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Etiology and Genes

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Understanding the etiology of microtia/atresia of the external auditory canal (EAC) is indispensable for explaining the condition to patients and their family members, planning surgery, predicting complications and coping with them in time, and for genetic counseling. The etiology of microtia/atresia of the EAC is classified into hereditary factors that influence the development of the external ear and environmental factors. Given that the auricle and the EAC develop from the same origin, microtia and atresia of the EAC often coexist, with atresia of the EAC being observed in nearly 74% of patients with microtia [1, 2].

Elucidation of Etiology Based on Investigation of Syndromes

Great progress was made in understanding the etiology of microtia and atresia of the EAC through studies of patients with microtia and atresia of the EAC that are syndromic complications of other anomalies (e.g. facial cleft, cardiac anomaly, anophthalmia, microphthalmia, limb deficiencies, and kidney malformations are commonly observed). This is because patients with the same underlying cause are easily identified based on characteristics other than the external ear, which makes genetic analysis more simple.

Microtia and atresia of the EAC are observed in patients with chromosomal aberrations of four types of trisomy (13, 18, 21, 22 chromosomes) and three types of chromosomal deletions (5p-, 18p-, 18q-) [1].

Given that anomalies of the first and second branchial arches and hemifacial microsomia, or Goldenhar syndrome (which is accompanied by epibulbar dermoid), complicated by anomalies of the upper limbs and kidney, presents sporadic cases in monozygotic twins, it is argued to be induced by environmental factors or multifacto-

rial heredity rather than monogenic heredity [3]. Vascular injury due to injury of the stapedial artery at the embryonic stage is also a hypothesized cause. Mutation of the *SALL1* gene was identified in patients with Townes-Brocks syndrome, which is autosomal-dominant heredity accompanied by anomalies of the first and second branchial arches, kidneys, limbs and anus [4]. In addition, mutation of the *TCOF1* gene was identified in patients with Treacher-Collins syndrome, which is autosomal-dominant heredity presenting anomalies of the first and second branchial arches [5]. Bilateral microtia, severe hearing loss, and partial cleft palate were reported as autosomal-recessive heredity due to mutation of the *HOXA2* gene, a homeobox gene that plays an important role in fetal development [6]. Microtia, small teeth and severe hearing loss accompanied by a severe inner ear anomaly were also reported as autosomal-recessive heredity due to mutation of the *FGF3* gene [7]. In addition, various causative genes have been identified in syndromes accompanied by microtia and atresia of the EAC.

Risk Factors of Nonsyndromic Microtia and Atresia of the External Auditory Canal

It is considered that multifactorial heredity and environmental factors are strongly involved in the etiology of microtia and atresia of the EAC that develops without complication by other anomalies, but it is difficult to identify patient groups with the same etiology based on symptoms, so the cause has not been elucidated. Heredity is considered to be involved in some patients because 9–34% of the diseases are familial, and they might be multifactorial heredity, chromosome aberration, or recessive or dominant monogenic heredity [8, 9]. Reported risk factors of environmental origin include anemia, drug use during pregnancy (antiepileptic: trimethadione; follicular hormone: estriol; ovulatory agent: clomiphene citrate; vitamin A; etc.), paternal age, maternal diabetes, and pregnancy toxemia [2, 10, 11].

Development of the Ear

Development of the ear is a key area directly linked with the clinical pathology of microtia and atresia of the EAC. The ear is composed of three parts – the external ear, middle ear, and inner ear. Formation of these parts starts at an early stage of fetal development, and they are ultimately functionally integrated after their respective routes of development. Given that the external ear and middle ear develop from adjacent origins, concomitant anomalies of the external and middle ear are often observed. However, the inner ear develops from an origin distinct from that of the external and middle ear, and combined anomalies of the external, middle and inner ear are rare. In some patients who develop an inner ear anomaly in association with external and middle ear anomalies, the presence of genetic factors common to the external, middle,

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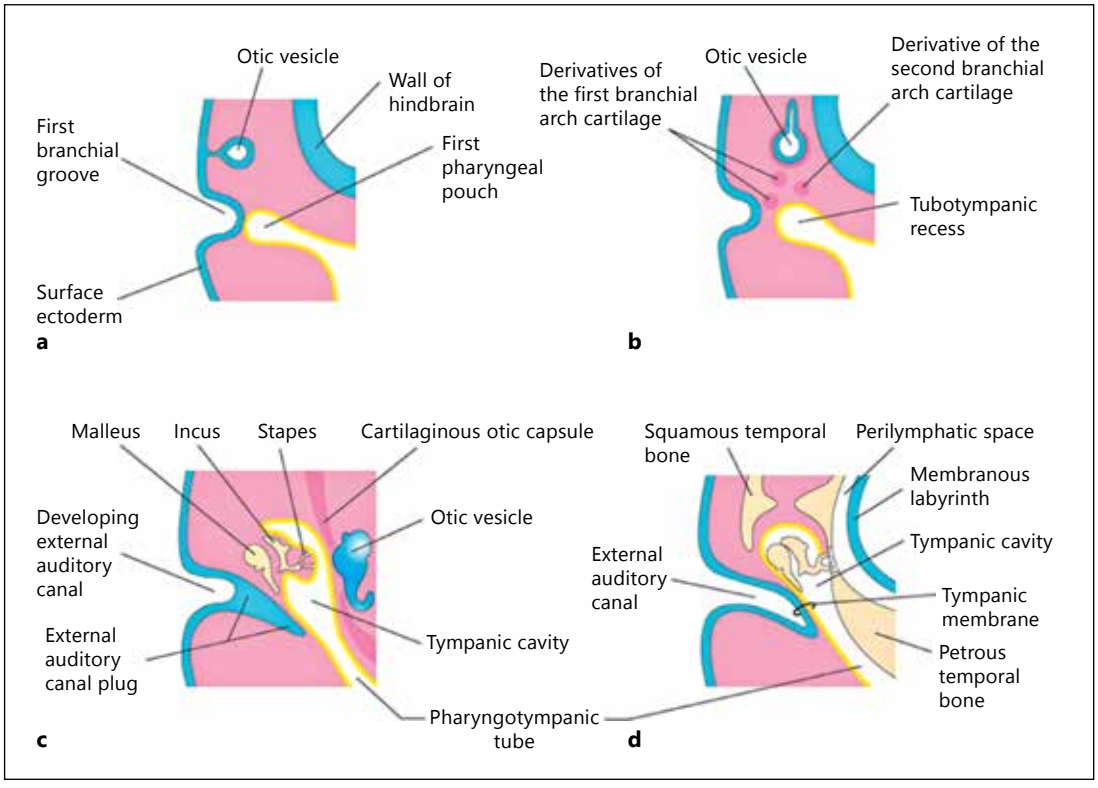

Fig. 1. Development of the external, middle, and inner ear. **a** Gestation week 4. **b** gestation week 5. **c** Gestation month 3. **d** Gestation month 7. Adapted from Moore et al. [23, p 444].

and inner ear or environmental factors that influence their development is presumed. We previously reported on a family with dominant heredity of an external/middle/inner ear anomaly, which suggested the presence of such heredity factors [12].

The inner ear is the oldest in terms of phylogeny. The membranous labyrinth of the inner ear is derived from otocyst of the ectoderm tissues, whereas the bony labyrinth is derived from the surrounding mesenchymal tissues (fig. 1). Involvement of the homeobox gene in the development of the inner ear has been demonstrated, and abnormalities in genes such as *Hox*, *Kreisler*, *Fgf3*, *Otx1*, *Nkx5–1*, *Hmx3*, *Pax2*, *Ngn1*, and *Dlx5* are known to cause abnormal morphogenesis of the inner ear [13, 14].

The middle ear develops mainly from the first and second branchial arches and the first pharyngeal pouch (fig. 1). Epithelial-mesenchymal interactions are required for development of the middle ear, and genes such as *ET-1* and *Fgf8* coordinate epithelial-mesenchymal interactions. *Eya1*, *Prx1*, *Hoxa1*, *Hoxa2*, *Dlx1*, *Dlx2*, *Dlx5,* and *Gsc* are involved in formation of mesenchymal tissues derived from the neural crest and play a key role in morphogenesis of the middle ear [15].

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