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Exploring Progression and Differences in Facial Asymmetry for Hemifacial Microsomia and Isolated Microtia: Insights from Extensive 3D Analysis

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Abstract

Background Aiming to measure and compare asymmetry of facial hard and soft tissues in patients with HFM and isolated microtia, examining how it evolves.

Methods This cross-sectional study assessed facial asymmetry in male East Asian patients aged 5–12 diagnosed with unilateral hemifacial microsomia (Pruzansky–Kaban types I and IIA) or isolated microtia. Using 3D imaging of computed tomography scans, it measured root-mean-square (RMS) values for surface deviations across facial regions. Statistical analyses explored differences between conditions and the relationship of age with facial asymmetry.

Results A total of 120 patients were categorized into four groups by condition (HFM or isolated microtia) and age (5–7 and 8–12 years). Patients with HFM exhibited the greatest asymmetry in the lower cheek, while those with isolated microtia showed primarily upper face asymmetry. Significant differences, except in the forehead and nasal soft tissue, were noted between the groups across age categories. Notable distinctions in hard tissue were found between age groups in the nasal and mid-cheek areas for patients with HFM (median RMS (mm) 0.9 vs. 1.1, $P = 0.02$; 1.5 vs. 1.7, $P = 0.03$) and in the nasal and upper lip areas for patients with isolated microtia (median RMS (mm) 0.8 vs. 0.9, $P = 0.002$; 0.8 vs. 1.0, $P = 0.002$). Besides these areas for HFM, no significant age–asymmetry correlation was detected.

Conclusions Significant differences in facial asymmetry were observed between HFM and isolated microtia, with the asymmetry in specific area evolving over time.

Level of Evidence IV This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Craniofacial abnormalities · Skeletal and soft tissue asymmetry · Three-dimensional analysis · Computed tomography · Craniofacial geometry

Introduction

Facial asymmetry can signify conditions such as hemifacial microsomia (HFM), a congenital craniofacial disorder attributable to uneven development of the face stemming from abnormalities in the first and second pharyngeal arches [1]. HFM, with an occurrence rate of approximately 1 in every 5500–26,000 live births, is ranked as the second most prevalent congenital craniofacial abnormality [2]. It affects multiple facial components, including the skeleton, ears, nerves, and soft tissues [3]. In contrast with isolated microtia, which is characterized solely by ear abnormalities, HFM typically exhibits pronounced facial asymmetry. This asymmetry can significantly impact patients' physical and mental well-being, underscoring the critical need for enhanced research in this domain [4].

There is a lack of comprehensive, quantitative studies featuring robust design and precise assessments in the research on facial asymmetry in HFM [5]. The debate also

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continues over whether isolated microtia represents the mildest form of HFM, as research has not yet thoroughly explored the facial geometry of isolated microtia or its distinction from HFM [6, 7]. Furthermore, there is no consensus on the progression of facial asymmetry in HFM, an understanding crucial for effective treatment planning. Research findings remain inconclusive, attributed to factors such as limited study designs, small sample sizes, methodological issues, and occasionally questionable conclusions.

This cross-sectional study is designed to comprehensively analyze facial asymmetry in cases of HFM and isolated microtia. It will assess asymmetry in both the skeletal structures and soft tissues across various facial regions in two age groups, utilizing precise three-dimensional imaging. Additionally, it intends to compare the facial asymmetry in these conditions and examine the evolvement of facial asymmetry.

Materials and Methods

This cross-sectional study was granted ethical approval by the Ethics Committee of Peking Union Medical College. It focused on the analysis of pre-treatment computed tomography (CT) images obtained from East Asian patients at the Center for Auricular Reconstruction, Plastic Surgery Hospital, which is affiliated with the Chinese Academy of Medical Sciences, spanning the period from 2020 to 2023. Pre-treatment CT images were acquired for diagnostic and therapeutic purposes, adhering to the manufacturer's guidelines for the CT scanner (CT 6000, Philips Healthcare, Netherlands), with imaging parameters including a 1-mm slice thickness, 120 kV, and 75 mA.

A total of 120 male patients aged 5–12 years with unilateral HFM or isolated microtia were included (see Table 1). Inclusion criteria are as follows: confirmed diagnosis of HFM or isolated microtia unilaterally, mild mandibular deformities (Pruzansky–Kaban types I and IIA) in HFM, the availability of pre-treatment CT images, absence of other craniofacial syndromes, and no history of maxillomandibular surgery or trauma. The diagnosis of the patients was carried out collaboratively by two experienced plastic surgeons.

Based on characteristics of craniofacial development and prior research [8–10], patients who met the inclusion criteria were categorized into four groups by age and diagnosis: (1) HFM group, ages 5–7 ($n = 30$); (2) HFM group, ages 8–12 ($n = 30$); (3) isolated microtia group, ages 5–7 ($n = 30$); and (4) isolated microtia group, ages 8–12 ($n = 30$).

Extraction and Registration of Hard and Soft Tissue

The DICOM images were imported into Mimics software (Materialise, Leuven, Belgium) for segmentation. Threshold values for hard tissues were established at 226–3071 Hounsfield units (HU) and for soft tissues at − 250–3071 HU. The segmented images were then imported into 3-Matic software (Materialise, Leuven, Belgium) for further processing.

According to the previous studies, thirteen landmarks both hard or soft tissues on the unaffected side and the middle were manually placed. Then based on the previous studies, proper midsagittal plane for patients with craniofacial deformity was defined [4]. Later, we delineated other planes and then segmented the facial area into eight subunits and a whole, using plane 8, the coronal plane, 7 and 9 to define the facial borders upside down [11–14] (see Tables 2 and 3, Fig. 1a–c). Eight anatomical units were subsequently delineated based on the previous studies of facial esthetic subunits [15] and facial fat compartments [16] (see Figs. 1d and 2).

Using the midsagittal plane as a reference, the anatomical regions were mirrored to ensure alignment of the left and right structures. Subsequently, the software conducted an unsigned point-based part comparison analysis to evaluate surface deviation between overlapped anatomical regions and to generate a heat map image (see Fig. 3). Root-mean-square (RMS) values for surface deviation across all nine units, which include eight anatomical units and the entire face, were subsequently collected.

Statistical Analysis

Statistical analysis utilized SPSS v20 (Chicago, III) software. The Shapiro–Wilk test indicated that the distributions of age and RMS values for surface deviation in both hard and soft tissues were non-normal (see Table 4). Differences between two independent groups were assessed using the Mann–Whitney U-test with two-tailed tests employed. Effect sizes from the Mann–Whitney tests were categorized as small ($r \leq 0.1$), small to medium ($0.1 < r < 0.3$), medium ($r = 0.3$), medium to large ($0.3 < r < 0.5$), and large ($r \geq 0.5$). Effect sizes were deemed clinically significant when medium or larger. The correlation between age and RMS values in merged groups of patients with the same disease was assessed using the Spearman correlation coefficient. A significance level of $P < 0.05$ was established.

Test of Reproducibility of the Procedure

For reproducibility assessment, 10 patients with HFM and 10 with isolated microtia were randomly selected from the

Table 1 Demographics for all cases and separate groups

Variables		Cases, No. (%) (N = 120)
Variables for all	Male	120 (100)
	East Asian	120 (100)
	Ear with unilateral microtia	120 (100)
Variables for HFM		
	Age, y	
	Mean (SD)	7.78 (1.81)
	Median (IQR)	7.5 (3.0)
	Range	5–12
Variables for isolated microtia		
	Age, y	
	Mean (SD)	7.66 (1.94)
	Median (IQR)	8.0 (3.0)
	Range	5–12
Variables for 5–7 HFM		Cases, No. (%) (N = 30)
	The O.M.E.N.S.+ classification[a]	
	Orbit (O)	O0, 13 (43); O1, 3 (10); O2, 10 (33); O3, 4 (13)[c]
	Mandible (M)/the Pruzansky–Kaban types[b]	M1, 18 (60); M2A, 12 (40)
	Ear (E)	E2, 1 (3); E3, 29 (97)
	Facial nerve (N)	N0, 26 (87); N2, 2 (7); N3, 2 (7)[c]
	Soft tissue (S)	S0, 8 (27); S1, 16 (53); S2, 5 (17); S3, 1 (3)
	The presence of extracraniofacial anomalies (+)	No, 0 (0)
Variables for 8–12 HFM		Cases, No. (%) (N = 30)
	The O.M.E.N.S.+ classification[a]	
	Orbit (O)	O0, 15 (50); O1, 2 (7); O2, 11 (37); O3, 2 (7)[c]
	Mandible (M)/the Pruzansky–Kaban types[b]	M1, 16 (53); M2A, 14 (47)
	Ear (E)	E2, 1 (3); E3, 29 (97)
	Facial nerve (N)	N0, 30 (100)
	Soft tissue (S)	S0, 18 (60); S1, 9 (30); S2, 3 (10)
	The presence of extracraniofacial anomalies (+)	No, 0 (0)

HFM hemifacial microsomia and *IQR* interquartile range

Groups: 5–7 HFM: HFM group, ages 5–7 and 8–12 HFM: HFM group, ages 8–12

[a]The most comprehensive classification system for HFM, categorizes five clinical manifestations based on dysmorphic severity, ranging from 0 to 3: orbital asymmetry, mandibular hypoplasia, ear deformity, nerve dysfunction, and soft tissue deficiency, and denotes the presence of associated extracraniofacial anomalies.

[b]The mandibular classification system for HFM, categorizes anomalies into four grades (types I, IIA, IIB, and III) based on increasing hypoplasia, focusing on ramus and condyle morphology, and is essentially replicated in the mandibular portion of the O.M.E.N.S.+ classification system

[c]Due to rounding to whole numbers, the percentages do not sum to 100%

total cohort of 120 subjects. The anatomical regions were then re-extracted twice, 14 days apart, by the same operator. Subsequently, the RMS values were remeasured, and intra-class coefficients were calculated, showing that the extraction and segmentation of the hard and soft tissue units were reproducible and responsible (see Table 5).

Results

Condition Groups Comparisons

Differences in median RMS values (mm) between the HFM and isolated microtia groups for ages 5–7 ranged from 0.01 to 1.1, with the 8–12 age groups from 0.06 to 0.98 (Table 6). Significant differences were observed in most regions, with the HFM groups displaying larger RMS values overall,

Table 2 Description of facial landmarks on hard and soft tissues

	Landmark[a]	Abbreviation	Definition
Hard tissue	Nasion	N	Middle point of the nasofrontal suture
	Porion	Po	Most upper point of meatus acusticus externus
	Orbitale	Or	Most inferior point of the infraorbital margin
	Anterior nasal spine	ANS	Most anterior point at the junction of the maxillary bones
	Gonion	Gon	Most protruding ponit located at the angle of the mandible
	Basion	Ba	Midpoint of the anterior foramen magnum
	Frontal eminence	Fe	Middle point of the rounded elevation situated about 3 cm above the supraorbital margin
Soft tissue	Commissure	Com	Com point at labial commissure
	Alare	Al	Most lateral point on alar contour
	Sublingual point	Si	Most concave point along the midline of the floor of the mouth
	Cervical point	Cp	Intersection point of neck and chin region
	Subnasal point	Sn	Most retruded point in the concavity between nose and upper lip
	Otobasion superius	Obs	Cranial point of attachment of ear to head

[a]Landmarks are positioned only on the unaffected side.

Table 3 Description of reference planes

Plane	Definition
Midsagittal plane	The plane passing through nasion (N) and anterior nasal spine (ANS) and basion (Ba) points
Horizontal plane	The plane passing through porion (Po) and orbitale (Or) points on the unaffected side and perpendicular to the midsagittal plane
Coronal plane	The plane passing through porion (Po) point on the unaffected side and perpendicular to the midsagittal and horizontal planes
Plane 1	Otobasion superius plane, the plane passing through otobasion superius (Obs) point on the unaffected side and parallel to the horizontal plane
Plane 2	Subnasal point plane, the plane passing through subnasal point (Sn) point in the middle and parallel to the horizontal plane
Plane 3	Commissure plane, the plane passing through commissure (Com) point on the unaffected side and parallel to the horizontal plane
Plane 4	Sublingual point plane, the plane passing through sublingual point (Si) point in the middle and parallel to the horizontal plane
Plane 5	Al–Com plane, the plane passing through commissure (Com) and alare (Al) points on the unaffected side and perpendicular to the coronal plane
Plane 6	Al–Com' plane, the plane mirrored from the Al–Com plane, taking the median plane as a reference
Plane 7	Po–Gon plane, the plane passing through porion (Po) and gonion (Gon) points on the unaffected side and perpendicular to the midsagittal plane
Plane 8	Fe–Obs plane, the plane passing through frontal eminence (Fe) and otobasion superius (Obs) points on the unaffected side and perpendicular to the midsagittal plane
Plane 9	Obs–Cp plane, the plane passing through gonion (Gon) and cervical point (Cp) points on the unaffected side and perpendicular to the midsagittal plane

except in the forehead and nasal units of soft tissue, where differences were not statistically significant (Table 7).

Age Groups Comparisons

For both HFM groups, median RMS values in hard and soft tissues were observed to share similar ranges, from 0.8 to 2.3 and 0.9 to 2.3, with differences remaining consistently below 0.3 across all areas. The greatest asymmetry was displayed by the lower cheek unit, with median RMS reaching up to 2.0 in hard and 2.3 in soft tissues (Table 6). With the exception of the nasal and medium cheek areas in hard tissues, where the 8–12 HFM group exhibited larger RMS values, most regions demonstrated no significant differences between groups (Table 7). Median RMS values for the 5–7 and 8–12 isolated microtia groups ranged from 0.6 to 1.4 in both tissues, with intergroup differences remaining below 0.2. Notably, the upper-mid cheek units in

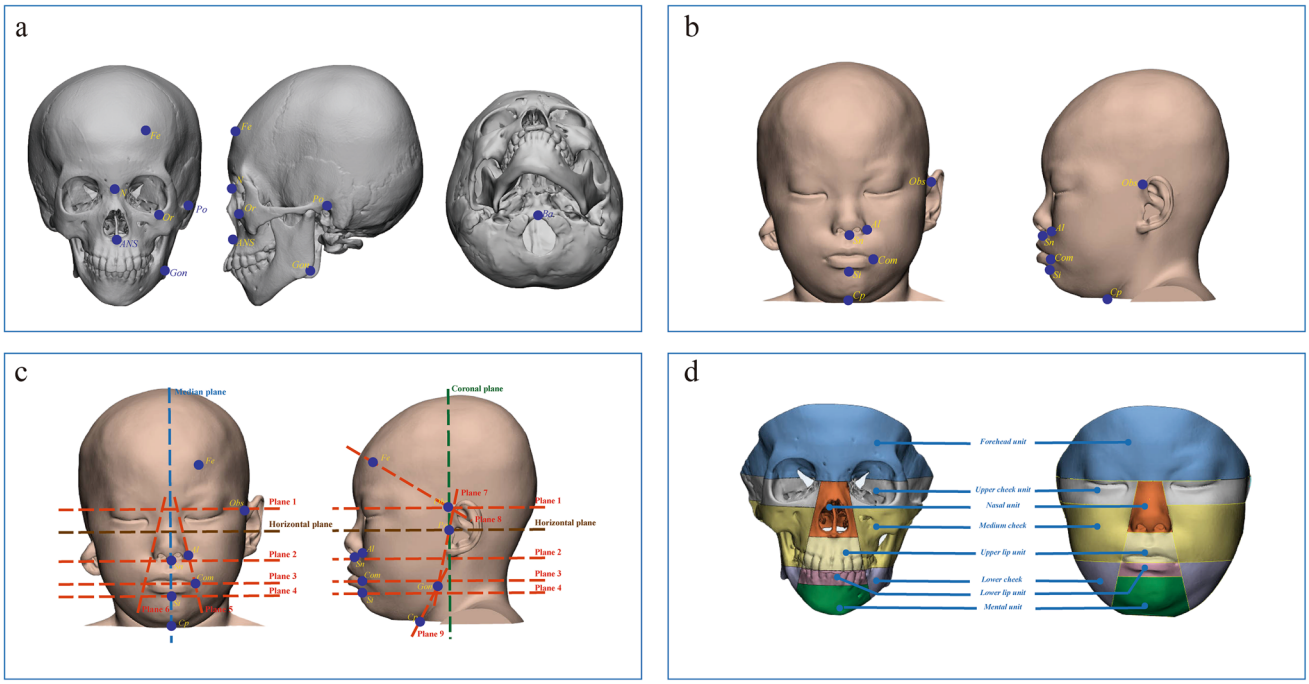

Fig. 1 Comprehensive facial mapping: landmarks and segmentation techniques for hard and soft tissues. **a** (above left) Seven facial landmarks on hard tissue; **b** (above right) six facial landmarks on soft tissue; **c** (below left) twelve reference planes; the blue, brown, and green dotted lines indicate the median, horizontal, and coronal planes, respectively; the red dotted lines indicate other reference planes for segmentation; and **d** (below right) eight facial units segmented according to facial esthetic subunits on both tissues

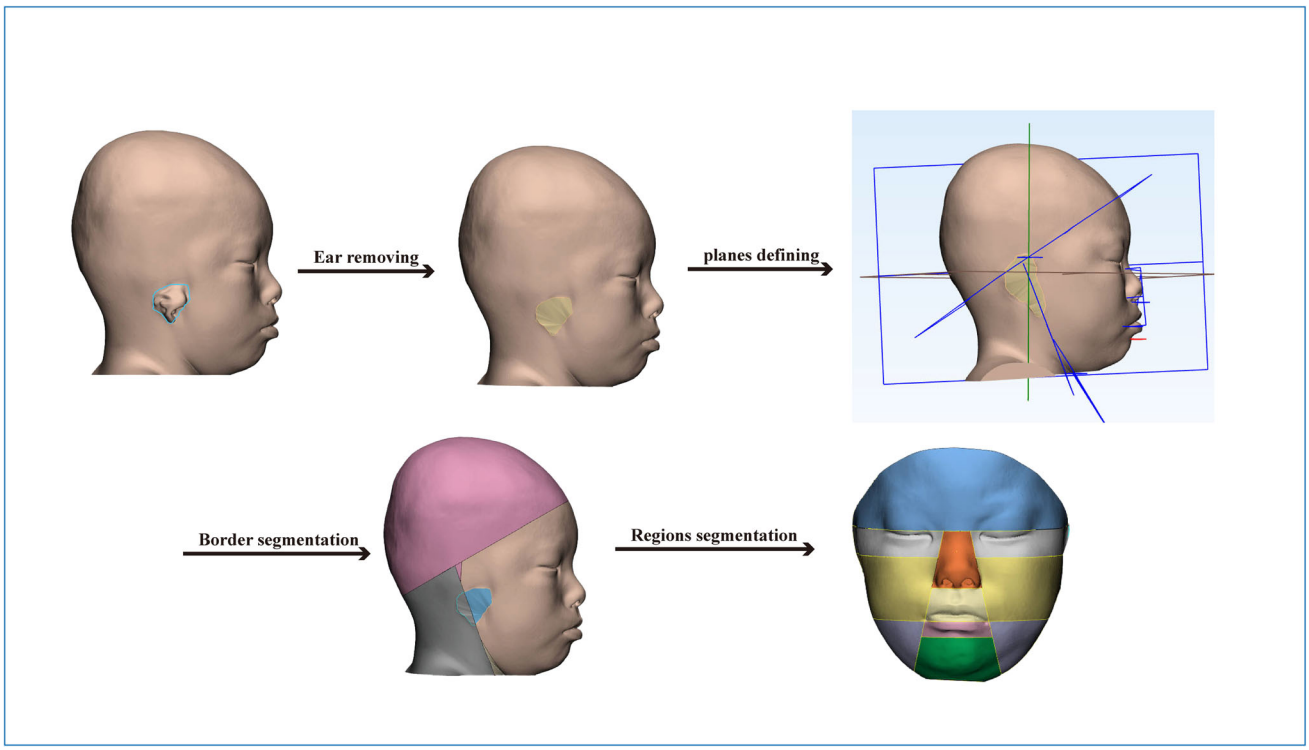

Fig. 2 Segmentation process of anatomical regions. After removing the ears on both sides and defining all planes, the entire head undergoes segmentation of facial borders and regions

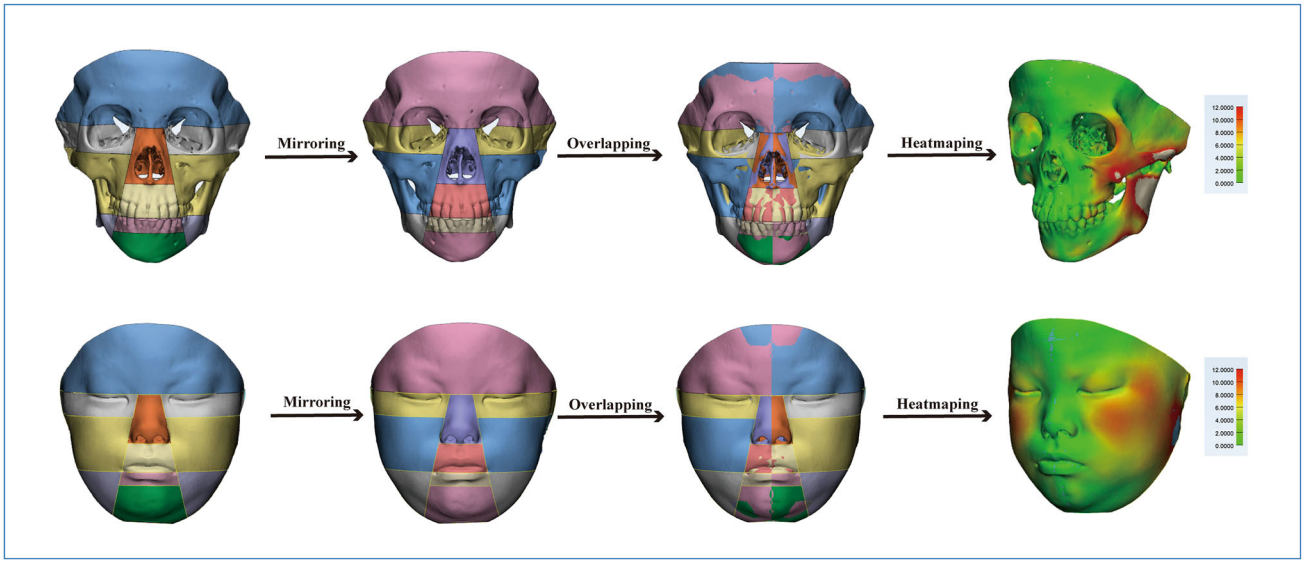

Fig. 3 The process for conducting symmetric analysis of craniofacial tissues. The original face is mirrored using median plane as a reference and then overlapped with the mirror face; a heat map showing the surface deviation is then generated

Table 4 The Shapiro–Wilk test results of RMS values for surface deviation of hard and soft tissues in various facial regions, grouped by condition and age

Group Anatomic region	5–7 HFM *P*	8–12 HFM *P*	5–7 isolated microtia *P*	8–12 isolated microtia *P*
Hard tissues				
Forehead	0.002	0.003	< 0.001	0.011
Upper cheek	0.002	0.56	0.02	0.047
Medium cheek	0.004	0.025	0.09	0.60
Lower cheek	0.006	0.028	< 0.001	0.002
Nasal	0.33[a]	0.85	< 0.001	0.98
Upper lip	< 0.001	0.042	< 0.001	< 0.001
Lower lip	< 0.001	0.004	0.07	0.25
Mental	0.05	0.065	0.006	0.01
Entire face	0.008	0.19	0.01	0.23
Soft tissues				
Forehead	0.002	< 0.001	0.08	0.025
Upper cheek	0.003	0.004	0.05	0.005
Medium cheek	0.002	0.007	0.69[a]	0.001
Lower cheek	0.031	0.019	0.01	0.006
Nasal	0.006	0.042	0.23[a]	0.022
Upper lip	0.003	0.026	0.03	0.004
Lower lip	< 0.001	0.044	< 0.001	0.004
Mental	< 0.001	0.004	0.002	< 0.001
Entire face	0.049	0.30	0.15[a]	0.002

HFM hemifacial microsomia and *RMS* root mean square.

Groups: 5–7 HFM: HFM group, ages 5–7; 8–12 HFM: HFM group, ages 8–12; 5–7 isolated microtia: isolated microtia group, ages 5–7; and 8–12 isolated microtia: isolated microtia group, ages 8–12.

[a]$P > 0.05$

hard and soft tissues showed the relative high asymmetry (Table 6). Significant age group differences were only identified in the nasal and upper lip areas of hard tissues for isolated microtia patients and in the nasal and median cheek area of hard tissues for patients with HFM, suggesting an increase in asymmetry with age (Table 7).

Table 5 The intraclass coefficients results of RMS values for surface deviation of hard and soft tissues in various facial regions

Anatomic region	ICC	*P*
Hard tissues		
Forehead	0.84	< 0.001
Upper cheek	0.85	< 0.001
Medium cheek	0.84	< 0.001
Lower cheek	0.95	< 0.001
Nasal	0.96	< 0.001
Upper lip	0.68	< 0.001
Lower lip	0.81	< 0.001
Mental	0.91	< 0.001
Entire face	0.90	< 0.001
Soft tissues		
Forehead	0.76	< 0.001
Upper cheek	0.81	< 0.001
Medium cheek	0.86	< 0.001
Lower cheek	0.88	< 0.001
Nasal	0.81	< 0.001
Upper lip	0.58	0.002
Lower lip	0.88	< 0.001
Mental	0.86	< 0.001
Entire face	0.87	< 0.001

ICC Intraclass correlation coefficient.

Groups: 5–7 HFM: HFM group, ages 5–7; 8–12 HFM: HFM group, ages 8–12; 5–7 isolated microtia: isolated microtia group, ages 5–7; and 8–12 isolated microtia: isolated microtia group, ages 8–12.

[a]$P > 0.05$

Age–Facial Asymmetry Correlation

Table 8 shows the Spearman correlation coefficients, indicating a moderate association ($P < 0.05$, $0.25 < r < 0.50$) between age and RMS values in specific facial regions. For the HFM group, age showed a moderate correlation with the medium cheek and nasal units. In the isolated microtia group, a similar correlation was found with the nasal and upper lip units. Other facial areas did not exhibit significant associations.

Discussion

Disputed Relationship Between HFM and Isolated Microtia

This study provides insights into facial asymmetry, utilizing one of the largest cohorts of patients with HFM and isolated microtia examined to date, and quantifies for the first time the differences between these two conditions, offering a more comprehensive understanding of their facial geometry. Both hard and soft tissue asymmetries were examined, with analyses conducted on regional and whole face asymmetry simultaneously. Significant discrepancies were identified, particularly in the mid-lower facial regions. These results were expected given that facial dysmorphology selectively affects maxillary and mandibular structures of patients with HFM [17]. Additionally, based on the knowledge that the forehead and nasal units both belong to the upper-third of the trigeminal area selection which corresponds to different embryological origins [18]. However, it was unexpected that the asymmetry differences of forehead and nasal units in hard and soft tissues showed inconsistency, with differences only significant in hard tissue. This may be attributed to the soft tissue's masking effect on hard tissue asymmetry [19, 20]. Besides, as our findings indicate that HFM exhibits the least asymmetry in the forehead and nasal units, these results might suggest that the deformity of HFM extends to the upper facial area, and unfortunately, soft tissue in the mid-lower face fails to fully mask the hard tissue asymmetry. Besides the significant discrepancies, the regions exhibiting the highest and lowest RMS values, along with those showing minimal RMS differences across age groups, also vary in two conditions. Therefore, it is imperative to consider specific asymmetry distribution patterns in diagnosis and treatment management.

The classification of isolated microtia as the mildest form of HFM continues to be debated [21]. Proponents of this classification cite similarities in ear malformations, higher incidence rates of microtia, and related anomalies in families with HFM as their rationale [22]. However, the recently introduced European HFM Guidelines do not recognize microtia as a mild HFM form [21, 23]. The quantitative findings from our study generally support separate examinations of the two conditions from a new dimension. Additionally, an overlap in the RMS ranges of these conditions was observed, suggesting that not all patients with HFM exhibit noticeable facial asymmetry, highlighting the challenge in management protocols making and distinguishing between isolated microtia and some HFM cases with sole skeletal defects.

Disputed Progression of Facial Asymmetry

The large cohort and well-controlled samples in our study offer greater statistical power compared to many previous reports. Our study concentrates on facial asymmetry during childhood and preadolescence, a period characterized by consistently high growth velocities prior to the onset of adolescence. We discovered that while asymmetry in certain hard tissue regions may vary over time, it generally remains stable across most facial areas, encompassing both

Table 6 Descriptive statistics of RMS values for surface deviation of hard and soft tissues in various facial regions, grouped by condition and age

Group	5–7 HFM (n = 30)					8–12 HFM (n =30)				
Anatomic region	Max	Min	Median (95% CI)	IQR	Mean (SD)	Max	Min	Median (95% CI)	IQR	Mean (SD)
Hard tissues										
Forehead	4.4	0.9	1.4 (1.1–2.1)[d]	1.2	1.8 (0.9)	3.4	0.7	1.5 (0.7, 3.2)[d]	1.6	1.7 (0.9)
Upper cheek	3.2	1.0	1.6 (1.4–1.7)	0.6	1.7 (0.6)	3.1	0.8	1.8 (0.8, 2.9)	0.9	1.8 (0.6)
Medium cheek	2.8	1.0	1.5 (1.3–1.5)	0.4	1.5 (0.4)	2.9	1.1	1.7 (1.2, 2.8)	0.6	1.7 (0.5)
Lower cheek	4.7	0.9	2.0 (1.7–2.7)[a,e]	1.9	2.4 (1.2)	4.5	1.0	2.0 (1.0, 4.2)[a,e]	0.8	2.2 (0.9)
Nasal	1.3	0.7	0.9 (0.9–1.0)[b,f]	0.2	1.0 (0.2)	1.6	0.6	1.1 (0.7, 1.6)[b,f]	0.3	1.1 (0.2)
Upper lip	4.8	0.7	1.3 (1.1–1.5)	0.6	1.5 (0.8)	2.6	0.8	1.5 (0.8, 2.6)	0.5	1.5 (0.5)
Lower lip	7.7	0.6	1.3 (1.1–1.8)[c]	1.0	1.9 (1.4)	4.2	0.7	1.6 (0.9, 3.6)[c]	0.8	1.8 (0.8)
Mental	3.4	0.5	1.7 (1.4–1.9)	0.8	1.8 (0.7)	3.1	1.1	1.7 (1.1, 2.7)	0.8	1.8 (0.5)
Entire face	2.8	1.0	1.4 (1.3–1.5)	0.5	1.5 (0.4)	2.6	1.0	1.5 (1.0, 2.5)	0.4	1.6 (0.4)
Soft tissues										
Forehead	7.2	0.6	1.6 (1.1–2.8)	2.3	2.3 (1.6)	6.4	0.5	1.3 (0.6, 5.7) [f]	2.1	2.1 (1.7)
Upper cheek	5.3	0.6	1.9 (1.3–2.2)	1.5	2.1 (1.3)	6.4	0.7	2.0 (0.7, 5.9)	2.2	2.4 (1.5)
Medium cheek	4.8	0.9	1.8 (1.6–2.3)[c]	1.2	2.1 (1.0)	5.5	0.8	2.1 (1.0, 5.4) [c]	2	2.5 (1.4)
Lower cheek	6.3	0.7	2.3 (1.7–3.0)[a,d,e]	1.8	2.6 (1.4)	5.9	0.8	2.3 (0.8, 5.7)[a,d,e]	2.1	2.7 (1.4)
Nasal	2.1	0.4	0.8 (0.6–1.0)[b,f]	0.6	0.9 (0.4)	1.3	0.4	0.9 (0.4, 1.3)[b]	0.5	0.8 (0.3)
Upper lip	2.8	0.0	0.9 (0.7–1.1)	0.6	1.1 (0.6)	2	0.5	1.0 (0.5, 1.9)	0.5	1.1 (0.4)
Lower lip	11.8	0.6	1.4 (1.0–2.1)	1.3	1.9 (2.0)	3.7	0.6	1.4 (0.6, 3.4)	0.9	1.7 (0.8)
Mental	6.1	0.5	1.4 (1.1–1.7)	0.9	1.7 (1.2)	4.9	0.4	1.6 (0.5, 4.7)	1.3	1.8 (1.1)
Entire face	3.9	1.1	2.0 (1.8–2.2)	0.9	2.1 (0.8)	4.7	0.7	2.0 (0.8, 3.9)	1.4	2.2 (1.0)
Group	5–7 isolated microtia (n =30)					8–12 isolated microtia (n =30)				
Anatomic region	Max	Min	Median (95% CI)	IQR	Mean (SD)	Max	Min	Median (95% CI)	IQR	Mean (SD)
Hard tissues										
Forehead	3.0	0.7	1.1 (1.0–1.2)	0.4	1.2 (0.5)	2.2	0.7	1.2 (0.8, 2.1)	0.4	1.2 (0.4)
Upper cheek	2.5	0.9	1.3 (1.2–1.4)[a,]	0.4	1.4 (0.4)	2	0.8	1.2 (0.9, 1.9)[a]	0.3	1.3 (0.3)
Medium cheek	1.7	0.8	1.1 (1.0–1.2)	0.3	1.1 (0.2)	1.6	0.8	1.2 (0.8, 1.5)	0.2	1.2 (0.2)
Lower cheek	2.4	0.6	1.0 (0.8–1.1)[d,e]	0.5	1.1 (0.5)	2.4	0.6	1.0 (0.7, 2.2)[d,e]	0.4	1.2 (0.4)
Nasal	2.9	0.6	0.8 (0.8–0.9)[f]	0.2	0.9 (0.4)	1.2	0.6	0.9 (0.7, 1.2)[b,f]	0.2	0.9 (0.1)
Upper lip	6.6	0.4	0.8 (0.7–0.9)[b]	0.3	1.0 (1.1)	5.6	0.5	1.0 (0.6, 2.7)	0.5	1.2 (0.9)
Lower lip	1.7	0.5	0.9 (0.8–1.0)[c]	0.4	0.9 (0.3)	1.8	0.4	1.0 (0.5, 1.8)[c]	0.6	1.0 (0.4)
Mental	2.6	0.3	0.9 (0.8–1.2)	0.6	1.0 (0.5)	1.8	0.6	1.0 (0.6, 1.8)	0.4	1.0 (0.3)
Entire face	1.8	0.7	1.0 (1.0–1.1)	0.2	1.1 (0.2)	1.6	0.9	1.1 (0.9, 1.5)	0.2	1.1 (0.2)
Soft tissues										
Forehead	3.5	0.4	1.4 (1.1–1.7)	1.2	1.4 (0.8)	3.6	0.4	1.3 (0.4, 3.1)[f]	0.9	1.4 (0.8)
Upper cheek	3.0	0.5	1.2 (1.1–1.7)	0.9	2.1 (0.6)	3.7	0.5	1.3 (0.6, 2.9)[a]	0.9	1.4 (0.7)
Medium cheek	3.1	0.3	1.4 (1.1–1.8)[a,c]	0.7	2.1 (0.6)	4	0.5	1.2 (0.6, 3.5)[c]	1.2	1.5 (0.9)
Lower cheek	3.0	0.5	1.2 (0.8–1.7)[e]	1.3	2.3 (0.7)	4.8	0.4	1.3 (0.5, 4.2)[e]	1.8	1.8 (1.2)
Nasal	1.4	0.4	0.8 (0.7–0.9)[f]	0.3	0.9 (0.2)	1.1	0.3	0.6 (0.4, 1.1)	0.4	0.7 (0.2)
Upper lip	1.3	0.3	0.6 (0.4–0.7)[b,d]	0.4	1.1 (0.3)	1.6	0.3	0.6 (0.4, 1.5)[b,d]	0.4	0.7 (0.3)
Lower lip	2.8	0.3	0.8 (0.6–1.0)	0.5	1.5 (0.5)	1.8	0.3	0.7 (0.3, 1.8)	0.5	0.8 (0.4)

Table 6 continued

Group	5–7 isolated microtia (n =30)					8–12 isolated microtia (n =30)				
Anatomic region	Max	Min	Median (95% CI)	IQR	Mean (SD)	Max	Min	Median (95% CI)	IQR	Mean (SD)
Mental	2.2	0.2	0.7 (0.5–0.9)	0.5	1.7 (0.4)	2.4	0.3	0.7 (0.3, 2.3)	0.7	1.0 (0.7)
Entire face	2.5	0.5	1.2 (1.0–1.4)	0.5	2.2 (0.5)	2.8	0.7	1.3 (0.7, 2.8)	0.7	1.3 (0.5)

HFM hemifacial microsomia, *RMS* root mean square, and *IQR* interquartile range.

Groups: 5–7 HFM: HFM group, ages 5–7; 8–12 HFM: HFM group, ages 8–12; 5–7 isolated microtia: isolated microtia group, ages 5–7; and 8–12 isolated microtia: isolated microtia group, ages 8–12.

[a]Region with the highest median RMS.

[b]Region with the least median RMS.

[c]Region showing maximal RMS differences across age groups within the same condition.

[d]Region showing minimal RMS differences across age groups within the same condition.

[e]Region showing maximal RMS differences across condition groups within the same age.

[f]Region showing minimal RMS differences across condition groups within the same age.

hard and soft tissues. Furthermore, we noted consistent patterns of asymmetry within the same condition across different age groups, as well as comparable levels of asymmetry across various conditions within the same age group, as detailed in Table 7.

Our findings align with the previous research on the stability of facial asymmetry in the normal pediatric population [24]. The observed correlation between age and asymmetry in midline regions may be attributed to differential growth phases of facial bones and the robust connectivity within the midfacial skeletal structures, including the nasal and maxillary skeletons [25, 26]. However, the literature presents conflicting views regarding the progression of facial asymmetry in patients with hemifacial microsomia (HFM). Kearns et al. analyzed facial angles relative to age and noted variations that suggest changes over time [7]. Similar findings were reported in follow-up studies by Kaban et al. and Ara et al. [27, 28]. Conversely, Meazzini et al. observed that the ratios between affected and unaffected ramal heights in HFM patients remained consistent throughout growth when left untreated [29]. These discrepancies in research outcomes likely stem from differences in sample selection, methodological approaches, and inherent limitations across studies. Challenges such as limited follow-up, selection bias, and inadequate control of confounding factors such as age, gender, and disease type are prevalent [30]. The use of small sample sizes and traditional 2D imaging techniques, which often result in distorted views, further complicates the accurate assessment of facial asymmetry [31, 32]. These constraints highlight the necessity for more robust and comprehensive evaluation methods in our study. However, due to the absence of a universally accepted method for assessing craniofacial asymmetry, direct comparison of results may not be feasible.

Our study introduces advancements in the measurement techniques and ensures homogeneity of the sample in terms of age and severity of the pathology. The results reveal that compared to patients with isolated microtia, those with hemifacial microsomia (HFM) exhibit an age-related increase in hard tissue asymmetry within the median region, which includes both mandibular and maxillary components. This suggests a progressive deterioration of the deformity in HFM patients over time. Despite this progression in hard tissue deformity, we observe that the asymmetry of soft tissues across all regions remains stable. Notably, this includes asymmetries in bone, muscle, and fat, indicating a compensatory effect from the soft tissues.

Diagnosis and Management

Our study emphasizes the importance of understanding the relationship between HFM and isolated microtia for defining, diagnosing, and facial asymmetry management in these conditions. Furthermore, the presence of subtle facial asymmetry in patients with HFM prompts concerns regarding underdiagnosis in those with solely skeletal deformities and emphasizes the risk of excessive use of radiographic examinations in patients with isolated microtia not in need of skeletal corrective treatment.

In terms of treatment, surgeons may opt to correct facial deformities in patients either during early development or after maturity, with treatment preferences varying among surgeons at different therapy stages [33]. For patients with HFM classified as Pruzansky–Kaban types I and IIA, treatment options include unilateral functional appliance treatment, fixed orthodontic treatment, distraction osteogenesis, and facial fat grafting [34, 35]. Our study observes that facial bone asymmetry, particularly in the median cheek region of patients with mild hemifacial microsomia

Table 7 Mann–Whitney U-test results comparing RMS values for surface deviation differences of hard and soft tissues in various facial regions between groups

Group	5–7 vs. 8–12 HFM			5–7 vs. 8–12 isolated microtia			5–7 HFM vs. 5–7 isolated microtia			8–12 HFM vs. 8–12 isolated microtia		
Anatomic region	*P*	*Z*	*r* (95% CI)	*P*	*Z*	*r* (95% CI)	*P*	*Z*	*r* (95% CI)	*P*	*Z*	*r* (95% CI)
Hard tissues												
Forehead	0.84	0.21	0.0[b] (− 0.2–0.3)	0.86	0.18	0.0 (− 0.2–0.3)	0.02[a]	2.29	0.3 (0.1–0.5)	0.02[a]	2.306	0.3 (0.0–0.6)
Upper cheek	0.50	− 0.69	− 0.1 (− 0.3–0.2)	0.59	0.55	0.1 (− 0.2–0.3)	0.009[a]	2.62	0.3 (0.1–0.6)	< 0.001[a]	3.578	0.5 (0.2–0.7)
Medium cheek	0.03[a]	− 2.13	− 0.3 (− 0.5 to − 0.0)	0.30	− 1.03	− 0.1 (− 0.4–0.1)	< 0.001[a]	4.07	0.5 (0.3–0.7)	< 0.001[a]	5.189	0.7 (0.4–0.9)
Lower cheek	0.72	0.37	0.1 (− 0.2–0.3)	0.25	− 1.17	− 0.2 (− 0.4–0.1)	< 0.001[a]	5.17	0.7 (0.5–0.9)	< 0.001[a]	5.056	0.7 (0.4–0.9)
Nasal	0.02[a]	− 2.44	− 0.3 (− 0.6 to − 0.1)	0.002[a]	− 3.15	− 0.4 (− 0.6 to − 0.2)	0.004	2.88	0.4 (0.1–0.6)	0.005[a]	2.794	0.4 (0.1–0.6)
Upper lip	0.17	− 1.39	− 0.2 (− 0.4–0.1)	0.002[a]	− 3.16	− 0.4 (− 0.6 to − 0.2)	< 0.001[a]	4.66	0.6 (0.4–0.8)	< 0.001[a]	3.888	0.5 (0.2–0.8)
Lower lip	0.23	− 1.21	− 0.2 (− 0.4–0.1)	0.34	− 0.95	− 0.1 (− 0.4–0.1)	< 0.001[a]	3.90	0.5 (0.3–0.7)	< 0.001[a]	4.421	0.6 (0.3–0.8)
Mental	0.90	− 0.13	− 0.0 (− 0.3–0.2)	0.84	− 0.21	− 0.0 (− 0.3–0.2)	< 0.001[a]	4.37	0.6 (0.4–0.8)	< 0.001[a]	5.515	0.7 (0.5–1.0)
Entire face	0.38	− 0.89	− 0.1 (− 0.4–0.1)	0.17	− 1.37	− 0.2 (− 0.4–0.1)	< 0.001[a]	4.75	0.6 (0.4–0.8)	< 0.001[a]	5.086	0.7 (0.4–0.9)
Soft tissues												
Forehead	0.60	0.53	0.1 (− 0.2–0.3)	0.48	0.71	0.1 (− 0.2–0.3)	0.15	1.43	0.2 (− 0.1–0.4)	0.19	1.316	0.2 (− 0.1–0.4)
Upper cheek	0.50	− 0.68	− 0.1 (− 0.3–0.2)	0.64	0.47	0.1 (− 0.2–0.3)	0.04[a]	2.07	0.3 (0.0–0.5)	0.01[a]	2.794	0.4 (0.1–0.6)
Medium cheek	0.51	− 0.67	− 0.1 (− 0.3–0.2)	0.61	0.52	0.1 (− 0.2–0.3)	0.007[a]	2.72	0.4 (0.1–0.6)	< 0.001[a]	3.134	0.4 (0.2–0.7)
Lower cheek	0.64	− 0.47	− 0.1 (− 0.3–0.2)	0.21	− 1.26	− 0.2 (− 0.4–0.1)	< 0.001[a]	3.81	0.5 (0.3–0.7)	< 0.001[a]	2.883	0.4 (0.1–0.6)
Nasal	0.56	0.59	0.1 (− 0.2–0.3)	0.07	1.82	0.2 (− 0.0–0.5)	0.40	0.84	0.1 (− 0.1–0.4)	0.03[a]	2.240	0.3 (0.0–0.5)
Upper lip	0.51	− 0.67	− 0.1 (− 0.3–0.2)	0.33	− 0.98	− 0.1 (− 0.4–0.1)	< 0.001[a]	3.37	0.4 (0.2–0.7)	< 0.001[a]	3.460	0.4 (0.2–0.7)
Lower lip	0.72	− 0.37	− 0.0 (− 0.3–0.2)	0.99	− 0.01	− 0.0 (− 0.3–0.3)	< 0.001[a]	4.18	0.5 (0.3–0.8)	< 0.001[a]	4.376	0.6 (0.3–0.8)
Mental	0.62	− 0.50	− 0.1 (− 0.3–0.2)	0.46	− 0.75	− 0.1 (− 0.3–0.2)	< 0.001[a]	4.52	0.6 (0.4–0.8)	< 0.001[a]	3.563	0.5 (0.2–0.7)
Entire face	0.90	− 0.13	− 0.0 (− 0.3–0.2)	0.72	− 0.37	− 0.0 (− 0.3–0.2)	< 0.001[a]	4.52	0.6 (0.4–0.8)	< 0.001[a]	3.681	0.5 (0.2–0.7)

HFM hemifacial microsomia and *RMS* root mean square.

Groups: 5–7 HFM: HFM group, ages 5–7; 8–12 HFM: HFM group, ages 8–12; 5–7 isolated microtia: isolated microtia group, ages 5–7; and 8–12 isolated microtia: isolated microtia group, ages 8–12.

[a] $P < 0.05$

[b] The limit of the 95% CI is reported as 0.0 owing to rounding but is slightly greater than zero.

[c] The limit of the 95% CI is reported as 0.0 owing to rounding but is slightly smaller than zero.

[d] The limit of the 95% CI is reported as 0.3 owing to rounding but is slightly greater than 0.3.

Table 8 Results of the Spearman correlation coefficient between age and RMS values for surface deviation of hard and soft tissues in various facial regions, grouped by condition

Anatomic region	HFM		Isolated microtia	
	r	*P*	*r*	*P*
Hard tissues				
Forehead	0.02	0.9	0.01	0.91
Upper cheek	0.13	0.31	− 0.10	0.47
Medium cheek	0.27	0.03[a]	0.05	0.7
Lower cheek	− 0.09	0.48	0.05	0.71
Nasal	0.37	0.003[a]	0.38	<0.001[a]
Upper lip	0.09	0.49	0.34	0.01[a]
Lower lip	0.03	0.82	0.10	0.45
Mental	− 0.02	0.87	0.07	0.62
Entire face	0.11	0.41	0.12	0.35
Soft tissues				
Forehead	− 0.06	0.65	− 0.06	0.65
Upper cheek	0.06	0.64	− 0.09	0.50
Medium cheek	0.13	0.33	− 0.04	0.76
Lower cheek	0.05	0.71	0.23	0.08
Nasal	− 0.07	0.59	− 0.02	0.91
Upper lip	0.01	0.92	0.21	0.10
Lower lip	− 0.13	0.31	0.09	0.50
Mental	− 0.09	0.5	0.17	0.20
Entire face	0.03	0.8	0.07	0.59

HFM hemifacial microsomia and *RMS* root mean square.

Groups: 5–7 HFM: HFM group, ages 5–7; 8–12 HFM: HFM group, ages 8–12; 5–7 isolated microtia: isolated microtia group, ages 5–7; and 8–12 isolated microtia: isolated microtia group, ages 8–12.

[a]$P < 0.05$

(HFM), increases over time. Given the progressive nature of the deformity, we advocate for early surgical intervention in children with HFM to support optimal growth and prevent further secondary distortions. However, several studies suggest that such treatments do not significantly alter the natural trajectory of facial growth, indicating that early orthopedic interventions may not substantially reduce asymmetry [36, 37]. Consequently, we recommend a cautious approach to early, single-stage interventions, especially in mild cases.

To focus our research, we studied two age groups of East Asian males with HFM limited to Pruzansky–Kaban types I and IIA, recognizing that significant craniofacial growth occurs mainly during childhood and adolescence, and HFM primarily affects males. This approach, aimed at reducing confounding factors, may limit the broad applicability of our findings. Instead of following strict anatomical guidelines, we segmented facial hard tissues into esthetic subunits to better understand the relationship between skeletal structures and soft tissues. This method, while not precise for individual bone analysis, offers insights into esthetic impacts, aligning with the needs of cosmetic and reconstructive surgery. Although using a semi-automatic method for image segmentation and labeling could introduce subjective errors, we ensured high image quality and utilized established craniofacial landmarks for accurate and reproducible measurements.

Conclusion

In conclusion, our study provides crucial reference data on the asymmetry of both soft and hard facial tissues in patients with HFM and isolated microtia as they grow. We highlight the importance of recognizing the distinct differences in facial asymmetry between these two conditions, as well as their evolvement over time, in their diagnosis and treatment. Although the specific characteristics of these disorders remain to be fully elucidated, our methods and results offer valuable insights for further research into these unique conditions.

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Declarations

Conflict of Interest The authors declare that they have no conflicts of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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