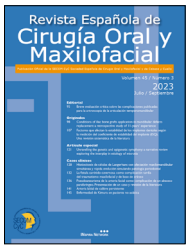
Rev Esp Cir Oral Maxilofac. 2023;45(3):121-127

Revista Española de
Cirugía Oral y
Maxilofacial

www.revistacirugiaoralymaxilofacial.es



Artículo especial

Unravelling the genetic and epigenetic symphony: a narrative review exploring the interplay in etiology of microtia

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ARTICLE INFORMATION

Article history:

Received: 18 de agosto de 2023
Accepted: 14 de diciembre de 2023

Keywords:

Microtia, epigenetic, genetic, HOXA4, CHST15.

A B S T R A C T

Microtia, a congenital anomaly of the external ear, serves as a model to explore the intricate synergy between genetics and epigenetics in shaping phenotypic outcomes. Genetics, residing in DNA, provides the blueprint for development, while epigenetic modifications modulate gene expression without altering the DNA sequence. This comprehensive review delves into their combined influence on microtia's etiology, unravelling the significance of DNA methylation, histone modifications, and microRNAs in ear formation and their susceptibility to environmental cues. Genetic investigations encompass pedigree analysis and whole-exome sequencing, spotlighting pivotal genes like HOXA4 and CHST15. Syndromic associations underscore the multifaceted genetic underpinning of microtia. This dynamic interplay between genetics and epigenetics enriches our understanding of developmental anomalies, offering insights for tailored interventions and clinical strategies to manage this condition in a personalized manner. The continuous exploration of these interactions opens avenues for deciphering intricate developmental processes and expanding our comprehension of related anomalies.

Desentrañando la sinfonía genética y epigenética: una revisión narrativa sobre la interacción en la etiología de la microtia

Palabras clave:

Microtia, epigenético, genético, HOXA4, CHST15.

R E S U M E N

La microtia, una anomalía congénita del oído externo, sirve como modelo para explorar la compleja sinergia entre la genética y la epigenética en la determinación de resultados fenotípicos. La genética, que reside en el ADN, proporciona el plano para el desarrollo, mientras que las modificaciones epigenéticas modulan la expresión génica sin alterar la secuencia del ADN. Esta revisión exhaustiva se adentra en su influencia combinada sobre la etiología

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http://dx.doi.org/10.20986/recom.2023.1475/2023

de la microtia, desentrañando la importancia de la metilación del ADN, las modificaciones de las histonas y los microARNs en la formación del oído y su susceptibilidad a las señales ambientales. Las investigaciones genéticas incluyen análisis de pedigrí y secuenciación del exoma completo, destacando genes esenciales como HOXA4 y CHST15. Las asociaciones sindrómicas subrayan la base genética multifacética de la microtia. Esta interacción dinámica entre la genética y la epigenética enriquece nuestro entendimiento de las anomalías del desarrollo, ofreciendo perspectivas para intervenciones a medida y estrategias clínicas para manejar esta condición de manera personalizada. La continua exploración de estas interacciones abre caminos para descifrar procesos de desarrollo complejos y expandir nuestra comprensión de anomalías relacionadas.

INTRODUCTION

Microtia, a congenital condition manifesting as underdeveloped or misshaped external ears, offers an intriguing window into the intricate dance between genetics and epigenetics in determining an organism's phenotype[1,2]. At its core, genetics provides the blueprint: genes, which are segments of DNA, encode the foundational instructions that guide the development and maintenance of an organism. These genes, housed on chromosomes, dictate everything from protein synthesis, which in turn influence an individual's observable physical and behavioral traits, to the more subtle regulatory roles that can switch other genes on or off[3].

However, it is important to note that genetics alone does not solely determine an individual's phenotype. Epigenetics, the study of heritable changes in gene expression without alterations to the underlying DNA sequence, also plays a crucial role[4]. Environmental factors, lifestyle choices, and developmental cues can induce these epigenetic changes, which range from DNA methylation –potentially silencing genes– to histone modifications that can both inhibit and activate gene transcription. The stakes are high; these epigenetic mechanisms play pivotal roles during developmental processes such as cellular differentiation, determining the trajectory from stem cells to specialized entities like nerve or muscle cells[4]. Moreover, epigenetic modifications have been implicated in various diseases, from cancers to metabolic disorders, underscoring their significant influence on health.

When one dives deeper into the realm of microtia, it's evident that both genetics and epigenetics are deeply interwoven in its etiology. Genetic mutations, both inherited and sporadic, can set the stage for microtia's manifestation. Genes such as the HOXA2 and CHST15, which play a crucial role in head and neck development, have been linked to the condition[5,6]. Yet, the story doesn't stop with genetics alone. Epigenetic mechanisms, which play a profound role in embryonic development, have emerged as potential influencers in the occurrence of microtia[7]. Aberrant patterns in DNA methylation or shifts in histone modifications during crucial developmental stages can throw off the delicate balance of gene regulation necessary for proper ear formation.

Thus, to study microtia is to explore the dynamic interplay between genetics and epigenetics, two forces that, in tandem, sculpt the landscape of biological development. In the subsequent sections, we will delve into the roles of genetic and epigenetic factors in microtia, and how their interactions might offer insights into both the condition and broader principles of developmental biology.

METHODS

The review aimed to explore the intricate relationship between epigenetic and genetic factors in microtia. A comprehensive search strategy was employed using databases such as PubMed, Web of Science, Embase, Google Scholar, and Scopus. Keywords like "Epigenetic factors", "Gene factors" and "Microtia" were combined using Boolean operators (AND, OR, NOT) to refine the search. The focus was on studies that thoroughly discussed both epigenetic and genetic factors associated with microtia. Eligibility for inclusion encompassed peer-reviewed articles, regardless of format (reviews, original research articles, case reports, clinical studies) and published in English. Conversely, studies solely addressing either genetic or epigenetic factors, non-English publications, and those with overlapping datasets were excluded.

During the study selection phase, titles and abstracts of the initially identified records were screened by two independent reviewers who are members of the Otorhinolaryngology-Head and Neck Surgery Department, with one being a senior consultant in the Division of Facial Plastic Reconstruction. Discrepancies between reviewers were addressed through consensus-building or consultation with a third reviewer who is a professor in the Division of Facial Plastic Reconstruction. Potentially relevant studies then underwent a full-text assessment against the stated eligibility criteria. For data extraction, a standardized protocol was employed, capturing essential details such as the study's methodology, findings on epigenetic and gene interplay in microtia, and any identified mechanisms or markers. While quality assessments are not customary for narrative reviews, provisions are in place to evaluate the reliability and validity of sources if deemed necessary. The culmination of this method aims to provide a comprehensive overview of the current knowledge, spotlighting potential areas for further research.

ROLES OF EPIGENETIC AND GENETIC FACTORS IN MICROTIA DEVELOPMENT

HOX genes as main culprit of microtia?

Microtia, a congenital anomaly of the external ear, arises from the nuanced interplay of both epigenetic and genetic

mechanisms. Epigenetic processes adjust gene expression without DNA sequence alterations, whereas genetic determinants encompass inherited and spontaneous mutations pivotal to craniofacial development. Central to this dynamic is the role of HOX genes, key transcription factors responsible for specifying an animal embryo's body plan along the head-tail axis and regulating myriad cellular behaviors and differentiation[8].

Recent findings suggest a potential linkage between HOX genes and the development of microtia. An increase in the expression of HOX genes was observed following the suppression of Cadherin-11 in chondrocytes derived from human microtia[9]. This implies a role for HOX genes in influencing the proliferation, migration, and extracellular matrix synthesis of ear cartilage cells[9]. Among them, anterior members such as HOX1, HOX2, and HOX4 —expressed prominently in the head regions of various animals— play significant roles in shaping cephalic segments, including the eyes, mouth, and brain[10]. Furthermore, their impact extends to the cell segregation and apical constriction processes of the neuroepithelium, which serve as precursors to the central nervous system[11].

Given the craniofacial implications of microtia, aberrations or regulatory disruptions in these anterior HOX genes might be central to its etiology. Yet, despite the intriguing nature of this proposition, tangible evidence is currently limited. Future explorations into the evolutionary trajectory and variability of HOX genes across diverse animal groups, like molluscs, promise to shed further light on their function and potential regulatory mechanisms in ear development. The complexities of microtia, as evident, necessitate a continued, multifaceted examination of the roles and interactions of HOX genes.

Epigenetic factors in microtia

DNA Methylation, histone modifications and microRNAs

Recent discoveries have reshaped our understanding of the development of ear structures, particularly the external auditory canal (EAC). Contrary to previous beliefs, which suggested that mesenchyme from the first and second arches contributed equally, emerging insights reveal that the mouse pinna predominantly originates from neural crest-derived mesenchyme expressing HOXA2 from the second pharyngeal arch[12]. This realization has significant implications for our comprehension of ear development.

DNA methylation stands as a pivotal epigenetic mechanism, wielding substantial influence over gene expression by attaching methyl groups to genomic DNA. These modifications can be inherited across cell divisions, exerting lasting effects. Notably, anomalies in the methylation of the SOX4 gene disrupt normal development by interfering with essential signal transductions and gene transcriptions[13]. Interestingly, with its possible contributions in acute myeloid leukemia proven, research is also underway to explore the potential regulatory roles of HOXA4 in relation to DNA methylation and its impact on ear development[14,15]. The precise influence of HOXA4 methylation on ear morphogenesis remains an active area of study.

Histone modifications and microRNAs, meanwhile, play equally vital roles in gene expression fine-tuning. Histone modifications alter chromatin structure, impacting gene accessibility, while microRNAs orchestrate post-transcriptional regulation[16]. Some preliminary studies suggest that HOXA4 may be subject to histone modifications, leading to variable expressions that impact the intricate processes governing ear formation[17,18].

Environmental factors such as maternal smoking have been linked to deviations in DNA methylation patterns, thereby elevating the risk of microtia. Similarly, exposure to maternal diabetes during pregnancy or retinoic acid can induce epigenetic changes that disrupt the orderly progression of ear development[19]. These findings align with studies indicating that maternal smoking and harmful exposures contribute to epigenetic alterations, possibly including those in genes like HOXA4, which can influence microtia development[19,20].

Genetic factors in microtia

Incidence, classification and syndromic associations

Microtia's prevalence varies widely among populations, ranging from approximately 0.83 to 17.4 cases per 10,000 births[3]. This variability may be attributed to a combination of genetic predisposition and environmental influences. To facilitate clear communication and data exchange among medical professionals, two significant classification systems have emerged: the Weerda classification and the Hunter et al. classification[21-23]. These frameworks categorize microtia based on the degree of dysplasia, aiding in accurate diagnosis and treatment planning.

Microtia's association with syndromes adds another layer of complexity to its etiology. Notably, its linkage to syndromes like Oculoauriculovertebral spectrum (OAVS), also known as Goldenhar syndrome, emphasizes its syndromic nature[3,24,25]. OAVS is a multisystem disorder characterized by anomalies in the craniofacial region, vertebral column, and cardiovascular system[25]. Microtia often presents as a part of OAVS, highlighting the condition's multifaceted impact beyond the ear itself.

The etiology of microtia is far from straightforward, as it results from the complex interplay of genetic and environmental factors, alongside potential epigenetic alterations. As previously mentioned, the role of HOX genes, particularly HOXA1 and HOXA2, in ear development is profound. These genes are crucial in establishing the anterior-posterior axis during embryonic development and play a pivotal role in shaping craniofacial structures, including the external ear[10]. Mutations in HOXA1 and HOXA2 have been implicated in microtia-atresia, where the development of both the external ear and the ear canal is affected[26]. Other than the HOX genes; BAPX1, TCOF1, and EYA1 are among the genes implicated in syndromic microtia-atresia[27]. Mutations in these genes disrupt developmental pathways critical for the proper formation of the ear and surrounding structures. This intricate genetic tapestry highlights the multifactorial nature of microtia's etiology, where disruptions at different points along developmental pathways can culminate in similar phenotypic outcomes.

Inheritance patterns in microtia-atresia can be categorized into both autosomal dominant and recessive modes, reflecting the diverse genetic mechanisms that contribute to the condition's presentation[2]. This genetic complexity underscores the need for comprehensive genetic studies to fully unravel the molecular basis of microtia. By understanding the specific genetic alterations associated with different inheritance patterns, researchers can gain insights into the mechanisms driving microtia's heterogeneity and offer potential avenues for targeted interventions and therapies.

Genetic studies in humans and animal models

Genetic studies serve as critical compasses guiding our journey through microtia's intricate landscape of etiology. These studies offer valuable glimpses into the underlying genetic architecture that contributes to this congenital anomaly. One of the cornerstones of such research is pedigree analysis, which has successfully identified specific genes associated with microtia-atresia susceptibility[2]. This approach involves studying the inheritance patterns within families to identify genetic markers that might be linked to the condition.

Discordant monozygotic twins, with identical DNA sequences but varying physical traits, provide a unique lens to study the genetic underpinnings of microtia. By examining the disparities in their genomes, we can pinpoint the genetic variations that potentially influence ear and auditory canal formation. Furthermore, this method sheds light on how external elements like environmental factors, epigenetic changes, or random events work in tandem with genetics to establish the extent and nature of microtia.

In a recent investigation involving six families of monozygotic twins discordant for congenital microtia-atresia, whole-exome sequencing was performed for each twin and their parents[28]. The objective was to identify new mutations, copy number variations, and inherited variants responsible for the observed phenotypic discordance. This research identified several key genes that exhibited mutations or varied expression in the twins with the condition, implying their potential role in microtia-atresia. Notable genes include:

- **CNOT1** (CCR4-NOT Transcription Complex Subunit 1) related to mRNA stability and degradation. An exclusive mutation in this gene appeared in one affected twin.
- **ODAD4** (Outer Dynein Arm Docking Complex Subunit 4) associated with ciliary functionality and movement. Another unique mutation in this gene appeared in an affected twin.
- **TBX15** (T-Box Transcription Factor 15) linked with mesoderm growth and skeletal organization. An exclusive mutation in this gene was seen in another twin.
- **GIPC3** (GIPC PDZ Domain Containing Family Member 3) connected with the growth and functionality of auditory hair cells. A distinct mutation in this gene emerged in a different affected twin.

The study also utilizes whole-exome sequencing (WES), a powerful genetic technique that focuses on the protein-coding regions of the genome, has been instrumental in uncovering recurring mutations associated with microtia-atresia. WES analysis of discordant monozygotic twins has revealed intriguing findings, highlighting genes like HOXA4 and CHST15 that are potentially central to the condition's pathogenesis[28]. These findings underscore the genetic complexity of microtia and provide promising targets for further investigation.

Copy number variations (CNVs), which involve the deletion or duplication of larger segments of DNA, have also come under the spotlight in microtia research. Genes such as UGT2B17, OVOS, KATNAL2, FGFR1, and EYA1 are implicated in microtia-atresia due to CNVs[3,28,29]. The intriguing twist is that some of these genes are also associated with osteoporosis and steroid metabolism, hinting at broader connections between seemingly unrelated conditions.

The genetic web underlying microtia extends beyond individual genes and encompasses intricate networks that regulate development and morphogenesis. As we delve deeper into the genetic tapestry, a picture emerges of a condition shaped by the interactions of multiple genes, their variations, and the intricate machinery that orchestrates their expression. This mosaic of genetic complexity forms the bedrock upon which microtia's multifaceted etiology is built.

Genetic insights: HOXA4 and CHST15 in microtia development

HOXA4: A critical regulator of ear development

HOXA4, a homeobox protein belonging to the HOX gene family, emerges as a pivotal player in the intricate orchestration of ear development[30,31]. This gene holds a central role in the precise positioning of cells along the anterior-posterior axis during embryogenesis. Its influence extends far beyond the confines of ear morphogenesis, as it wields a multifaceted impact on various cellular processes.

At the heart of HOXA4's regulatory prowess lies its ability to bind to specific DNA sequences[31]. This binding, in turn, exerts a meticulous control over the expression patterns of genes that contribute to ear formation[15]. This precision-guided gene expression plays a vital role in sculpting the intricate structures that constitute the external ear. Moreover, the same mechanism reverberates across various developmental contexts, highlighting the gene's broader cellular influence.

The genetic anomalies in the HOXA4 gene have emerged as key players in the enigmatic landscape of microtia-atresia. Notably, a recurrent mutation (c.920A > C, p.H307P) shared among several affected families stands as a stark indication of its potential pathogenicity[28]. This mutation, through functional studies, has been shown to disrupt DNA binding in the crucial early stages of embryonic development[12,28]. As a result, the delicate process of auricle cartilage development is thrown off balance, leading to the characteristic phenotypic presentation of microtia.

The unraveling of the precise mechanisms through which HOXA4 mutations contribute to microtia-atresia presents a promising avenue for peering deeper into the genetic foundations of this condition. By dissecting the intricate details of how this mutation disrupts normal ear development, researchers are uncovering the molecular intricacies that underpin the formation of the external ear. This deeper understanding not only

enriches our comprehension of the genetic basis of microtia but also opens doors to potentially targeted therapeutic interventions that could alleviate the burden of this congenital anomaly. The exploration of HOXA4's role in microtia-atresia exemplifies the power of genetic insights in shedding light on the complexities of developmental disorders.

CHST15: bridging extracellular matrix and cartilage development

CHST15, the gene encoding carbohydrate sulfotransferase 15, emerges as a captivating contender in the intricate tapestry of microtia-atresia[32]. This gene orchestrates reactions that are pivotal for the synthesis of extracellular matrix (ECM) components, a critical player in the orchestration of tissue development and maintenance[28]. As an integral part of tissue homeostasis, the ECM acts as a scaffold that not only provides structural support but also serves as a dynamic platform for cellular interactions and signaling.

A noteworthy facet of CHST15's function lies in its involvement in the formation of rare E-disaccharide units. These units have been linked to processes like local fibrosis and tissue remodeling[32,33]. This highlights the gene's role in shaping the microenvironments within tissues, which in turn influences their structural integrity and functional properties. It's fascinating to note that the implications of CHST15 stretch far beyond the confines of craniofacial development. Mutations in this gene have been associated with the metastasis and invasion of certain cancers, underscoring its wide-reaching impact on diverse physiological processes[34,35].

Unraveling the genetic mutations within the CHST15 gene, particularly frameshift mutations, offers valuable insights into the complex web that drives microtia-atresia. These mutations have the potential to disrupt the gene's enzymatic activity, thereby compromising the formation of the extracellular matrix that is essential for proper cartilage development[28]. This disruption can have cascading effects, altering the microenvironment required for the precise organization of cells into functional tissues. The mechanistic link between CHST15 mutations and microtia-atresia's pathogenesis presents a new layer of understanding in our quest to decipher the condition's genetic underpinnings.

To solidify these findings and gain a more comprehensive view, further validation is crucial. This validation could entail leveraging advanced techniques, including functional assays and animal models. By recreating these genetic mutations and observing their impact on ear development, researchers can shed light on the precise role that CHST15 plays in the formation of the external ear. This endeavor holds the potential to not only enhance our understanding of microtia-atresia but also contribute to broader insights into tissue development, ECM dynamics, and potential therapeutic strategies for conditions influenced by similar genetic anomalies.

Epigenetic and genetic interplay: unveiling microtia's complex etiology

The journey to unravel the intricate etiology of microtia encompasses a delicate interplay between epigenetic and genetic factors. While genetic mutations provide a blueprint, epigenetic modifications act as the skilled craftsmen, shaping the final masterpiece of ear development. This dynamic interplay between genes and their epigenetic regulation orchestrates the symphony of molecular events that guide the formation of intricate ear structures[1,4,5].

Epigenetic alterations hold a special place in the microtia narrative. The impact of environmental cues, such as maternal smoking and retinoic acid exposure, can create ripples that extend far beyond the immediate developmental stages. These external influences disrupt the epigenetic landscape, leading to modifications in DNA methylation and histone structure[19,20]. Consequently, the precise choreography of gene expression is disrupted, potentially derailing the intricate process of ear development.

Interestingly, the interaction between epigenetics and genetics in microtia presents a two-way street. Genetic mutations, such as those found in the HOXA4 and CHST15 genes, contribute to microtia's complex tapestry by directly influencing developmental pathways[6,28]. Yet, these genetic alterations can also initiate a cascade of epigenetic changes. Aberrant genetic sequences can lead to shifts in epigenetic marks, initiating a feedback loop where genetics and epigenetics influence each other, sometimes in unpredictable ways.

Moreover, the concept of gene-environment interactions adds another layer of complexity. Epigenetic modifications act as mediators, allowing environmental factors to sculpt genetic expression[31,32]. The severity of microtia may be determined not just by a single genetic mutation, but by how that mutation interacts with the individual's unique epigenetic makeup and the external environment. This intricate dance of factors makes each case of microtia a mosaic of genetic predisposition, epigenetic responses, and environmental influences.

As researchers delve deeper into the mysteries of microtia, this interplay of genetics and epigenetics opens exciting avenues for therapeutic interventions[7,8]. Manipulating epigenetic marks to counteract the effects of genetic mutations could potentially guide ear development back onto its intended trajectory. Unlocking the intricacies of these mechanisms could pave the way for targeted therapies that address the root causes of microtia, offering new hope to affected individuals and their families.

In the grand tapestry of microtia's development, the relationship between genetics and epigenetics is a central thread that weaves together the complexities of this condition[35]. Understanding how these factors harmonize and sometimes clash provides profound insights into the delicate orchestration of ear formation. This understanding, in turn, holds the potential to reshape our diagnostic and therapeutic approaches, making strides towards mitigating the impact of microtia on individuals' lives.

Implications and future directions

Microtia's complex genetic and epigenetic landscape necessitates thorough exploration of both hereditary and somatic genetic variations. The elucidation of syndromic links and candidate genes, although significant, only represents a fraction of the intricate web that underpins microtia's development. As we

peer into the realm of epigenetic changes, induced by environmental exposures, a new layer of complexity emerges.

Larger studies involving monozygotic twins hold immense promise in unraveling the genetic and epigenetic intricacies governing microtia-atresia. By comparing the genetic and epigenetic profiles of twins discordant for microtia, researchers can tease out the contributions of genetics and environmental factors. Additionally, leveraging advanced techniques such as functional validation and animal models will further validate the findings and provide mechanistic insights into how specific genetic and epigenetic alterations lead to microtia development.

The intertwined nature of genetics and epigenetics mandates a holistic approach to understanding microtia's etiology. By piecing together the intricate puzzle of how genes, epigenetic modifications, and environmental factors intersect, we can pave the way for more precise diagnostic methods and targeted therapeutic strategies. Ultimately, the convergence of genetics and epigenetics in microtia research offers the potential to transform our understanding of developmental anomalies, with implications reaching far beyond this specific condition.

DISCUSSION

The etiology of microtia is characterized by a dynamic interplay of genetic and epigenetic factors. DNA methylation, a crucial epigenetic mechanism, plays a significant role in regulating gene expression, particularly in embryonic craniofacial development. This review emphasizes the foundational role of DNA methylation, especially in the methylation of the SOX4 and HOXA4 genes, in modulating essential signal transductions and gene transcriptions during crucial stages of morphogenesis[13,14,28].

Environmental factors, such as maternal smoking and exposure to retinoic acid, induce epigenetic alterations, including aberrant DNA methylation patterns, which elevate the risk of microtia. These environmental influences disrupt the orderly progression of ear development, suggesting a link between external exposures and epigenetic modifications impacting genes like HOXA4[19,20,25,31].

The role of noncoding RNAs in microtia, particularly microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), is pivotal in the regulatory processes governing gene expression. Histone modifications, alongside these noncoding RNAs, fine-tune gene expression, impacting the formation of ear structures. Preliminary studies indicate that HOXA4 may be subject to such histone modifications, influencing ear morphogenesis[16-18,24].

Advancements in genetic techniques, such as whole-exome sequencing (WES), have been instrumental in identifying recurrent mutations associated with microtia, particularly in genes like HOXA4 and CHST15. These genetic studies provide insights into the molecular basis of microtia and highlight the potential for targeted therapeutic interventions[27,28,34].

The complex interplay of genetics and epigenetics in microtia's etiology, encompassing everything from gene mutations and DNA methylation to the impact of environmental factors and the role of noncoding RNAs, underscores the multifaceted nature of this condition. This intricate web of factors calls for a multifaceted approach in understanding and managing microtia, potentially leading to more precise diagnostic tools and targeted treatments35.

CONCLUSION

In summary, the investigation of microtia underscores the nuanced interplay between genetics and epigenetics in moulding its intricate origins. Genetic mutations set the stage for developmental anomalies, with epigenetic alterations and environmental influences adding layers of complexity. This comprehensive understanding sheds light on the delicate balance between these factors, offering insights into both microtia and broader principles of developmental biology. Looking ahead, continued research into the genetic and epigenetic underpinnings of microtia promises to unveil novel therapeutic avenues and advance our comprehension of congenital anomalies, offering hope for improved diagnostics and interventions in the future.

CONFLICT OF INTEREST

None.

FUNDING

None.

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