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Review

# Molecular Mechanisms of Inner Ear Development and Disease

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The inner ear constitutes a complex organ responsible for auditory perception and equilibrium. It comprises diverse cellular entities operating collaboratively to perceive and transmit sensory information to the brain. Inner ear disease is a sophisticated and multifactorial scenario substantially impacting the quality of life of affected individuals. Gaining insights into the developmental process of the inner ear is crucial for diagnosing and treating inner ear diseases, which can lead to hearing loss and impaired balance. Recent research in inner ear development and associated pathophysiology has focused on several pivotal domains, including identifying new genes and signaling pathways involved in inner ear development, using stem cells for inner ear regeneration, and developing novel therapies for inner ear diseases. Recent advances in genetics research have shed new light on the fundamental etiologies of inner ear diseases, with a growing body of evidence suggesting that genetic mutations might exert a pivotal influence on the development and progression of this condition. In this review, we have delved into certain common genetic mutations linked to inner ear disorders. We also discussed ongoing research endeavors and future directions for understanding the genetic mechanisms underlying this condition and potential therapeutic avenues.

**Key Words:** Inner ear, Ear diseases, Mutation, Transcription factors

## INTRODUCTION

The inner ear develops during embryonic development from a small patch of the ectoderm termed the otic placode (Sai and Ladher, 2015; Andrew and Donna, 2012). The otic placode undergoes invagination, giving rise to an otic pit that ultimately detaches from the surface ectoderm, leading to the formation of an otocyst. Subsequent differentiation of the otocyst results in the emergence of three principal domains: the utricle and saccule, semicircular canals, and cochlea. The utricle and saccule recognize head positioning and linear acceleration, whereas the semicircular canals specialize in detecting rotational acceleration (Zine and Fritzsch, 2023; Basch et al., 2016). Within the cochlea, which is responsible for auditory function, specialized hair cells, responsive to sound waves and signal transmission to the brain, are situated (Driver and Kelley, 2020). The development of the inner ear is a complex process involving the expression of numerous genes and the interplay of multiple signaling pathways. Any disruption in this intricate sequence can lead to hearing and balance disorders.

### Genetic and molecular mechanisms of inner ear development

Several potential anomalies and malformations can arise

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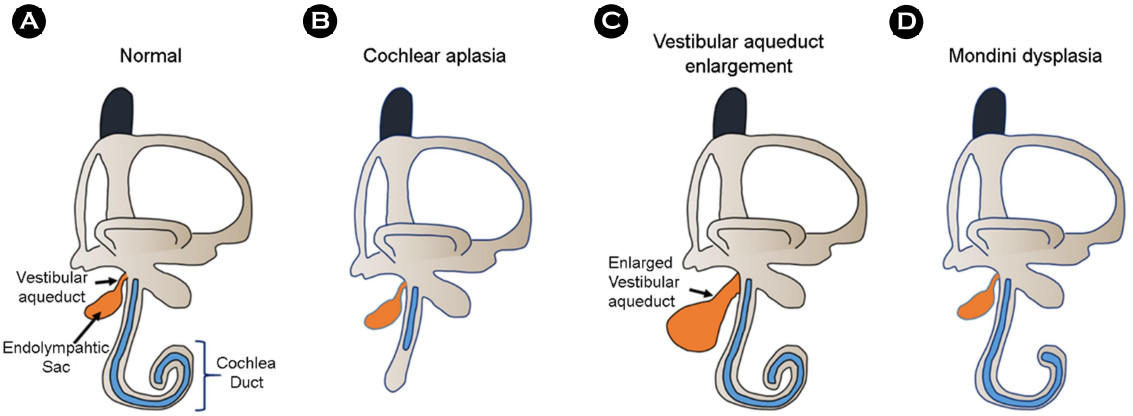


**Fig. 1. Major malformations and defects in the mammalian inner ear.** Schematic representation of normal cochlear formation (A), cochlear aplasia, as a result of an arrest in the development of the cochlear bud at early inner ear developmental stage (B), vestibular aqueduct enlargement (C), and Mondini dysplasia, as a result of incomplete partition of cochlea (D).

during inner ear development (Fig. 1). These include:

(1) Cochlear aplasia: Imperfect cochlear development culminating in hearing impairment.

(2) Vestibular aqueduct enlargement: An abnormal enlargement of the vestibular aqueduct, the bony canal linking the inner ear to the brain, which can cause hearing loss and impaired balance.

(3) Mondini dysplasia: Characterized by an underdeveloped and atypically shaped cochlea, Mondini dysplasia contributes to hearing loss and balance irregularities.

Recent research has been directed at comprehending the genetic and molecular architectures that govern the progression of inner ear development (Roberts et al., 2014; Schrauwen et al., 2020; Griffith and Wangemann, 2011; Joo et al., 2023). Studies have identified key genes and signaling pathways indispensable for the formation and differentiation of inner ear structures, including hair cells and supporting cells. Notably, investigators have delved into the roles of transcription factors, such as Atoh1, Gata3, and Sox2, in regulating cellular fate determinations throughout inner ear development (Driver and Kelley, 2020; Zhong et al., 2019; Moriguchi et al., 2018; Pan et al., 2013). Additionally, they have explored the functions of signaling molecules, such as Wnt and fibroblast growth factor (FGF), in orchestrating cellular proliferation and differentiation (Yang et al., 2013; Tambalo et al., 2020).

Atonal homolog 1 (Atoh1) represents a transcription factor crucial in the maturation of hair cells, the sensory receptors of the inner ear responsible for converting sound and motion into neural signals (Zhong et al., 2019). Atoh1 is vital for the differentiation of hair cells from their precursor counterparts, with its expression tightly controlled by several transcription factors, including Sox2, Gata3, and Neurog1 (Elliott et al., 2021). Notably, mutations in Atoh1 have been linked to hearing loss and balance disorders (Xie et al., 2017). Furthermore, Atoh1 emerges as a potential target for regenerative therapies aimed at restoring hair cell functionality in individuals with hearing loss (Baker et al., 2009).

GATA3 is expressed in the otic placode and is required for the formation of sensory hair and supporting cells (Fig. 2). Several signaling pathways are involved in the GATA3-mediated promotion of inner ear development (Luo et al., 2013; Duncan and Fritzsch, 2013). Among these pathways, the Notch signaling pathway assumes a prominent role, influencing cell fate determination and differentiation. GATA3 interacts with Notch signaling components, including Jagged-1 and Hes5, regulating the progression of hair and supporting cells (Gilels et al., 2022). GATA3 is also involved in the Wnt signaling pathway, which is essential for cell fate determination and differentiation. The interaction of GATA3 with Wnt signaling components, such as β-catenin, regulates the development of hair cells and supporting cells (Alvarado et al., 2009).

SOX proteins are a large family of transcription factors

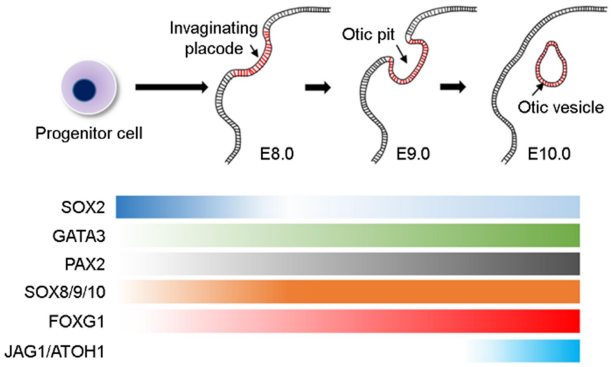


**Fig. 2. Sequentially expressed gene profile during otic vesicle induction.** Summary shown the expected order of marker gene expression based on studies of mammalian embryos.

with pivotal roles in embryogenesis, including inner ear development. SOX protein dysfunction has been implicated in diverse human disorders associated with inner ear development, including sensorineural hearing loss, vestibular dysfunction, and balance disorders (Szeto et al., 2022). Understanding the roles of SOX proteins in the progression of inner ear development could potentially herald novel therapeutic modalities. SOX2 is a key protein expressed in the nascent otic placode (Fig. 2). The loss of SOX2 results in defective inner ear development and hearing impairment in mice and humans (Steevens et al., 2017). Other SOX proteins, including SOX9 and SOX10, are also involved in inner ear development. SOX9 is expressed in the developing otic capsule enveloping the inner ear, and its absence results in defective otic capsule formation and subsequent hearing loss (Park and Saint-Jeannet, 2010; Szeto et al., 2022). SOX-10 is expressed in the neural crest cells that differentiate into sensory neurons within the inner ear; loss of SOX10 leads to defective development of these neurons and ensuing hearing loss (Wakaoka et al., 2013; Wen et al., 2021).

The Notch signaling pathway plays a crucial role in inner ear development. It is involved in the differentiation of hair cells and supporting cells, pivotal constituents for auditory function and balance (Murata et al., 2012). During inner ear development, the activation of the Notch pathway within the prosensory domain is consequential, catalyzing the genesis of hair cells and supporting cells, thereby culminating in the expression of genes that induce cell differentiation (Hartman et al., 2010).

Likewise, the FGF signaling pathway is also critical for inner ear development. Its involvement is implicated in the formation of the otic placode, which gives rise to the inner ear (Wright and Mansour, 2003). During inner ear development, the FGF signaling pathway regulates the expression of genes instrumental in otic placode formation. Additionally, this pathway substantially influences the development of hair cells and supporting cells (Tan et al., 2022).

**Transcriptional regulatory mechanism Related to inner ear development**

During inner ear development, a complex interplay of transcription factors and signaling pathways control the expression of genes regulating cell fate and differentiation. Among the central transcriptional regulators in this process is Pax2, which is critical for the development of the otic placode—a precursor to the inner ear (Burton et al., 2004). Pax2 is essential for the expression of additional transcription factors, including Sox9 and Gata3, which contribute to the differentiation of diverse cell types within the inner ear, including hair cells and supporting cells (Fig. 2, 3) (Christophorou et al., 2010). Furthermore, Pax2 is also involved in the regulation of pivotal signaling pathways such as Wnt and Fgf, which are crucial for cellular proliferation and differentiation (Tan et al., 2022).

Epigenetic factors, such as DNA methylation and histone modification, have demonstrated the capacity to govern gene expression during inner ear development. DNA methylation refers to the addition of methyl groups to DNA molecules, resulting in the suppression of gene expression. Concurrently, histone modifications such as acetylation and methylation regulate gene expression by modulating the accessibility of DNA to transcription factors (Balendran et al., 2022).

**Regulation of FoxG1 in otic vesicle development**

FoxG1 is a transcription factor that plays a crucial role in the development and function of otic vesicles—the precursors to the inner ear (Fig. 2, 3). FoxG1 expression is regulated by various mechanisms, including transcriptional, post-transcriptional, and epigenetic processes (Ding et al., 2020).

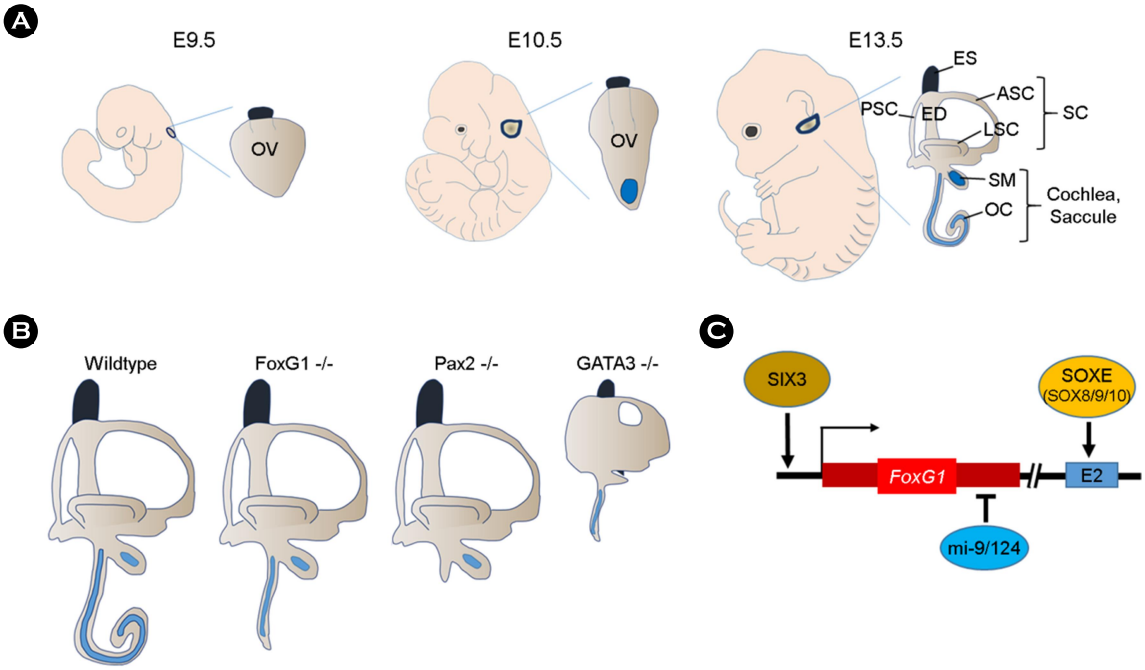


**Fig. 3. Schematic representation of the morphogenesis, the phenotypes, and the transcriptional regulatory mechanisms for FoxG1 expression of during mouse inner ear development.** (A) Morphogenesis of the mouse inner ear during early development. The labyrinth develops from a simple otic vesicle. Between embryonic day 10.5 (E10.5) and E13.5, the major structure of the inner ear develops its shape, whereas cell specification and differentiation continue for a longer time. OV, otic vesicle; ES, endolymphatic sac; ED, endolymphatic duct; ASC, anterior semicircular canal; PSC, posterior semicircular canal; LSC, lateral semicircular canal; SM, saccular macula; OC, organ of Corti; SC, semicircular canal. (B) Schematic representation of the phenotypes that result in gene knockout. In FoxG1-/-, a reduction in the size of the cochlear duct is shown. Lack of Pax2 leads to complete loss of the cochlear duct. Additionally, a reduction of the cochlear duct and abnormal morphology of the semicircular canal was observed in Gata3 knockout mice. (C) Cis-regulation of FoxG1 expression during otic vesicle development. Binding of SIX3 in the promoter region results in transcriptional activation of FoxG1, whereas the mir-9/124 represses FoxG1 expression by binding to 3'-UTR of FoxG1. The otic vesicle-specific expression of FoxG1 is regulated by SOXE (SOX8/9/10) via E2 enhancer.

The transcriptional regulation of FoxG1 predominantly ensues through the binding of various transcription factors to its promoter region. These transcription factors include Pas2, Six1, Gata3, and Sox2. The contextual nuances and developmental stage dictate whether these factors activate or repress FoxG1 expression (Kumamoto and Hanashima, 2017). SoxE subfamily transcription factors (Sox8, Sox9, and Sox10) reportedly induce the otic vesicle-specific expression of FoxG1 through interaction with non-coding DNA located approximately 30 kbp downstream from the ATG of FoxG1 (Fig. 3C) (Yang et al., 2022).

At the post-transcriptional level, FoxG1 expression is regulated by various mechanisms, including RNA stability and translation. For example, the RNA-binding protein HuR has been identified as a stabilizer of FoxG1 mRNA, leading to increased expression (Kraushar et al., 2014). Conversely, microRNAs such as miR-9 and miR-124 can bind to FoxG1 mRNA, inhibiting its translation and consequently dampening its expression (Fig. 3C) (Shibata et al., 2011).

Epigenetic mechanisms, including DNA methylation and histone modification, also play a role in regulating FoxG1 expression (Muthamilselvan et al., 2022). Notably, the promoter region of FoxG1 may undergo hypermethylation, which subsequently leads to diminished expression. Similarly, histone modifications such as acetylation and methylation can also affect FoxG1 expression by modulating the accessibility of its promoter region to transcription factors (Akol et al., 2023).

## Common genetic mutations associated with inner ear disease

Inner ear diseases encompass a spectrum of disorders

affecting the components of the inner ear, including the cochlea and vestibular system, with implications for hearing loss, balance disturbances, and allied symptoms (Rinkwitz et al., 2001). Amidst the array of causative factors for inner ear diseases, including infections, trauma, and exposure to high decibel levels, genetic mutations are also a common cause. Notably, mutations in genes, such as GJB2, MYO7A, and CDH23, have been identified as common causes of inner ear disease (Masindova et al., 2012; Toms et al., 2020; Dai et al., 2023).

One of the most common is the connexin 26 (GJB2) mutation, which can affect the function of the encoded protein. GJB2 is involved in the transmission of sound signaling in the inner ear, and GJB2 mutations are linked to an inherited form of deafness termed nonsyndromic hearing loss and deafness (DFNB1), which occurs without any other associated symptoms. MYO7A encodes myosin VIIA, which plays a pivotal role in inner ear development and function (Mammano, 2019). Notably, myosin VIIA is implicated in the formation and maintenance of stereocilia and hair-like structures in the sensory cells of the inner ear, which recognize sound and movement. Mutations in MYO7A can result in Usher syndrome, which is characterized by hearing loss and vision impairment. This syndrome affects approximately 1 in 10,000 individuals worldwide (Delmaghani and El-Amraoui, 2022).

CDH23 codes for cadherin-23, a protein localized in the sensory hair cells of the inner ear, which convert sound vibrations into electrical signals for neural processing (Yang et al., 2023). CDH23 has potential implications for gene therapy in inner ear disorders, such as Usher syndrome. This therapeutic strategy involves introducing a functional gene copy to replace a defective one, with CDH23 potentially enhancing sensory hair cell function, leading to improved hearing and balance. CDH23 also interacts with other proteins, including harmonin, myosin VIIA, and protocadherin 15, implicated in inner ear development. These interactions are likely crucial for the proper assembly and function of hair cell stereocilia (Castiglione and Möller, 2022).

An additional prevalent genetic mutation in inner ear disease is the mitochondrial 1555 A>G mutation, linked to deafness accompanied by balance issues (Kouzaki et al., 2007). Furthermore, mutations in TMC1 can lead to childhood-onset cases of both deafness and balance problems. TMC1 is crucial for the formation of stereocilia, which are structures vital for mechanical-to-electrical signal conversion (Asai et al., 2018). Dysfunctional TMC1 can result in defective stereocilia and subsequent hearing impairment. Additionally, TMC1 may regulate calcium ion levels in the inner ear, which is pivotal for hair cell function and homeostasis. Dysregulation owing to TMC1 mutations could contribute to hair cell degeneration and ensuing hearing loss (Smith et al., 2020).

## CONCLUSIONS

The implications of these genetic mutations on auditory function and overall health can vary depending on the specific mutation as well as auxiliary factors, including age and environmental exposures. Typically, mutations in genes involved in the developmental and maintenance processes of hair cells within the inner ear can cause a gradual deterioration of auditory function. This auditory decline may manifest progressively or suddenly, impacting one or both ears. Concurrently, balance perturbations, such as dizziness and vertigo, can manifest. Tinnitus, characterized by a sensation of ringing in the ears, might also be present. Further symptoms include ear pain, pressure, or a sensation of fullness, along with a feeling of disequilibrium or instability. In certain instances, patients might experience episodes of nausea or vomiting.

Comprehending the genetic and molecular mechanisms of inner ear development has crucial implications for the diagnosis and management of inner ear diseases. Mutations have been identified in several genes involved in inner ear development that are associated with hearing loss and equilibrium disorders. Additionally, disruptions in signaling pathways during inner ear development can lead to structural abnormalities and functional deficits within the inner ear. This knowledge lays the groundwork for the development of novel therapeutic modalities and interventions tailored to address inner ear diseases.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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