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ABSTRACT

Purpose

Microtia describes a spectrum of auricular malformations ranging from mild dysplasia to anotia. A vast majority of microtia patients demonstrate congenital aural atresia (CAA). Isolated microtia has a right ear predominance (58 – 61%) and is more common in the male sex. Isolated microtia is a multifactorial condition involving genetic and environmental causes. The aim of this study is to perform describe the phenotype of children with unilateral isolated microtia and CAA and to search for a common genetic cause trough DNA analysis.

Methods

Phenotyping included a complete clinical examination. Description on the degree of auricular malformation (Weerda classification – Weerda 1988), assessment for hemifacial microsomia and age-appropriate audiometric testing were documented. Computerized tomography of the temporal bone with 3-D rendering provided a histopathological classification (HEAR classification – Declau *et al.* 1999). Genetic testing was carried out by single nucleotide polymorphism (SNP) microarray.

Results

Complete data are available for 44 children (50% ≤ 33 days old at presentation; 59.1% boys; 72,7% right ear). Type III microtia was present in 28 patients. Type 2b CAA existed in 32 patients. All patients had a normal hearing at the non-affected side. Genome wide deletion duplication analysis using microarray did not reveal any pathological copy number variant (CNV) that could explain the phenotype.

Conclusion

Type III microtia (peanut-shell type) in combination with a type 2b CAA was the most common phenotype, present in 23 of 44 (52.3%) patients with isolated unilateral microtia. No abnormalities could be found by copy number variant (CNV) analysis. Whole exome sequencing in a larger sample with a similar phenotype will be future diagnostic approach.

HIGHLIGHTS

- Type III microtia (peanut-shell type) of the auricle and type 2b CAA were the most common occurring phenotype of unilateral isolated microtia.
- Crosstabulation of the Weerda and HEAR classification suggests an association between the classification of the visible auricular deformities (Weerda) and the anatomical status (HEAR).
- Genome wide microarray analysis did not reveal any pathological copy number variant (CNV) that could explain the phenotype.

KEYWORDS

Microtia, phenotype, genotype, children, hearing loss, congenital aural atresia

1. Introduction

1.1 General background (microtia, congenital aural atresia, prevalence and causes)

Microtia (*OMIM 600674, OMIM 251800*) is a congenital anomaly of the auricle, characterized by a small, abnormally shaped ear lobe. It ranges in severity from mild structural abnormalities to complete absence of the auricle (this condition is called anotia). It can occur as an isolated abnormality, as part of a spectrum or as a syndrome. More than 80% of patients with microtia have a congenital stenosis or atresia of the external auditory canal (congenital aural atresia (CAA); *OMIM 607842*). In most cases, the grade of malformation of the auricle and the severity of the middle ear dysplasia are related. Conductive hearing loss is present in 80 – 90% of patients [1].

According to a global review of prevalence rates by Luquetti *et al.,* the overall prevalence of the microtia – anotia complex is 2,06 per 10.000 births (CI 2,02 – 2,10) [2]. An overall prevalence of microtia is 1,55 per 10.000 births (CI 1,50 – 1,60). The study of Luquetti *et al.* used data from EUROCAT, a European birth defect surveillance program, which reported a microtia – anotia complex prevalence of 0,39 per 10.000 births (CI 0,19 – 0,72) in Antwerp, Belgium during the period 1990 - 2007 [2].

Although microtia and/or CAA may be part of a syndrome or associated with other malformations, the majority (70%) present as an isolated condition. A variable combination of genetic and environmental factors (related to insults during pregnancy) is thought to be involved in the development of isolated microtia.

1.2 The characteristic phenotype

Previous research reports that malformations of the outer and the middle ear show right ear predominance (58 – 61%) and the majority of malformations (70 – 90%) are unilateral [3].

In Europe, there have been a few reports on the characteristics of microtia patient populations. A study by van Nunen *et al.* in 2014 on microtia in the Netherlands revealed that microtia was commonly associated with CAA (76,0% of patients). In their study group of 204 patients, microtia (with or without CAA) was present in 54,9% of patients as an isolated condition [4].

A significant subgroup of patients with microtia (40% in the study of Keogh *et al.*) presents with hemifacial microsomia. Microtia could be an early marker of asymmetrical facial growth [5]. Most common associated anomalies are vertebral defects, oral clefts, facial asymmetry, renal abnormalities, cardiac defects, microphthalmia, holoprosencephaly and polydactyly [6].

1.3 Genetics

Although environmental factors are likely to play an important role in the pathogenesis of microtia/CAA, genetic causes are also involved. Autosomal dominant and autosomal recessive inheritance patterns have been described in familial cases [7, 8]. Furthermore, chromosomal abnormalities, such as trisomy 13, 18 and 22, as well as complex chromosomal rearrangements, microdeletions and distinct hereditary genomic copy number variants (CNV) have been described [9].

Disruption of teashirt zinc finger homeobox 1 (*TSZH1*, chromosome 18q22) is associated with CAA [10]. Terminal deletions starting at chromosome 18q23, are associated with CAA in 66% of cases. In a study by Veltman *et al.* a critical region of 5 Mb (18q22.3 – q23) was deleted in all patients [11].
In addition, the *HOXA1* and *HOXA2* homeobox genes have been associated with microtia/CAA and with inner ear malformations in family studies. Furthermore, several other genes have been linked to microtia/CAA, including *PRKRA*, *PACT*, *GSC* and *SIX2,* but these genes only account for a minority of patients [12].

Isolated microtia may be the mildest form of the Oculo-auriculo-vertebral spectrum (OAVS). The spectrum ranges from unilateral isolated microtia to the complete picture of Goldenhar syndrome, with hemifacial microsomia as the intermediate form. In this spectrum malformations of the eyes, ears and spine are involved, and sometimes other congenital anomalies are present, for example of the heart or kidneys. The picture shows a great variability and range in severity.

Hemifacial microsomia tends to affect only the right side of the face, with underdevelopment of the jaw and/or eye on the affected side. The external ear may be smaller (microtia) or even absent (anotia), and hearing loss may occur. Intelligence is unaffected.

Most cases of OAVS appear to occur sporadically, however some familial cases are reported in literature. No specific chromosomal rearrangements have been identified, although the 4p16.1 and Xp22.33 regions and recurrent 22q11.21 microdeletion may be relevant for OAVS etiology [13]. Presumably most cases of the disorder are caused by the interaction of many genes in combination with environmental factors (multifactorial inheritance).

1.4 What remains to be investigated

Evaluation by a clinical geneticist, genetic testing and subsequent genetic counseling are advocated to exclude possible associated anomalies and syndromal causes and to delineate the inheritance pattern. The results of genetic testing may be used to predict the recurrence risk. However, if no genetic cause can be identified the estimated recurrence risk for isolated microtia/CAA is 2%.

Unfortunately, genetic counseling for parents of unilateral microtia/CAA patients is hampered by the lack of a genetic test with high clinical sensitivity or other tests allowing to pinpoint the cause of the phenotype. We are unaware of any previous studies which systematically used CNV analysis by micro-array in children with unilateral isolated microtia/CAA. Because this analysis can be easily implemented in routine clinical practice, this choosen as a first step genetic screening.

Luquetti *et al.* emphasized a wide phenotypic variability in microtia/CAA cases and underscored the need for a detailed description of the malformation as a prerequisite to the discovery of causative genes [14]. A detailed description of the most common phenotype by the Weerda classification for microtia and by the HEAR classification for CAA is valuable. Until recently, few studies have focused on the genetic causes of isolated non-syndromal microtia and most research has been devoted to syndromal cases or patients with bilateral microtia/CAA [9, 2]. It remains to be investigated whether certain chromosomal abnormalities are associated with the most common phenotypes of isolated unilateral non-syndromal microtia/CAA.

1.5 The aim of the study

The aim of this study was to perform a descriptive analysis on phenotype and genotype of patients with isolated unilateral microtia/CAA. Sub-phenotyping of isolated unilateral microtia/CAA cases as performed in the present study may allow for the identification of new genes involved in microtia/CAA.

2. Methods

2.1 Patients and ethics

All patients with microtia/CAA are seen at a multidisciplinary otogenetics clinic and since 2017 at a multidisciplinary microtia clinic. A protocol for collection of phenotype/genotype data and subsequent analysis was approved by the Ethical Review Board (ref. B300201214490).
A retrospective chart review was performed for all patients that were diagnosed with microtia/CAA, referred to the Antwerp University Hospital over the period 2001 – 2020. Children with bilateral microtia/CAA and syndromal cases were excluded. Patients with incomplete phenotypic data or a lack of genetic data were excluded for analysis.

2.2 Protocol for the diagnostic approach to microtia/CAA

In the multidisciplinary microtia clinic of the Antwerp University Hospital, the first step in the approach of microtia is a complete phenotyping including a complete examination of the ear and face, a clinical examination looking for associated anomalies or syndromic features.
Phenotypic features were documented by digital photography. The degree of microtia was classified as described by Weerda (Table 1) [15]. Associated clinical signs, syndromic features, and signs of hemifacial microsomia were documented.

Weerda class	Clinical features
I	All anatomical subunits of the pinna are present, although abnormally formed
II	Recognizable subunits, although rudimentary and malformed
III	The peanut ear
IV	No structures recognized

Table 1. The Weerda classification of auricular malformations with phenotype description

Each patient undergoes an age-appropriate audiometric work-up with assessment of air and bone conduction thresholds in the affected ear. For newborns and infants, hearing status is documented by Auditory Brainstem Evoked Responses (ABR) with air and bone conduction thresholds, tympanometry and click-evoked otoacoustic emissions (OAE). Pure tone thresholds are obtained as soon as the child is able to participate in behavioral or play audiometry. In younger children, the mean hearing threshold is calculated for 500 – 1000 – 4000 Hz (3PTA) and reported in decibel (dBHL). For older and cooperative children, a pure tone average across 4 frequencies (500 – 1000 – 2000 – 4000Hz; 4PTA) is calculated.

Imaging (high resolution computerized tomography of the temporal bone with 3D rendering) is performed around the age of 1 year. Children presenting for the first time at our clinic at a later age are scheduled for imaging without delay. This exam provides information on the extent and type of the atretic plate, the status of the middle ear, the ossicular and inner ear development, the position of the facial nerve and the pneumatisation of the middle ear and mastoid cavity and therefor allows for classification of the middle and inner ear deformities. Postprocessing of the images with 3-dimensional rendering was performed to apply the HEAR classification. The HEAR classification represents an anatomical classification and was used to classify CAA [16]. A detailed description of the HEAR classification is presented in Table 2.

Type 1: tympanic membrane is present but smaller than normal, various kinds of ossicular malformations may be present
Type 2: an atretic plate is present, the tympanic bone may be hypoplastic or absent, the tympanic cavity is within normal limits
Type 2a: tympanic bone is hypoplastic, the course of the facial nerve is normal in his 3rd segment
Type 2b: tympanic bone is absent, abnormal course (more anteriorly) of the facial nerve in his 3rd segment
Type 3: severely hypoplastic tympanic cavity, no external ear canal

Table 2. The HEAR CAA classification

A blood sample is taken from the patient and from both parents. CNV analysis by micro-array is performed to exclude chromosomal CNVs. Genome-wide CNV data are generated using HumanCytoSNP-12v2.1 beadchip single nucleotide polymorphism (SNP) arrays, according to manufacturer instructions (Illumina, San Diego, CA). CNV analysis was performed with CNV-WebStore using human genome build hg19 [17].

2.3 Statistical analysis

Demographic data is reported to describe the phenotype. Statistical analysis is performed with SPSS version 27.0 and significance accepted at $p < 0,05$. Due to the lower number of study subjects, non-parametric testing is always used. Association analysis between the Weerda classification and the HEAR CAA classification is performed by the Fisher-Freeman-Halton Exact Test. The independent-Samples Mann-Whitney U test is used to assess the difference between hearing levels in right- and left-sided microtia. Independent-Samples Kruskal-Wallis test is performed to check the distribution of 3PTA and 4PTA across the different Weerda and HEAR CAA categories.

3. Results

3.1 Inclusion flowchart

During the study period, 64 children were admitted. Seven cases were excluded because of bilateral microtia, 3 were excluded because they presented with a unilateral microtia as part of a syndrome. Incomplete data were the reason for exclusion in another 10 patients. The patient flow is illustrated in Figure 1. A vast majority of the children (84,1%) was admitted before their first birthday. Almost half of the children (44,4%) visited the multidisciplinary clinic before or at the age of 1 month.

Insert Figure 1 here

3.2 Characteristics of the study population

Most children were referred by a pediatrician (34,1 %) or an otorhinolaryngologist (38,6 %). Only three children were referred by their general practitioner, one child at 18 days old and the other children only at six and eight years old. One child was referred by an oral- and maxillofacial surgeon. Two children requested a second opinion at the multidisciplinary microtia clinic. The referral status of six children remained unknown. About two thirds of the study population (61,4%) had a Caucasian ethnicity. Seven children in the study population had North-African ethnicity, accounting for 15,9% of the study population. Five children (11,4%) were of Middle Eastern descent. Twenty-six out of 44 patients were male, representative of 59,1% of the population. Thirty-two children had right ear involvement (72,7%).

3.3 The Weerda classification

The results of the Weerda classification are displayed in Table 3. All children presented with microtia *and* CAA. Weerda type III (peanut-shell deformity) was most prevalent in the study population (63,6%).

	Right-sided microtia *(number of patients)*	**Left-sided microtia** *(number of patients)*	**Overall study population** *(number of patients)*	**Overall study population** *(percentage; %)*
I	8	4	12	27,3
II	3	1	4	9,1
III	21	7	28	63,6
Total	32	12	44	100,0

Table 3. The distribution of the Weerda classification of microtia reported in the overall study population and in the study subjects with right- and left-sided microtia separately.

3.4 The HEAR classification.

3.4.1 Distribution across the study patients

An overview of the HEAR classification applied to the computerized tomography data of the study patients is presented in Table 4. All patients had microtia and CAA. Type 2b is the most common type of CAA encountered in the study population.

	Right temporal bone		**Left temporal bone**		**Overall study population**	
	N	Percentage in population with right ear microtia (%)	N	Percentage in population with left ear microtia (%)	N	Percentage in the study population (%)
Type 1	5	15,6	3	25,0	8	18,2
Type 2a	2	6.3	0	0	2	4,5
Type 2b	24	75,0	8	66,7	32	72,7
Type 3	1	3,1	1	8,3	2	4,5
Total	32	100,0	12	100,0	44	100,0

Table 4. Distribution of the HEAR classification of CAA in the affected ear and in the overall study population

3.4.2 Association between WEERDA classification and HEAR classification

Twenty-three children presented with Weerda type III and type 2b HEAR classification. This represents the most common phenotype in this population of isolated unilateral microtia. A typical example of this phenotype is presented in Figure 2A and Figure 2B.

Insert Figure 2A and 2B here

A significant association between the Weerda and the HEAR CAA classification was found. The value of the Fisher-Freeman-Halton Exact Test was 11,628 and the corresponding p-value of the test statistic was p = 0,026 *(< 0,05)*. This indicates a more severe malformation of the outer ear is associated with a more serious CAA. A graphic display of the association between Weerda and HEAR CAA classification is presented in Figure 3.

Insert Figure 3 here.

3.5 Hearing levels

Hearing levels were assessed by ABR and tonal audiometry according to age at assessment. Average air conduction levels reported by 3PTA are shown in Table 5. Hearing of the unaffected ear was normal in all patients.

Average air conduction levels reported by 3PTA could be determined for 17 patients and when reported by 4PTA for 11 patients. Median 3PTA of the affected ears was 60,00 dBHL (20,00 – 76,70 dBHL). Median 4PTA of the affected ears was 68,00 dBHL (43,00 – 79,00 dBHL).

3PTA in the affected ear was significantly higher in patients with left-sided microtia compared to right-sided microtia (U = 7,0; p = 0,032). 4PTA levels also showed to be significantly higher in patients with left-sided microtia (U = 2,5; p = 0,048).

	Right-sided microtia		**Left-sided microtia**	
	Right ear (n=13)	Left ear (n=22)	Right ear (n=10)	Left ear (n=4)
Median	58,30	15,00	18,35	68,35
Minimum	20,00	0,90	13,30	66,70
Maximum	73,30	30,00	31,70	76,70

Table 5. Air conduction thresholds in both ears (dBHL) reported by 3PTA (pure tone average; 500 – 1000 – 4000 Hz)

There was no statistically significant difference in 3PTA and 4PTA across different Weerda types (respectively p = 0,123; p = 0,359). Furthermore, the distribution of 3PTA and 4PTA showed no significant difference among HEAR CAA categories (respectively p = 0,788; p = 0,905). Thus it was not proven that the degree of hearing loss is related to the degree of outer ear malformation nor to the severity of CAA.

3.6 Genetic testing

The CNV analysis employed in this study, did not reveal any potential pathogenic CNV in 28 patients (63,3 % of tested children). In 16 patients, certain deletions and duplications were found (Table 6). Only class III CNV of unknown significance (UV) were detected. One female patient presented a duplication in the *GJB1* gene on the X chromosome that could not be detected in one of her parents.
The clinical significance of the above findings is unclear. In all patients with available data from parents, paternal or maternal inheritance of the deletion/duplication was proven. No recurrent CNVs were found.

DNA	Paternal DNA	Maternal DNA
dup1p36.33 and delXq13.1 (*GJB1* gene) = de novo	-	-
dup10q26.3	+ (dup10q26.3)	-
del1p31.1	?	-
del5q23.2 en dup17p13.1	+ (del5q)	+ (dup17p)
del6q26	?	?
dup2p22.3	-	+
dupXp22.33	?	?
dup8p23.2-p23. and dup 15q21.2	+ (dup15q21.3)	+ (dup8p23.2-p23.1)
dup2p22.3, del3p26.3, dup16q24.3		+ (dup2p22.3, del3p26.3, dup16q24.3)
dup7p14.3	+	-
del4q21.12 and dup7p21.3	+ (dup7p)	+ (del4q)
dup8q21.2	-	+
dup1q25.3 (*ACBD6* gene)	-	+ (dup1q25.3)
del2p22.3	?	-
dup2p25.2, dup11q22.3, dup22q13.32	+ (dup2p25.2, dup11q22.3)	+ (dup22q13.32)
del7p21.3	+ (del7p21.3)	-

Table 6. Genetic variants (UV) in the study population

UV = unclassified variant; + = inheritance; - = no inheritance; ? = no available data

4. Discussion

To our best knowledge, this is the first study which provides a complete phenotypical description of a population with microtia by the Weerda as well as the HEAR classification system and the first to correlate phenotypical findings with hearing status and genetic analysis.

A phenotypical analysis of children with isolated unilateral microtia was performed and Weerda type III was most prevalent in the study population (63,6%). The peanut-shell malformation is a common presentation of microtia in the patient population of the Antwerp University Hospital (65,6% of the right ear malformations, 58,3 % of the left ear malformations). Type III microtia (peanut-shell deformity) combined with a type 2b CAA represents the common phenotype, present in 23 out of 44 patients (52,3%). Genotyping with SNP microarray did not reveal a pathogenic CNV associated with this phenotype.

Secondary findings are in line with previous reports: a male and right ear preponderance and an association between the degree of outer ear malformation and CAA was reported [3, 1]. New insights showed that left-sided microtia was associated with more severe conductive hearing loss than right-sided microtia.

An anatomical classification according to the severity of aural atresia was first described by Altmann in 1995. This author divided his cases into three categories: mildly, moderately and severely malformed. In mild cases (type I), the tympanic membrane is present but hypoplastic. In moderate cases of type 2 atresia an atretic plate is present but the tympanic bone is hypoplastic or absent. Declau *et al.* proposed a further anatomical subdivision of type 2 CAA in correlation with the surgical and functional outcome (Table 2). Type 2a has a normal course of the facial nerve in its third segment. Type 2b has a more anteriorly situated course of the third segment of the facial nerve. In type 3 CAA, the above-mentioned abnormalities can be found together with a severely hypoplastic tympanic cavity [16].

A CT scan of the temporal bone may be obtained for classification purposes, to exclude associated anomalies such as inner ear malformation, to plan reconstruction purposes and to rule out a congenital cholesteatoma [18]. In the present study, CT scanning was done to exclude associated anomalies and for classification purposes. None of the scans was performed under general anesthesia. There are no standard rules regarding the most appropriate age to obtain imaging studies in children with microtia. The team prefers to obtain the imaging by the age of 1 year. At this time, the patients are seen by the multidisciplinary team to discuss the results of the genetic testing, to discuss various possibilities of outer ear reconstruction and to discuss the possibilities for hearing rehabilitation. As such, parents will have a view on the complete trajectory and timing of any interventions when applicable. In cases of type 2b or type 3 CAA, canaloplasty and middle ear reconstruction is associated with a significant risk of injury to the facial nerve (because of its abnormal course) and should be discouraged.

The risk of X-ray exposure at a young age should be balanced against the benefit of this approach. However, considering that low dose CT scans are the standard of care nowadays, we believe that our approach allows for shared decision making and timely organization of the clinical care for the patient during childhood. In cases where a stenotic outer ear canal was documented on CT, regular follow-up by magnetic resonance imaging is recommended to exclude the development of cholesteatoma.

Crosstabulation of the Weerda and HEAR classification suggests an association between the severity of the visible auricular deformities (Weerda) and the anatomical status (HEAR) documented by imaging. Weerda type III combined with type 2b HEAR classification was the most common presentation of isolated unilateral microtia in this study population. This might suggest the co-occurrence of type III Weerda and type 2b HEAR malformations.

Hearing status was normal in the unaffected ears and bone conduction was unaffected in all ears, as has already been demonstrated [19, 1]. In accordance with previous research, there was no significant difference in air conduction across the Weerda and the HEAR classification [20]. Pure tone average of the affected ear was significantly higher in left-sided microtia than in right-sided microtia. However, careful interpretation of 4PTA is necessary, due to the small number of study subjects (n = 11), however a larger population could be tested for 3PTA (n = 17). Presumably, a difference in hearing levels across left- and right-sided microtia and CAA has never been described. A study by Jensen *et al.* showed that children with unilateral CAA had a higher risk of poor speech development and language difficulties, comparable to children with unilateral sensorineural hearing loss [21].

The hypothesis that a significant genetic contribution in the development of microtia is present, emerged from previous twin studies reporting a higher concordance in monozygotic twins and from familial cases with autosomal dominant or recessive inheritance patterns [22, 23]. Gene-inactivation experiments in vitro have identified possible involved genes and signaling molecules, such as endothelin 1 and fibroblast growth factor 8. Other proteins possibly involved are: *EYA1, PRX1, TSZH1, HOXA1, HOXA2, DLX1, DLX2, DLX5* and *GSC*. Estimates on the percentage of familial cases vary widely, from 3 to 34% [12, 24, 9]. It was postulated that sub-phenotyping of isolated unilateral microtia cases would allow for the identification of new genes involved in microtia/CAA.

At the time we started this study, some chromosomal alterations had been found in cases of bilateral microtia/CAA [9, 11]. Therefore, Single Nucleotide Polymorphism (SNP) array was performed on all patients as this is the standard technique for detection of copy number variations (such as chromosomal deletions and duplications). Although we found chromosomal abnormalities in some patients, SNP microarray did not reveal any potential pathological copy number variant (CNV) that was associated with a specific microtia/CAA phenotype. These findings may be, at least partially, related to the limitations of genome wide SNP array [25] which may not detect very small deletions/duplications, balanced rearrangements or small/single nucleotide variants. Recent studies using whole exome sequencing (WES) in cases of isolated microtia yielded promising results [24, 26]. During WES, the

entire exome is analyzed to investigate for variants in the coding part of the human genome (the exomes) that could explain the development of CAA/microtia. Data obtained by WES in discordant monozygotic twins with a consistent clinical phenotype (unilateral type 3 microtia and CAA) revealed *HOXA4* as a likely pathogenetic variant for microtia-atresia [26]. Soon, we aim to perform WES in a large group of microtia/CAA patients with a similar phenotype. We expect a higher chance to reveal a genetic alteration that cannot be detected by SNP array. However, most case of microtia have a multifactorial origin or are most likely a polygenic disorder and more than one gene may be involved in the development of this condition [27].

Our study is limited by its retrospective nature. Consequently, a complete data set was available for only 44 cases. The limitations inherent to micro-array have been discussed in the previous paragraphs. Data collection is continuing in all newly referred patients, and we plan to perform WES in the very near future on a larger patient sample.

5. Conclusion

This study confirms the feasibility of a phenotypic description based upon the Weerda and HEAR classification of patients with isolated unilateral microtia. SNP array could not identify a specific genotype responsible for this phenotype. The approach of this study, however, paves the way for future studies based upon next generation sequencing technology in a large group of patients with a similar phenotype. Ultimately, this approach may elucidate genetic factors associated with isolated unilateral microtia/CAA.

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FIGURES

Figure 1. Inclusion flowchart

Figure 2A and B. These pictures illustrate the most common phenotype in our study of isolated unilateral microtia/CAA. Figure 2A is a clinical picture of an infant with a peanut-shell ear malformation. Figure 2B is a computerized tomography image in the coronal plane of a right ear. It presents a typical type 2b HEAR CAA with an absent tympanic bone and fusion of a dysplastic malleus with the atretic plate.

Figure 3. Graphic distribution of HEAR type according to Weerda classification in patients with unilateral, non-syndromal microtia/CAA (n = 44)

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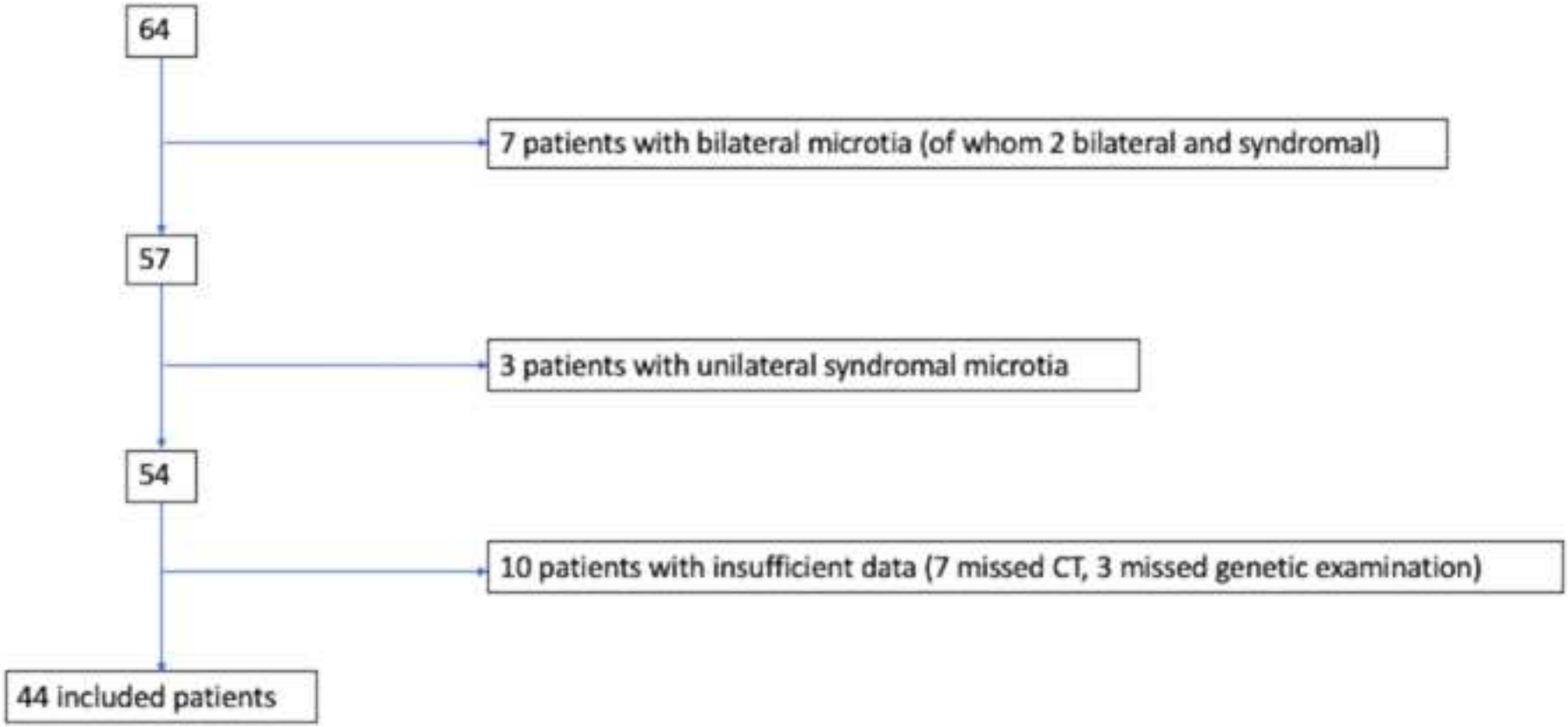
Figure



Figure

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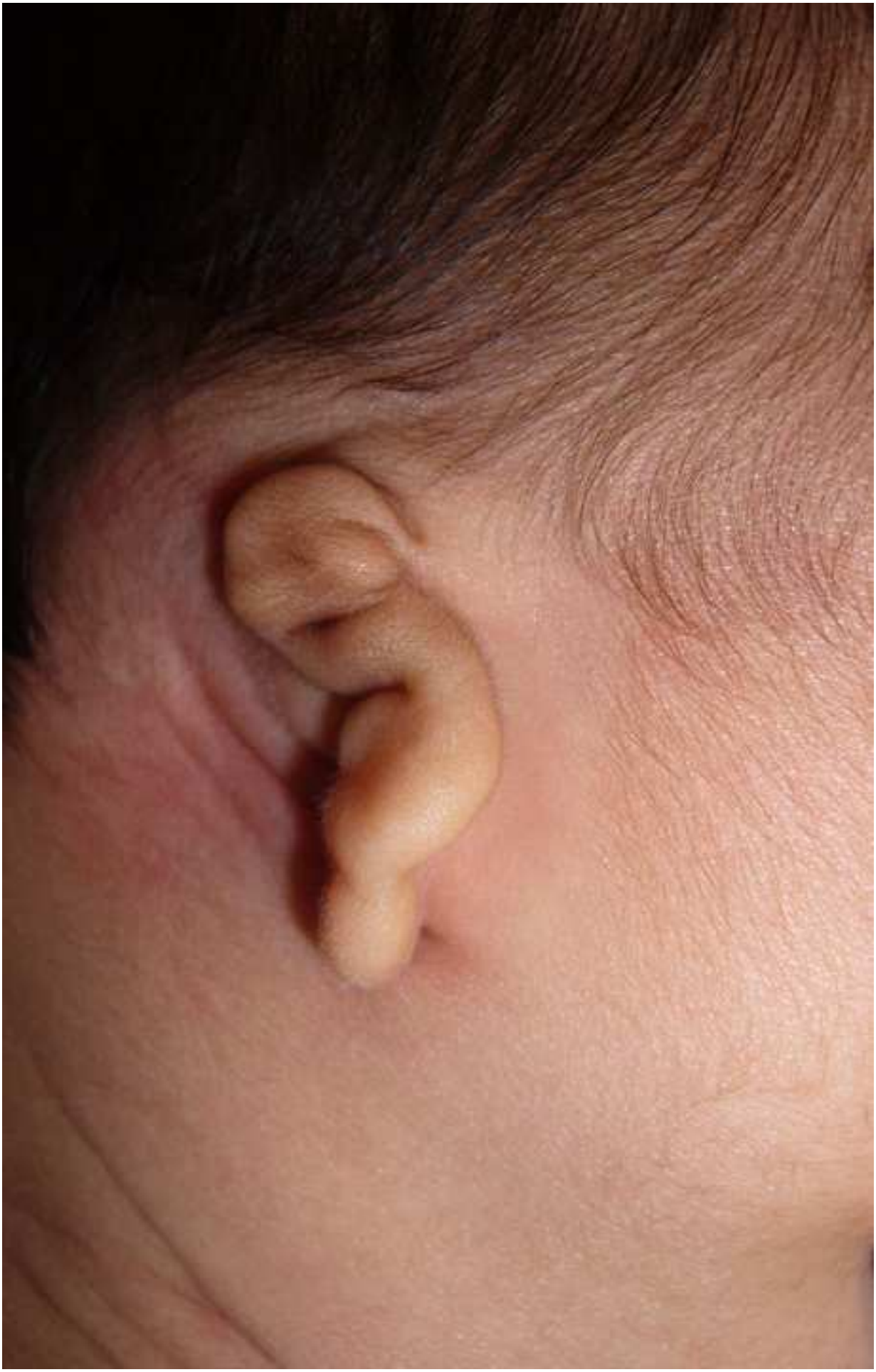

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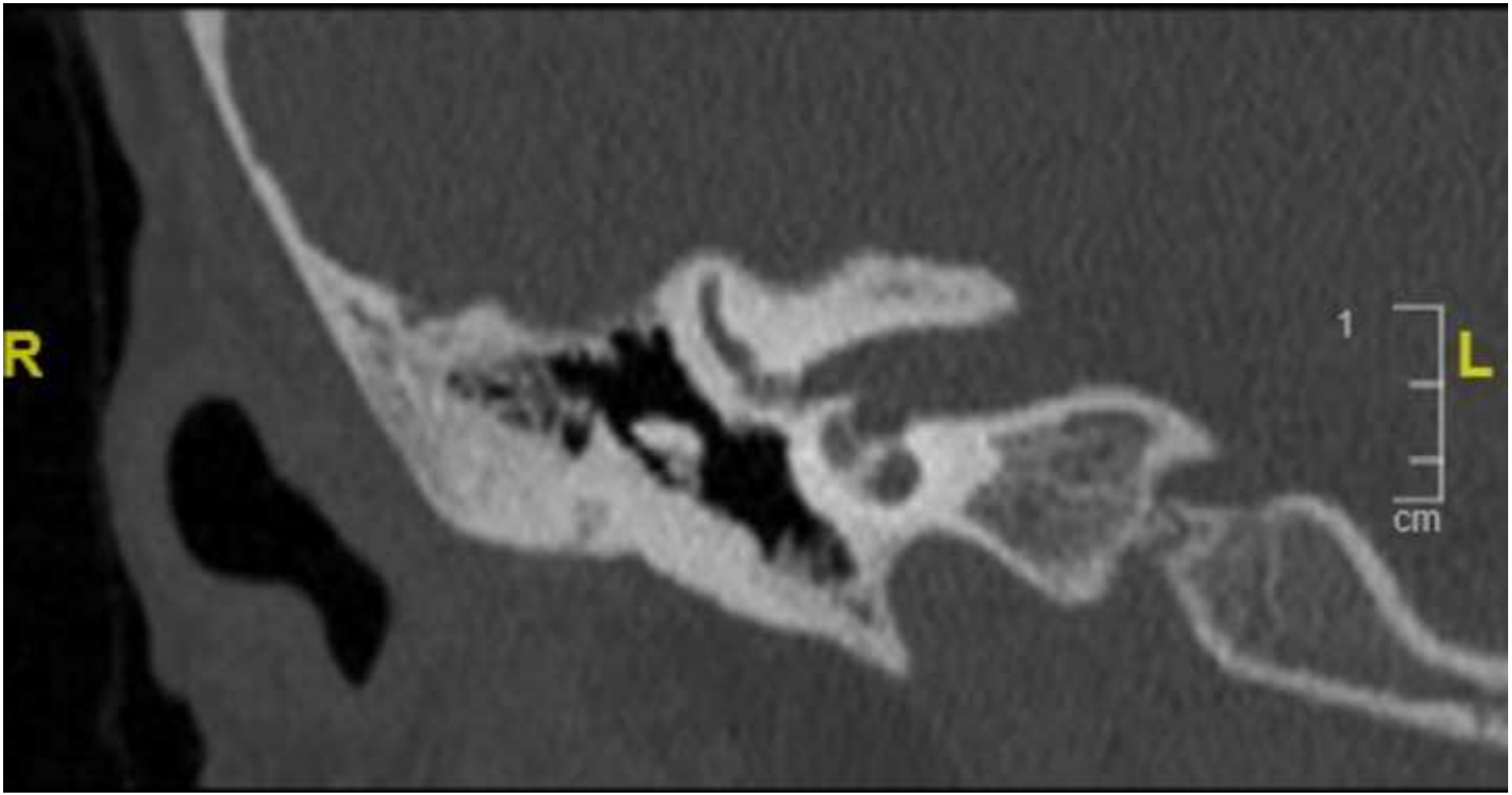

Figure