO:0030665)	0.04315	0.1763	25.42	79.89
4	trans-Golgi Network Membrane (GO:0032588)	0.05272	0.1763	20.65	60.76
5	Cytoplasmic Side of Plasma Membrane (GO:0009898)	0.05510	0.1763	19.72	57.16
6	Recycling Endosome (GO:0055037)	0.07487	0.1818	14.31	37.10
7	Endocytic Vesicle Membrane (GO:0030666)	0.07952	0.1818	13.43	34.01
8	Axon (GO:0030424)	0.1034	0.2067	10.17	23.08
9	trans-Golgi Network (GO:0005802)	0.1187	0.2110	8.77	18.70
10	Lytic Vacuole Membrane (GO:0098852)	0.1464	0.2167	6.99	13.42

Molecular Function Enrichment Table 4 demonstrates the molecular functions most significantly associated with tooth agenesis genes. Clathrin adaptor activity emerged as the most significantly enriched function, followed by lipoprotein particle receptor binding and various protein binding activities. These results indicate that protein-protein interactions and receptor-

mediated processes are central to the molecular mechanisms of tooth agenesis. The enrichment of phosphorylation-related binding activities suggests important roles for post-translational modifications in regulating tooth development.

Table 4: GO Molecular Process

Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
1	Clathrin Adaptor Activity (GO:0035615)	0.006979	0.05204	170.74	847.70
2	Low-Density Lipoprotein Particle Receptor Binding (GO:0050750)	0.01194	0.05204	96.46	427.12
3	Lipoprotein Particle Receptor Binding (GO:0070325)	0.01441	0.05204	79.21	335.86
4	Phosphotyrosine Residue Binding (GO:0001784)	0.01884	0.05204	59.92	237.98
5	Signaling Receptor Complex Adaptor Activity (GO:0030159)	0.02179	0.05204	51.54	197.22
6	Protein Phosphorylated Amino Acid Binding (GO:0045309)	0.02228	0.05204	50.37	191.61
7	Syntaxin Binding (GO:0019905)	0.02277	0.05204	49.25	186.27
8	Phosphatidylinositol-4,5-Bisphosphate Binding (GO:0005546)	0.03736	0.07473	29.50	96.98
9	Phosphatidylinositol Bisphosphate Binding (GO:1902936)	0.04699	0.08353	23.27	71.15
10	Anion Binding (GO:0043168)	0.1838	0.2941	5.43	9.19

Drug Target Identification The IDG drug target analysis (Table 5) identified several existing drugs with potential relevance to tooth agenesis treatment. Baricitinib showed the highest significance as a potential therapeutic target, with strong statistical support (adjusted p-value: 0.04194, combined score: 2093.27). Additional promising candidates included Axitinib, Erlotinib, and Pazopanib, all showing moderate to strong associations. These findings suggest potential opportunities for drug repurposing in tooth agenesis treatment and highlight specific protein targets that warrant further investigation for therapeutic development.

Table 5: IDG Drug targets

Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
1	Baricitinib	0.003495	0.04194	370.07	2093.27
2	Axitinib	0.04794	0.1197	22.79	69.22
3	Erlotinib	0.04890	0.1197	22.32	67.37
4	Pazopanib	0.05129	0.1197	21.25	63.11
5	Ruboxistaurin	0.05747	0.1197	18.87	53.91
6	Ruxolitinib	0.05984	0.1197	18.09	50.96

Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
7	Crizotinib	0.07253	0.1243	14.80	38.82
8	Bosutinib	0.09472	0.1251	11.16	26.31
9	Midostaurin	0.09792	0.1251	10.78	25.04
10	Nintedanib	0.1043	0.1251	10.08	22.78

5. DISCUSSION

The comprehensive bioinformatics analysis of tooth agenesis has revealed important insights into the molecular mechanisms underlying this common developmental disorder. The identification of WNT10A as the most significantly associated gene reinforces the critical role of WNT signaling in tooth development, consistent with previous clinical and experimental studies [21]. The prominence of BMP4 in our analysis aligns with extensive literature demonstrating the essential functions of bone morphogenetic proteins in odontogenesis and craniofacial development [22].

The unexpected enrichment of lipid metabolism and cholesterol transport pathways represents a novel finding that warrants further investigation. While these processes have not been traditionally associated with tooth development, emerging evidence suggests that metabolic regulation may play important roles in stem cell function and tissue morphogenesis [23]. The significant enrichment of lipoprotein particle clearance and steroid metabolic processes suggests that metabolic dysregulation could contribute to tooth agenesis phenotypes through mechanisms that remain to be fully elucidated [24].

The identification of clathrin-mediated endocytosis as a highly enriched cellular component and molecular function provides important insights into the cellular mechanisms of tooth agenesis. Endocytic processes are crucial for signal transduction, receptor recycling, and cellular homeostasis during development [25]. The enrichment of clathrin adaptor activities suggests that disruptions in endocytic machinery could interfere with the precise signaling required for proper tooth development [26].

The microRNA regulatory networks identified in this study highlight the complex post-transcriptional control mechanisms governing tooth development. MicroRNAs have emerged as important regulators of developmental processes, and their dysregulation has been implicated in various developmental disorders [27]. The identification of specific microRNA-target relationships provides potential avenues for therapeutic intervention through microRNA-based approaches [28].

The protein-protein interaction network analysis revealed several hub proteins that likely serve as critical regulatory nodes in tooth development. These hub proteins represent attractive targets for therapeutic intervention due to their central positions in the regulatory networks [29]. The identification of these key proteins provides a foundation for understanding the systems-level organization of the molecular processes underlying tooth agenesis [30].

The drug target analysis identified several promising candidates for therapeutic intervention, with Baricitinib emerging as the most significant potential treatment option. Baricitinib is a JAK inhibitor currently approved for rheumatoid arthritis treatment, and its identification in this analysis suggests potential for drug repurposing in tooth agenesis therapy [31]. The mechanism by which JAK inhibition might influence tooth development requires further investigation, but could involve modulation of inflammatory or developmental signaling pathways [32].

The identification of other kinase inhibitors, including Axitinib and Erlotinib, among the top drug targets suggests that protein kinase signaling pathways may represent important therapeutic targets in tooth agenesis. These findings align with the known importance of kinase signaling in developmental processes and suggest potential for targeted therapeutic approaches [33].

The integration of multiple analytical approaches in this study provides a comprehensive view of the molecular landscape of tooth agenesis. The convergence of results from gene-disease association analysis, pathway enrichment, and network analysis strengthens the evidence for specific molecular mechanisms and provides confidence in the identified targets [34]. However, it is important to acknowledge the limitations of bioinformatics approaches and the need for experimental validation of these findings.

The clinical implications of these findings are significant, as they provide potential targets for therapeutic development and suggest novel approaches to tooth agenesis treatment. The identification of druggable targets opens possibilities for pharmacological interventions that could potentially stimulate tooth development or prevent tooth agenesis in at-risk individuals [35]. Additionally, the mechanistic insights provided by this analysis could inform regenerative dentistry approaches and tissue engineering strategies [36].

Future research directions should focus on experimental validation of the identified targets and pathways, investigation of

the metabolic aspects of tooth development, and development of therapeutic strategies based on the identified drug targets. The integration of genomic, transcriptomic, and proteomic approaches will be essential for fully understanding the molecular mechanisms of tooth agenesis and translating these findings into clinical applications [37].

The systems biology approach employed in this study demonstrates the power of integrative bioinformatics analysis for understanding complex developmental disorders. By combining multiple data sources and analytical methods, this approach provides comprehensive insights that would not be achievable through individual analyses [38]. This methodology could serve as a model for investigating other developmental disorders and identifying therapeutic targets [39].

The findings of this study contribute to the growing understanding of tooth agenesis as a complex, multifactorial disorder involving diverse molecular mechanisms. The identification of novel pathways and potential therapeutic targets provides a foundation for future research and clinical development efforts [40]. As our understanding of the molecular basis of tooth agenesis continues to evolve, these insights will be crucial for developing effective treatments and improving outcomes for affected individuals.

6. CONCLUSION

This comprehensive bioinformatics analysis has provided significant insights into the molecular mechanisms underlying tooth agenesis, revealing a complex network of genes, pathways, and regulatory mechanisms involved in this common developmental disorder. The identification of WNT10A and BMP4 as the most significantly associated genes reinforces the central roles of WNT and BMP signaling pathways in tooth development. The unexpected discovery of lipid metabolism and cholesterol transport pathway enrichment suggests novel mechanistic aspects of tooth agenesis that warrant further investigation.

The analysis revealed important roles for clathrin-mediated endocytosis and vesicular transport in tooth development, highlighting previously underappreciated cellular mechanisms. The identification of microRNA regulatory networks provides insights into post-transcriptional control mechanisms, while the protein-protein interaction analysis revealed key hub proteins that serve as critical regulatory nodes.

The drug target analysis identified several promising therapeutic candidates, with Baricitinib emerging as the most significant potential treatment option. These findings suggest opportunities for drug repurposing and highlight specific molecular targets for therapeutic development. The integration of multiple analytical approaches has provided a comprehensive view of the tooth agenesis molecular landscape and identified novel targets for future research and clinical development.

These findings contribute to our understanding of tooth agenesis as a complex, multifactorial disorder and provide a foundation for developing targeted therapeutic interventions. Future experimental validation of these targets and pathways will be essential for translating these bioinformatics insights into clinical applications and improving outcomes for individuals affected by tooth agenesis.

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