The role of genetic factors in microtia: A systematic review

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Abstract

Background: Microtia is a congenital malformation of the outer ears caused by improper embryonic development. The origin of microtia and causes of its variations remain unknown. Because of the lack of clarity regarding the role of genetic variables in microtia, we conducted a systematic review to qualitatively identify the genes most important in the development of microtia to provide an up-to-date review.

Methods: Using six search engines, we searched all published studies related to the genetic factors of isolated microtia and syndromic microtia. The identified publications were screened and selected based on inclusion and exclusion criteria by the authors and assessed for methodological quality using the Joanna Briggs Institute (JBI) critical appraisal tools. We found 40 studies, including 22 studies on syndromic microtia and 18 studies on isolated microtia. Data extraction of each study was arranged in tabulation for syndromic and isolated microtia. The extracted data were: first author’s surname, year of publication, country of origin, study design, sample characteristic and gene assessed.

Results: After the data were extracted, analyzed, and reviewed, the most common gene suspected to be involved in isolated microtia was Homoeobox A2 (HOXA2, 12.1%). Conversely, in syndromic microtia, the two most common genes supposed to play a role were Fibroblast Growth Factor 3 (FGF3, 47.2%) and Treacher–Collins–Franceschetti syndrome 1 (TCOF1, 30.2%). From the studies, the three most prevalent genes associated with microtia were HOXA2 (10%), FGF3 (8.4%), and TCOF1 (5.4%). In syndromic microtia, the most common mutation types were deletion in TCOF1 (46.9%) and missense and deletion in FGF3 (both 38%), and in isolated microtia, the most common mutation
type was silent in HOXA2 (54.2%).

**Conclusions:** In summary, genetic factors are involved in microtia; thus, molecular analysis is strongly advised.

**PROSPERO registration:** CRD42021287294 (25/10/21).

**Keywords**
Microtia, Genetic Mutation, isolated, syndromic, Genetic Diversity, FGF3, HOXA2, TCOF1
Introduction
Microtia is a congenital malformation of the outer ears caused by improper embryonic development. It is distinguished by small, irregularly shaped external ears, and it can occur unilaterally or bilaterally. The prevalence of microtia varies among ethnic groups (0.83–17.4 per 10,000 births). Microtia occurs unilaterally in 80%–90% of cases and bilaterally in 10%–20% of cases. Boys are approximately twofold more likely than girls to have microtia, and the right–left bilateral ratio is typically 6:3:1. Roughly one-third to one-half of patients with microtia have craniofacial microsomia. Microtia is easily misdiagnosed during pregnancy. If pregnancy ultrasonography suggests microtia, the diagnosis is easily confirmed and diagnosed following birth based on physical examination.

The etiology of microtia and the causes of its variations remain unknown. Although there is compelling evidence that environmental factors such as maternal sociodemographic variables, multiple gestation, diseases (gestational diabetes, cold-like syndrome), and related drug treatments such as isotretinoin use during pregnancy play roles, genetic factors are also believed to influence the embryonic development of microtia. Estimates of the prevalence of inherited microtia vary greatly, ranging from 3 to 34%. Although certain studies discovered candidate genetic variations for microtia, no causal genetic mutation has been identified.

Research on animals with isolated microtia as a prominent feature revealed mutations in homeobox A2 (HOXA2), sine oculis homeobox (SIX), eyes absent transcriptional coactivator and phosphatase (EYA), TBX1, IRF6, and CHUK. Genes identified to be involved in the development of major syndromic microtia were PLCB4 and GNAI3 for auriculo-condylar syndrome; TFAP2A for branchio-oculo-facial (BOF) syndrome; SIX1 and SIX5 for branchio-oto-renal (BOR) syndrome; CHD7 (SEMA3E) for CHARGE syndrome; FRAS1, FREM2, and GRIP1 for Fraser syndrome; MLL2 and KDM6A for Kabuki syndrome; GDF6 for Klippel–Feil syndrome; fibroblast growth factor 3 (FGF3) for labyrinthine aplasia, microtia and microdontia (LAMM) syndrome; FGFR2, FGFR3, and FGFR10 for lacrimo-auriculo-dento-digital syndrome; EFTUD2 for mandibulofacial dysostosis with microphaly; ORC1, ORC4, ORC6, CDT1, and CDC6 for Meier–Gorlin syndrome; HOXA2 for microtia, hearing impairment, and cleft palate; DHODH for Miller syndrome; SF3B4 for Nager syndrome; H6 family homeobox 1 transcription factor gene (HMX1) for oculo-auricular syndrome (OAS); SALL1 for Townes–Brocks syndrome; and Treacher–Collins–Franceschetti syndrome 1 (TCOF1), POL1RC, and POLIRDT for Treacher–Collins syndrome (TCS).

FGF3 mutations are commonly found in LAMM syndrome. The FGF3 protein regulates a cascade of chemical processes inside cells by binding to its receptor, thereby signaling cells to undergo particular changes, such as proliferating or maturing to perform specialized activities. TCOF1 mutations can cause TCS in up to 78% of patients. HOXA2 encodes key developmental transcription factors of the second branchial arch, which contributes significantly to the development of the external and middle ear in embryonic development, and it was previously linked to autosomal recessive bilateral microtia.

Because of the unclear role of genetic factors in microtia, we conducted the first systematic review to qualitatively identify the most important genes in the development of microtia. This may help to improve our understanding of microtia, underline the necessity of gene screening and even make prevention of microtia in the near future possible with the help of gene modification.

Methods
Protocol and registration
We have registered our protocol with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021287294 (25/10/21)). We have also screened PROSPERO for similar systematic reviews. No registered protocol reviewing the genetic factors of microtia was identified. The report of this systematic review was formulated according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.

Eligibility criteria
We performed an extensive and systematic search of all published studies related to genetic factors implicated in the development or outcome of microtia. Rather than focusing on a single disease, we aimed to provide systematic evidence on all types of microtia, including isolated microtia and syndromic microtia. First, the identified publications were assessed for relevance to the topic of interest using their titles and abstracts. The identified articles were then examined for any duplication using Mendeley. Then, the complete text of all screened papers was reviewed for the inclusion criteria, which were observational studies and case reports/series in the English language that assessed genetic factors in microtia. The exclusion criteria were duplications, reviews, non-English articles, animal studies, and articles in which sufficient details on genetic factors of microtia were not provided.
Search strategy
Three of the four authors (A.S, I.L.P, and R.P) performed the search and study selection, which was supervised by the fourth author (C.D.K.W). We used six electronic bibliographic databases, PubMed, Web of Science, Science Direct, Proquest, Springerlink, and Clinicaltrials.gov, to conduct systematic searches from 1 to 31 October 2021. We checked Medline (PubMed) to identify controlled vocabulary Medical Subject Headings terms related to genetics and microtia. Searching strategies for PubMed are presented in Supplementary Table 1 (see Extended data) and modified for other electronic databases.

Data extraction
Data extraction was conducted independently by three reviewers (A.S., I.L.P., and R.P.) through a standardized form. The methodological quality of studies in this systematic review was assessed using Joanna Briggs Institute (JBI) critical appraisal tools. We extracted data once all of the screening and selection steps had been completed. For both syndromic and isolated microtia, two different extraction forms were produced. The following data were extracted: first author’s surname, year of publication, country of origin, study design, sample population, sex, age, type of microtia, analysis method, affected genes, and mutations. Disagreements between the three reviewers were settled by discussion with the fourth reviewer (C.D.K.W.).

Results
All supplementary files can be found in the Extended data.

Systematic review outline
We discovered 3,742 articles after searching six electronic bibliographic databases. In total, 183 publications were removed because they were not available in English, they were animal studies, their full text was not available, or they were duplicated studies. Only 55 articles were eligible for more extensive evaluation after title and abstract screening. Only 40 papers were included in this study after a comprehensive full text analysis (Figure 1). The included studies were reviewed, utilizing a checklist questions form provided by JBI based on the studies’ methodology. Based on the JBI Tools for case reports, case series, and case controls, all publications involved were assessed as low-risk bias (Supplementary Tables 2–4).

![Figure 1. Systematic review flow diagram of included studies.](image)
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<th>Study design</th>
<th>Family history</th>
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<th>Grade</th>
<th>Disorder level</th>
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Abbreviations: CC, case control; CNV, copy number variation; CS, case series; CR, case report; EYA1, eyes absent transcriptional coactivator and phosphatase 1; F, female; FGF3, fibroblast growth factor 3; FOXI3, forkhead box 13; M, male; PAX1, paired box 1; SF3B2, splicing factor 3b subunit 2; TCOF, Treacher–Collins syndrome.

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Abbreviations: CC, case control; CC2D2A, coiled-coil and C2 domain containing 2A; CNV, copy number variation; CS, case series; CYP, cytochrome p450; DRD5, dopamine receptor 5; eNOS, endothelial nitric oxide synthase; EVC, EVC ciliary complex subunit 1; F, female; FGFR3, fibroblast growth factor 3; GSC, goosecoid homeobox; HOXA, homeobox A; HMX, H6 family homeobox; HTRA3, HtrA serine peptidase 3; IFN, interferon; IL, interleukin; M, male; NKX3-2, NK3 homeobox 2; PRKIR, protein kinase R; RMP1, rat monoclonal PD1 antibody; SIX2, sine oculis homeobox 2; SLC2A9, solute carrier family 2 member 9; TGF, transforming growth factor; TNF, tumor necrosis factor.
**Study characteristics**

Following the screening, selection, and data extraction of all included studies, we discovered 22 articles of syndromic microtia involving 106 patients (Table 1 and Supplementary Table 5) and 18 articles of isolated microtia involving 486 patients (Table 2 and Supplementary Table 6). China had the most cases of syndromic microtia (32 subjects [30.2%] in five studies), followed by Turkey (13 subjects [12.3%] in one study); the USA and Belgium (six subjects [5.7%] in three studies each); Poland and Saudi Arabia (four subjects [3.8%] each); and Pakistan, India, Italy, Germany, and Austria (three subjects [2.8%] each). China had the most cases of isolated microtia (415 subjects [85.4%] in 10 studies), followed by Turkey (38 subjects [7.8%] in two studies), the USA (20 subjects [4%]), Belgium (five subjects [1%]), and Iran and Italy (three subjects [0.6%] each). China had the most cases of microtia among all investigations, being the site of 447 of 592 cases (75.5%). Concerning the study design, there were two case reports, 34 case series, and five case control studies included in this analysis.

Regarding studies of syndromic microtia (Table 1), the family history was known for 104 of 106 subjects (98.1%), whereas the family history was not discussed in two subjects (1.9%). Of the 104 subjects, 84 (80.8%) had family histories of microtia. We also discovered that, of the 106 subjects, the gender was known for 105 subjects (99%), which included 62 males (59%). The severity of microtia was known for 158 of the 173 ears (91.3%) involved in this analysis. Of the 158 ears, 98 (62%) had grade I microtia, 44 (27.9%) had grade II microtia, and 16 (10.1%) had grade III microtia. The type of microtia was known in 72 of 106 subjects (67.9%); of these subjects, 15 (20.8%), 4 (5.6%), and 53 (73.6%) had right unilateral, left unilateral, and bilateral microtia, respectively. Based on the gene disorder levels in 22 studies including 106 subjects, 105 subjects (99%) in 21 studies had DNA-level disorders, and one subject (1%) in one study had a chromosomal disorder. We discovered that of the 106 subjects, 32 subjects (30.2%) in seven studies had TCOF1 gene mutations, whereas 50 subjects (47.2%) in five studies had FGF3 gene mutations.

According to studies of isolated microtia (Table 2), 274 of 486 subjects (56.4%) had a family history of microtia. The genders of the 486 subjects were known for 461 subjects (94.9%), which included 269 males (58.4%). Based on the severity of microtia, the grading of 551 ears was known for 208 subjects (37.7%), among whom 2 (1%), 67 (32.2%), 135 (64.9%), and 4 subjects (1.9%) had grades I, I, III, and IV microtia, respectively. The type of microtia was specified for 103 subjects (21.2%), being right unilateral, left unilateral, and bilateral in 15 (14.6%), 11 (10.7%), and 77 subjects (74.7%), respectively. Regarding the genetic disorder level, 486 subjects in 18 studies, 485 subjects (99.8%) in 17 articles had DNA-level disorders, and one subject (0.2%) had a chromosomal disorder. We discovered that 59 subjects (12.1%) in seven studies had mutations in the HOXA2 gene.

We discovered that of 592 subjects, the family history was known in 590 subjects (99.7%). In total, 358 of the 590 subjects (60.7%) had family histories of microtia. The genders of 566 of the 592 total subjects (95.6%) were known. Among the 566 subjects, 331 (58.5%) were male, and 235 (41.5%) were female. The severity of microtia was known in 366 of the 724 ears (50.5%) examined in this study. Among these ears, 100 (27.3%) had grade I microtia, 111 (30.3%) had grade II microtia, 151 (41.3%) had grade III microtia, and 4 (1.1%) had grade IV microtia. Based on the type of microtia, the type of microtia was known for 175 of 592 subjects (29.6%). Among these 175 subjects, 30 (17.1%) had right unilateral microtia, 15 (8.6%) had left unilateral microtia, and 130 (74.3%) had bilateral microtia. Based on the gene disorder levels described in all 40 studies, 586 subjects (99%) in 38 studies had DNA-level disorders, whereas six subjects (1%) in two studies had chromosomal disorders. We discovered that FGF3 was the most common gene involved in isolated microtia (50 subjects [8.4%]), followed by TCOF1 (32 subjects [5.4%]), and HOXA2 was the most common gene involved in isolated microtia (59 subjects [10%]).

Based on the type of mutation (Table 3), we discovered that in syndromic microtia, the most common type of mutation in TCOF1 was deletion, being detected in 15 of 32 subjects (46.9%). In FGF3, the most common mutation types were missense and deletion, being present in 19 of 50 subjects (38%) each, and in isolated microtia, the most common mutation type in HOXA2 was silent mutation, being present in 32 of 59 subjects (54.2%).

**Discussion**

Microtia is a congenital external ear deformity that can range in severity from minor anatomical problems to full ear absence (anotia). Microtia can be a single birth abnormality or part of a broader set of defects or syndrome. This systematic review attempted to describe the genes that play important roles in the development of syndromic and non-syndromic microtia. Only 40 studies on genetically linked microtia met our selection criteria. In this study, China had the highest number of microtia cases. The findings of this study contradict epidemiological data reported by Klokars et al., who recorded the highest prevalence of microtia in Quito, Ecuador, South America, (17.4/10,000), and Luqueti et al., who stated that the highest prevalence of microtia was in Finland, North Europe (4.3/10,000). This could be because...
China has a higher overall birth rate than other countries\(^2\); therefore, even if it has a greater number of microtia cases, the prevalence rate is low.

We discovered that most patients with microtia had a family history of the disease, including 56.4% of patients with isolated microtia and 80.8% of patients with syndromic microtia. This is consistent with the existing literature, which describes Mendelian hereditary variants of microtia with an autosomal dominant or recessive mode of inheritance.\(^1,4,20\) The rates of familial microtia ranged from 3 to 34%.\(^10\)

Based on the gender classification of each study, we discovered nearly 60% of all patients were male, including 59% of patients with syndromic microtia and 58.4% of patients with isolated microtia. In prior research, microtia was more common in male patients than in female patients, with a sex ratio of 1.5:1 and an estimated 20–40% greater risk in males than in females.\(^4,21\)

Although microtia can arise bilaterally, 77–93% of patients have unilateral involvement.\(^4,21\) The most common form of syndromic microtia is bilateral microtia.\(^1\) Although bilateral microtia was more common in this study, the type of microtia was only known for 29.6% of subjects. Because of the inadequate data, this could represent a biased outcome for the most prevalent type of microtia.

Most published research on microtia reported the existence or absence of microtia and/or anotia with no further details on severity. Marx (1926), Weerda (1988), Roger (1977), Tanzer (1978), and Hunter (2009) all provided classifications of microtia.\(^5\) Their classification system was nearly identical, consisting of four grading levels.\(^4,22\) The lobule type, grade III microtia, was the most common microtia type in the literature, accounting for 60% of all cases. The most prevalent severity of syndromic microtia was grade I owing to the high rate of mutations in **FGF3**, which can cause **LAMM** syndrome with a grade I microtia presentation.\(^13,14,23,24\)

From all examined studies involved, the most common genes associated with microtia were **HOXA2**, **FGF3**, and **TCOF1**. We discovered that in syndromic microtia, the most common types of mutation were **TCOF1** deletion (46.8%), and missense and deletion in **FGF3** (38%), whereas in isolated microtia, the most common type of mutation in **HOXA2** was silent mutation (54.2%). This was consistent with the literature, which indicated that the most common genes involved in microtia were **HOXA2**, **FGF3**, **HOXD**, **ORC1**, **ORC4**, **ORC6**, **CDT1**, **CDC6**, **DHODH**, **HMX1**, **EYA1**, and **TCOF1**.\(^2\)

**FGF3** encodes a protein member of the FGF family.\(^15\) The FGF family has extensive mitogenic and cell survival activities and is involved in various biological processes such as embryonic development, morphogenesis, tissue repair, cell growth and inner ear formation in mice and chicken.\(^15\) **FGF3** activates a cascade of chemical reactions inside cells that activate certain changes, such as dividing or maturing to take on specialized functions, by attaching to another protein known as a receptor.\(^1\) **FGF3** haploinsufficiency could also be related with dental and hearing problems. **FGF** signaling is required for the appropriate development of the otic placode, a thickening of the ectoderm on the outer surface of a developing embryo from which the ear develops.\(^22\) **FGF3** mutation is often found in syndromic microtia, mainly in **LAMM** syndrome. Congenital deafness with **LAMM** syndrome is an autosomal recessive disorder characterized by significant bilateral congenital sensorineural deafness coupled with inner ear defects, grade I bilateral microtia, and microdontia (small teeth).
as its major phenotypic features. The finding of biallelic pathogenic mutations in FGF3 on molecular genetic testing confirms the diagnosis of LAMM syndrome in the proband. 

The TCOF1 gene, which encodes a suspected nucleolar phosphoprotein known as treacle, has been identified as the cause of TCS, an autosomal dominant craniofacial development disorder, in up to 78% of patients. Inhibition of mature RNA ribosomal (rRNA) production and gene transcription in neural folds prefusion during the early stage of embryogenesis may cause abnormal development due to treacle haploinsufficiency, caused by mutation in the TCOF1 gene, thus affecting proliferation and proper differentiation of these embryonic cells. To date, more than 50 mutations have been identified in the TCOF1 gene, most of which are insertions or deletions. TCS is characterized by cleft palate, hypoplasia of facial bones (particularly the mandible and zygomatic complex), downward slanting of palpebral fissures with colobomas of lower eyelids, external ear deformity, conductive hearing loss, and defects in brain development such as microcephaly and mental retardation. TCOF1 was the most prevalent gene found in this systematic review. This was because TCOF1 is a causative gene for TCS, which features microtia as one of its clinical symptoms. In addition to clinical findings, TCS diagnosis is also confirmed by detection of pathogenic variants of TCOF1, POLR1D, or POLR1B using molecular genetic testing, mainly inherited in an autosomal dominant pattern. In accordance with our result, TCOF1 gene deletions were reported to range from a single exon to a whole gene. Despite the fact that >97% of reported cases contained a pathogenic mutation identifiable by sequencing, Bowman et al. (2012) reported 5% of cases (5/92) with a big deletion, suggesting that the rate of large deletions may be higher than current data suggest.

**Homeobox** genes participate in the formation of the pharyngeal arches. They encode transcription factors that determine cell positional identity and morphogenesis during development, as well as switch on cascades of other genes. The Hox gene family was discovered to be grouped inside the genome and ordered on the chromosome in the order of expression during development. This ordered pattern of gene expression could be part of a mechanism that generates morphogenetic specification. HOX2 was discovered to be highly expressed in the second branchial arches (BA2), to express critical developmental transcription factors BA2, to play an important role in the development of the external and middle ear during embryonic development, and to be associated with autosomal recessive bilateral microtia as a member of the HOX gene family. In humans, abnormal or lost HOX2 function, as well as early and late HOX2 inactivation, results in auditory system malformations, primarily in the external and middle ear, such as a duplicated or absent auricle. Consequently, HOX2 has been proposed as a key transcriptional regulator of auricle morphogenesis. Individuals with a homozygous HOX2 mutation have far more severe clinical symptoms than those with a heterozygous mutation. In a mouse model, inactivation of Hox2 early in development results in the absence of the pinna, whereas late inactivation results in a hypomorphic auricle. Aside from HOXA2, FGF3, and TCOF1, other genes linked to microtia include HOXD, ORC1, ORC4, ORC6, CDT1, CDC6, DHODH, HMX1, and EYA1. Among these, HMX1 located on chromosome 4p16.1 is prominent. It is involved in the differentiation of the lateral facial mesenchyme downstream of embryonic patterning genes. In humans, recessive loss-of-function mutations in HMX1 have been linked to OVAS, which is characterized by external ear and eye deformity. In a five-generation Chinese family with isolated bilateral microtia, a 10-Mb linkage locus covering 4p16 was discovered. We hypothesized that a link existed between the types of genes involved and the grade of microtia. For example, FGF3 deletions in LAMM syndrome have been clinically identified as grade I microtia. According to the MARX classification, the HOXA2 gene was common in the form of microtia type II and was exclusive to isolated microtia. However, no specific type of microtia has been linked to the deletion of TCOF1.

The field of genetic variables in microtia research is still relatively extensive. More research on genetic variables that contribute to microtia is required, particularly using the next generation sequencing (NGS) and DNA microarray approach. NGS, massively parallel sequencing, or deep sequencing are all terms that refer to DNA sequencing technology that has transformed genomic research. In comparison to other technologies, NGS can sequence the entire human genome in a single day. Genomes may be examined without prejudice, allowing mosaic mutations to be detected. On the other hand, DNA microarray is a revolutionary technique for gene expression profiling. Microarrays were created as a method for mapping and sequencing vast amounts of DNA. DNA microarrays offer a far higher throughput and are less time consuming than previous approaches. By applying NGS and microarray for screening of genetic risk factors in microtia, the diagnosis of microtia could be made earlier and the patients could get a more comprehensive treatment.

**Strengths and limitations of the study**

This systematic review used recent available evidence and is the first systematic review to describe genetic factors in microtia. All studies included in this review were assessed as being of high quality. However, the limitations of this study
included the heterogeneity of studies on the genetic evaluation of microtia in online databases, as well as the absence of information on the details of the subjects; thus, we could not perform a meta-analysis in this study. Gender information was unknown in 4.4% of patients, severity was unknown in 49.5% of subjects, and the type of microtia was unclear in 70.4% of patients. Case reports and case series were the most common study types in this systematic review. More observational research on genetic microtia is required to perform a more comprehensive systematic review and even meta-analysis.

Conclusions
According to this study, most cases of microtia (75.5%) occurred in China, 60.7% of subjects had a family history of microtia, 58.5% of cases occurred in males, 74.2% of cases were bilateral, and 41.3% of cases were grade III microtia. From the studies involved, the three most common genes associated with the development of microtia were HOXA2 (10%), FGF3 (8.4%), and TCOF1 (5.4%). The most prevalent syndromes related to microtia were TCS and LAMM syndrome. Deletion mutations in TCOF1 were found in 15 patients (46.9%), deletion and missense mutations were present in FGF3 in 19 patients (38%), and silent HOXA2 mutations were present in 32 patients (54.2%).

Approximately 76.2% of the genetic factors that contribute to microtia remain unknown. More research on genetic variables in microtia is required, particularly the use of NGS, massively parallel sequencing, or deep sequencing. We recommend that investigations on genetically associated microtia be conducted using observational studies, and the features of patients involved should be described more clearly and comprehensively in the future for better systematic reviews or even meta-analysis.

By understanding the three most dominant genes associated with microtia (HOXA2, FGF3, and TCOF1), we could promote the early screening and detection of microtia in the next generation, allowing us to provide better education and genetic counseling to patients with microtia regarding the possibility of microtia development in their children, and we hope that this systematic review will serve as a reference for the establishment of a global database of patients with microtia.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Extended data
Harvard Dataverse: The Role of Genetic Factors in Microtia: A Systematic Review. https://doi.org/10.7910/DVN/4RRHH0.72

This project contains the following extended data:

- Supplementary Files.docx (Table 1. Medline (Pubmed) search strategy to identify published literature, tables 2-4 Risk of bias evaluation of studies involved in this systematic review using JBI Checklist, tables 5-6 additional characteristics of studies involved in this systematic review)

- Table Manuscript.docx (Tables 1-2 main characteristics of studies involved in this systematic review, table 3 type of mutation found on analysis)

Reporting guidelines
Harvard Dataverse: PRISMA checklist and flowchart for ‘The role of genetic factors in microtia: A systematic review’. https://doi.org/10.7910/DVN/4RRHH0.72

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