MICROTIA

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ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty of the University of Helsinki, for public examination in the auditorium of the Department of Otorhinolaryngology, Haartmaninkatu 4E, on January 24th 2014, at 12 noon.

Helsinki 2014
To my Family
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by Roman numerals.


IV. **Suutarla S**, Rautio J, Klockars T. Cleft lip and/or palate and auricular malformations. Accepted for publication in Cleft Palate and Craniofacial Journal.
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABG</td>
<td>Air-bone gap</td>
</tr>
<tr>
<td>BAHA®</td>
<td>Bone anchored hearing aid</td>
</tr>
<tr>
<td>BOR</td>
<td>Branchio-oto-renal syndrome</td>
</tr>
<tr>
<td>BTE</td>
<td>Behind-the-ear</td>
</tr>
<tr>
<td>CHARGE</td>
<td>Coloboma, Heart defect, Atresia of choana, Retarded growth and development, Genital abnormality, Ear abnormality</td>
</tr>
<tr>
<td>dB HL</td>
<td>Desibel hearing level</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FGF2</td>
<td>Fibroblast growth factor-2</td>
</tr>
<tr>
<td>FMT</td>
<td>Floating mass transducer</td>
</tr>
<tr>
<td>HFM</td>
<td>Hemifacial microsomia</td>
</tr>
<tr>
<td>HRCT</td>
<td>High resolution computed tomography</td>
</tr>
<tr>
<td>ITE</td>
<td>In-the-ear</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OAVS</td>
<td>Oculo-auriculo-vertebral spectrum</td>
</tr>
<tr>
<td>PPE</td>
<td>Porous polyethylene</td>
</tr>
<tr>
<td>SNHL</td>
<td>Sensorineural hearing loss</td>
</tr>
<tr>
<td>SGF</td>
<td>Subgaleal fascia</td>
</tr>
<tr>
<td>TCOF1</td>
<td>Treacher Collins-Franceschetti 1 gene</td>
</tr>
<tr>
<td>TCS</td>
<td>Treacher Collins syndrome</td>
</tr>
<tr>
<td>TPF</td>
<td>Temporoparietal fascia</td>
</tr>
</tbody>
</table>
ABSTRACT

Microtia is a congenital malformation that is characterized by variation in severity and its association with other anomalies. Microtia may be a clinical sign of certain syndromes. A typical microtia patient has such a visible malformation that reconstructive surgery of the auricle is desired. In addition to the malformed auricle, both the ear canal and middle ear are usually anomalous causing considerable hearing impairment.

This thesis identifies the characteristics of microtia in the Finnish population and detects the existence of familial (hereditary) microtia in Finland. The first learning curve study of reconstructive surgery for microtia is presented. In addition, we have studied the association between auricular malformations and orofacial clefts. The study population for phenotypic characterization consisted of 190 patients referred for reconstruction of the auricle. Of this population, 109 patients were involved in the hereditary study. The learning curve study is based on 51 microtia reconstructions. The study of auricular malformations and clefts includes 100 patients.

These studies show that the characteristics of microtia in Finland are for the most part similar to other populations, but there is a high variation in prevalences in different populations. The overall global prevalence is around 2.1/10,000 births compared to 4.3/10,000 in Finland. The proportion of familial microtia in the Finnish population is over 20% and the mode of inheritance seems to be autosomal dominant with incomplete penetrance. The learning curve for microtia reconstruction is long and this finding strongly suggests national centralization of treatment. Microtia seems to be the most common ear malformation in cleft patients. The prevalence of microtia increases as the severity of cleft lip increases. This trend was not present in patients with cleft palate only.

Improvement in surgical techniques, the development of biocompatible reconstructive materials, and advances in audiological equipment and diagnostic imaging have improved the ways that a patient with microtia is examined and treated.
1. Introduction

Microtia means small auricle. Although the term itself is relatively simple to comprehend, the clinical findings associated with microtia, hearing impairment, heredity and surgical reconstruction of the auricle or the middle ear are far more complex. The overall conception of the characteristics and the adequate treatment for this malformation will be brought forth in this thesis.

A moderate amount of literature has been published on microtia. An early microtia classification done by H. Marx in 1926 is still in clinical use and is widely referred to in the literature (Marx, 1926). Since the 1950’s, the evolution of microtia reconstruction has been notable. The pioneering work by Tanzer was the starting point for the use of autogenous rib cartilage in the reconstruction of a malformed auricle (Tanzer, 1959). This method, though difficult to perform, is still the recommended and most popular way to reconstruct the auricle. In addition, developments in health technology have yielded artificial materials that can be successfully used in place of cartilage (Wellisz T, 1993; Reinisch et al. 2009). Over the past decade, the research in tissue engineering has been intensive (Van Osch et al. 2004; Kamil et al., 2004; Reiffel et al., 2013). Today, rib cartilage can be substituted with tissue engineered cartilage in the reconstruction of the auricle (Yanaga et al., 2009).

The reconstruction of the malformed auricle is one important part in the treatment of a microtia patient. However, understanding and solving the possible associated malformations, heredity issues, and hearing problems are as much, if not even more, important.

The prevalence of microtia has considerable variation (Luquetti et al., 2011). This variation may be partially a consequence of the way that artefacts are registered. The use of different classification systems and diverse manners of characterizing microtia patients may alter the definition of real or actual prevalence. Both the healthcare system and the environment are rather similar in Finland and Sweden. However, the birth prevalence of microtia is 2.4 / 10 000 in Sweden (Harris et al. 1996) and approximately 4.3 / 10 000 in Finland (Finnish Register of Congenital Malformations, 2006). The almost two-fold difference in prevalence between these two countries may come from register bias, but
may also come from heredity. Both the environmental factors and genes are likely to predispose these two populations to first and second branchial arch malformations and microtia. It is likely that there are also real differences in the global prevalence of microtia due to the variation in predisposition related factors. Single gene mutations causing isolated microtia have not been found, although microtia is related to many known single gene syndromes or disorders.

External auditory canal atresia and middle ear anomalies are usually (80-90%) associated with microtia (Mayer et al. 1997; Llano-Rivas et al. 1999). Thus, the typical hearing loss is associated with hearing thresholds between 55 to 65 dB HL. The gross magnitude of sensorineural hearing loss in microtia is 3-5 % (Eavey, 1995; Carvalho et al., 1999). Hearing restoration surgery or the use of hearing aids can be considered obligatory in bilateral microtia, but is a debatable issue with regard to unilateral microtia.

This thesis consists of four original studies and the first one describes the characteristics of microtia in Finland and compares it to other populations. The second study detects the pattern of inheritance of microtia in Finland and includes a comparison of the phenotypes between sporadic and familial patients. The reconstruction of the auricle is the topic of the third study. The use of rib cartilage as a frame for the auricle and the coverage of the frame by skin and fascial flaps is the method used in Finland. The learning curve for this kind of surgery and patient satisfaction with this laborious procedure were also researched. In the fourth study, the relationship between orofacial clefts and external ear malformations is examined. Both orofacial and ear structures are the derivatives of the first and second pharyngeal arches. We have a high volume register of up to 8200 patients at The Cleft and Craniofacial Centre at the Helsinki University Central Hospital. These factors motivated us to study the relationship between these anatomically close malformations. This is the first detailed and high volume study on this topic.

It is believed that the new information on microtia we have found in these four studies is beneficial for professionals working with ear anomalies, microtia patients themselves and a microtia patient’s parents. In addition to the original research, central issues concerning the assessment and the treatment of a patient with microtia are gathered in this thesis.
2. Review of the literature

2.1. The auricle

“Large ears indicate long and successful life” (Chinese trad.). The possible explanation for this correlation is discussed at the end of this chapter. However, the functional purpose of the human auricle is debatable. In physiological studies, the auricle seems to amplify middle frequencies (2-4 kHz) and facilitate the localization of a sound source in three-dimensional space (Hofman et al. 1998).

The basic elements of the normal pinna are: 1. the lobulus inferiorly, 2. helix, scapha and antihelix with its cruses posterosuperiorly, 3. tragus, antitragus, concha and crus helicis as the atrium to the auditory meatus and 4. fossa triangularis between the cruses of the anthelix and the helix (Figure 1). The blood supply to the auricle comes via a. auricularis posterior (branching directly from a. carotis externa), branches of a. temporalis superficialis and a. occipitalis. All arteries are accompanied by corresponding veins (Jackson, 2002).

Four cranial nerves (CN) are involved in the sensory innervation of the auricle: n. auriculotemporalis (mandibular branch of nervus trigeminalis, CN V) anteriorly, n. facialis (CN VII) posterosuperiorly, n. vagus (CN X) and n. glossopharyngeus (CN IX) in the conchal region, mastoid skin and external auditory canal. N. auricularis magnus and n. occipitalis minor from the cervical plexus innervate lobulus and submastoid area (Schünke et al., 2007).

There are plenty of anthropometric studies on the auricle. By one year of age, ear length has reached roughly 75% of its adult size, and a width of 90% correspondingly. On average, ear width reaches its mature size in males at 7 years and in females at 6 years. On average, ear length reaches maturity in males at 13 years and in females at 12 years (Farkas et al. 1992). Ethnic group and sex seem to influence the size and growth of the auricle. The vertical length of the auricle increases throughout one’s life. Its estimated
velocity is 0.22 mm per year. Aging and gravity cause this increase (Heathcote, 1995; Alexander et al. 2011).

**Figure 1.** The human auricle.
2.2. Embryology

2.2.1. General concept

During the late embryonic (gestational weeks 5-8) and early fetal (weeks 8-16) period the human appearance takes shape (Figure 2). The development of the head and neck is rapid and the essential and sensitive stages are over within 7 weeks. By week 12, ears and facial structures are established and the rest of the fetal period is for growth and maturation (Schoenwolf et al., 2009).

Figure 2. The embryo measuring approximately 15 mm by the seventh gestational week. Forthcoming auricle is marked with red. (Illustration by Julius Niiniranta, 2013).
In humans, five pairs of pharyngeal (or branchial) arches start to form on gestational day 22. On that day the first pharyngeal arch appears under the developing eye and by day 29, all pharyngeal arches are distinguishable. These tuberosities are like short sausages fused to each other. The outer recesses between the arches are called pharyngeal clefts and the inner recesses are called pharyngeal pouches. The first pharyngeal arch forms the permanent structure discussed below. The second pharyngeal arch grows rapidly during the 4th and 5th weeks and expands caudally covering the remaining three arches. Anterior fusion of the pharyngeal arches is completed by week 10. The derivatives of pharyngeal arches, clefts and pouches concerning the face and ears are detailed in Table 1.

Table 1. The fate of the first and second pharyngeal arch, the first pharyngeal cleft and pouch.

<table>
<thead>
<tr>
<th>Embryologic origin</th>
<th>Skeletal elements</th>
<th>muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st pharyngeal arch</td>
<td>Incus, malleus, maxilla, zygoma, squamous portion of temporal bone, mandible, auricle</td>
<td>Temporalis, masseter, mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini</td>
</tr>
<tr>
<td>1st pharyngeal cleft</td>
<td>External auditory meatus, external part of the tympanic membrane</td>
<td>-</td>
</tr>
<tr>
<td>1st pharyngeal pouch</td>
<td>Middle ear cavity, Eustachian tube, mastoid air cells, internal part of the tympanic membrane</td>
<td>-</td>
</tr>
<tr>
<td>2nd pharyngeal arch</td>
<td>Stapes, styloid process, lesser horns and upper rim of hyoid, auricle</td>
<td>Muscles of facial expression, posterior belly of digastric, stylohyoid, stapedius</td>
</tr>
</tbody>
</table>
2.2.2 Embryology of the ear

The ear is derived from multiple embryonic origins. The external and middle ear develop from the first and second pharyngeal arches and the cleft in between them. The first cleft forms the external acoustic meatus and the external part of the tympanic membrane. In addition, the first pharyngeal pouch is opposed to the cleft from inside and extends to build up the Eustachian tube and the middle ear mucosa. Each pharyngeal arch consists of a mesenchymal core that is lined on the outside with ectoderm and on the inside with entoderm. Apart from these structures, the inner ear develops separately from an ectodermal otic placode. This is important to recognize because this is the explanation for why the inner ear is normal in most microtia cases. Embryogenesis also explains why some degree of external ear canal and middle ear hypoplasia is very often related to microtia. The mammalian middle ear develops through cavitation of a neural crest mass. In a recent study, it has been shown that the epithelium derived from endodermal cells develops cilia, which are important to clearing pathogenic infections from the middle ear (Thompson and Tucker, 2013). These endodermal derived cells are located in the Eustachian tube and extend slightly beyond the eardrum. In the middle wall and attic, the mucosa is of neural crest origin and is non-ciliated. Thus, the middle ear mucosa is of dual origin. The auricle develops from six hillocks that appear on the outer (ectodermal) surface of the first and second auricular arches during the 5th gestational week. Anterior (or ventral) hillocks are derivatives of the first pharyngeal arch and are called tragus, helix and cymba concha. Posterior (or dorsal) hillocks are derivatives of the second pharyngeal arch and are called antihelix, antitragus and concha (Schoenwolf et al., 2009). These names indicate the eventual structures that they build up, though the exact contribution of each hillock still remains in doubt (Hunter et al. 2005) (Figure 3).
Figure 3. Rough and schematic illustration of fetal origin of the auricle. Green area originates from the first pharyngeal arch and red area originates from the second pharyngeal arch.
2.3. Microtia

2.3.1. Definition

*Micro* is a Greek word meaning small and *otia* means ear related status. Thus microtia means congenitally small auricle (pinna), with or without structural abnormalities. Anotia is an extreme case of microtia where no normal ear structures are present. There is a wide range in size and shape of the normal human ear and thus a slightly small ear without structural deviations should be distinguished from real microtia (Marx et al. 1926). Also minor dysplasias, such as cup ear, protruding ears, isolated tragal and lobular abnormalities are not considered to be microtia.

2.3.2 Classification

In order to characterise the severity of microtia, many grading systems have been developed. It would be important to have some uniform classification system in order to define diagnosis, standardize research results and to improve treatment protocols.

Hermann Marx’s microtia classification, published in 1926, was the first and has been one of the most widely used. He designated three categories: grade I microtia is characterized by an abnormally small auricle with all identifiable landmarks, grade II microtia consists of an abnormal auricle without some identifiable landmarks, and grade III microtia is recognized only by a small auricular remnant. According to Marx’s original classification, the mildest form of microtia (Marx grade I) structural abnormality was not an obligatory criterion. In addition, the definition for the normal size of the auricle was imprecise. Anotia (Marx grade IV) was not included in the original classification (Marx et al. 1926). Marx microtia grades are presented in Figure 4.
In 1957, Finnish otolaryngologist Y. Meurman grouped microtia into four categories. Type I: the auricle is small and retains most of its normal structure (the external auditory meatus is usually present). Type II: the auricle is moderately anomalous and can be hook, S, or question mark shaped in appearance. Type III: the auricle is a rudimentary soft tissue structure with no cartilage. Type IV: anotia, where all auricular structures are absent. Meurman’s classification is more precise and comprehensive than Marx’s classification when distinguishing between a normal small ear and microtia, and when considering the most extreme cases of anotia (Meurman, 1957).

In 2009, Hunter and co-authors provided a classification system for microtia. Their classification is a mixture of those done by Marx and Meurman, but as a new aspect they included the actual size of the auricle in the classification. The criterion for microtia is fulfilled if the median longitudinal length of the auricle is more than 2 SD below the mean (Hunter et al. 2005).

Another aspect used to classify microtia is surgical planning. A rough allocation based on the lobulus or concha type microtia is a justifiable classification scheme because the surgical method is different with these two variations. The pioneer of modern microtia surgery, R.C. Tanzer, classified ear abnormalities based on the surgical approach. In his grading system, type 1 is anotia, type 2 is divided into a) microtia with auricular canal

**Figure 4.** Microtia in order of severity, Marx’s grades I-IV.
ataresia and b) without auricular canal atresia. Tanzer’s grading is not confined to microtia. In his types 3-5, hypoplasia of the middle or upper third of the auricle and prominent ear are also included (Tanzer, 1978). One of the ear reconstruction pioneers Satoru Nagata has adapted this classification according to the surgical approach to lobular type that corresponds to Marx III and small concha type that corresponds to Marx II. Additionally, small concha type microtia, anotia and atypical microtia are sorted out in his classification (Nagata, 2000).

2.3.3. Birth defects

Structural defects (congenital malformations, disruptions and dysplasias) are a major cause of infant mortality, childhood morbidity and long-term disability. They are a major cause of fetal and newborn death. To investigate and prevent the burden of birth defects, register-based surveillance programmes have been introduced. The aim of surveillance programmes is to provide epidemiologic information on congenital anomalies. This enables a warning system for new teratogenic exposures. In addition, international programmes can be utilized to evaluate the effectiveness of primary prevention and to assess the impact of prenatal screening (www.eurocat-network.eu/aboutus/whatiseurocat).

The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) is a voluntary non-profit international organization affiliated with the WHO. The organization was established in Helsinki in 1974. The Clearinghouse collects information on birth defect surveillance and research programs from around the world (www.icbdsr.org).

EUROCAT (European surveillance of congenital anomalies) can be considered a European WHO Collaborating Centre for the Clearinghouse. This population-based data is collected from 43 registries in 23 countries in Europe, including Finland. Live births, fetal deaths, still births, terminated pregnancies because of fetal anomaly following prenatal diagnosis are all included in the data. Overall more than 1.7 million births are surveyed per year covering almost 30% of the European birth population (www.eurocat-network.eu).

In addition to the Clearinghouse and EUROCAT, there are also other programs gathering data from national registers.
Most of the microtia surveillance programs are population-based (such as EUROCAT), where information is derived from birth defect registers and usually includes live and stillbirths. In addition, a few programs are hospital-based, where information is gathered from distinct hospitals rather than population registers. The advantage of a hospital based register is that more uniform inclusion and diagnostic criteria are used when assessing features of the disease or clinical condition.

### 2.3.4. Prevalence

Based on register studies, the overall global prevalence for microtia is around 2.1/10,000 (Luquetti et al. 2011). However, there is great variation among different registers. The highest reported prevalence is over 20 times higher than the lowest, ranging from 0.83 to 17.4/10,000 births. Forrester and Merz (2005) reported that Far East Asians, Pacific Islanders and Filipinos have greater prevalence than Caucasians. Quito of Ecuador is exceptional, representing the highest prevalence, 17.4/ 10,000, as mentioned above (Castilla and Orioli, 1986).

Variation in prevalence may sometimes partly result from methodological factors. In a recent review by Luquetti et al. (2011), it was observed that microtia prevalence was higher in hospital-based and active ascertainment surveillance programs. However, the difference between population and hospital register settings was insignificant and the prevalence rates can be compared with each other. Thus the range in the prevalence of microtia is so clear that it also refers to real differences and cannot be explained by methodological factors. Examples of the prevalence of microtia are presented in Table 2.

**Table 2.** Examples of the prevalence of microtia extracted from the literature.

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence of microtia per 10,000 births</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central-East France</td>
<td>0.8</td>
<td>Harris et al 1996</td>
</tr>
<tr>
<td>Sweden</td>
<td>2.4</td>
<td>Harris et al 1996</td>
</tr>
<tr>
<td>Hawaii (USA)</td>
<td>3.8</td>
<td>Forrester &amp; Merz 2005</td>
</tr>
<tr>
<td>Texas (USA)</td>
<td>2.9</td>
<td>Canfield et al 2009</td>
</tr>
<tr>
<td>Quito in Equador</td>
<td>17.4</td>
<td>Castilla et al 1986</td>
</tr>
</tbody>
</table>
2.3.5. Risk factors

In population studies, many risk factors for microtia have been suggested. Both environmental and genetic factors may predispose to the occurrence of microtia.

Drugs

Drugs, such as retinoids, thalidomide and mycophenolate mofetil (immunosuppressant) are known risk factors for microtia (Anderka et al., 2009). The exact mechanism is not known. Folic-acid intake during pregnancy seems to reduce the risk of microtia among non-obese women (Ma et al. 2010).

Altitude

High altitude may be a risk factor (Castilla et al. 1999). In high altitude cities such as Quito (altitude 2800 m), La Paz (3250-4100 m) and Bogota (2600 m) the prevalence of microtia is substantially higher than in other locations. Ethnicity and nutritional factors (i.e. agriculture at high altitudes) may confound these results.
Ethnicity

Population studies performed in the United States report variations in prevalence according to race with a higher risk for individuals of Asian heritage, Pacific Islanders and individuals of Hispanic descent when compared to Caucasians and African-Americans. The ethnicity-based risk for microtia seems to be higher in isolated cases (Harris et al. 1996; Shaw et al. 2004; Forrester and Merz, 2005; Canfield et al. 2009). Castilla et al. (1986) used data that is not solely population-based and reported higher microtia prevalence for Ecuadorians (Castilla and Orioli, 1986). These variations might be in part due to genetic variation, environmental factors or a combination of gene-environment interactions.

Inheritance

Estimations of familial microtia range from 3-34% (Mastroiacovo et al. 1995; Llano-Rivas et al. 1999). Both autosomal dominant and recessive traits have been described (Llano-Rivas et al. 1999; Tasse et al. 2005). Tasse and co-authors reported a positive family history in 5/53 microtia patients. In addition, they reported that patients with familial disease are more often bilaterally affected (Tasse et al. 2005).

Other risk factors

In addition to race, drugs and high altitude, numerous risk factors have also been suggested. For example, male sex, low birthweight (<2500 g), first parity, high parity, high paternal age and low maternal education are mentioned as general risk factors (Castilla and Orioli, 1986; Mastroiacovo et al., 1995; Harris et al., 1996).

2.3.6. Characteristics

The severity of microtia varies greatly. The diversity of both grading systems and clinical assessment have impact on accuracy in evaluating microtia. Marx grade I may be over or...
underdiagnosed, grades II+III are occasionally pooled and anotia is not always separately reported. Marx’s grades I and IV form minorities in most reports. In a well-designed and reported study by Mastroiacovo et al. (1995), the proportion of Marx grade I was 20 %, grade II-III was 60 % and grade IV was 20 % (Mastroiacovo et al. 1995). In two other reports, the proportion of anotia is considerably less at under 10% (Harris et al. 1996; Forrester and Merz, 2005).

Most microtia cases are unilateral (79-91%) and there is a right-side dominance. Approximately 60% of unilateral microtia is right-sided. This is an exceedingly uniform observation in the literature and a definite explanation for this has not been reached. In 9-21 % of patients, microtia is bilateral and some of these cases are asymmetrical (Mastroiacovo et al. 1995).

In population studies, there is a clear male predominance for microtia. This predominance varies between 58-64% and cannot be explained by register-based artefacts. The reason for this higher prevalence amongst males remains unknown (Mastroiacovo et al. 1995; Harris et al. 1996; Okajima et al. 1996; Forrester and Merz, 2005).

External auditory canal atresia is associated with microtia in 55-92 % of cases (Castilla and Orioli, 1986; Okajima et al. 1996; Llanorivas et al. 1999). Atresia means the absence of the ear canal. There is variation in the magnitude of the atresia. It can be mostly bony, constituting a very thick barrier, or it can be a relatively thin layer of soft tissue. Narrowing of the canal is called stenosis, which is seen (or reported) less often in association with microtia. High-resolution computed tomography (HRCT) is the best way to evaluate the status of atresia and the middle ear (Kountakis et al. 1995). In a Japanese study, there is highly significant correlation between microtia grade and external auditory canal existence (Table 3) (Ishimoto et al. 2005).

Table 3. Correlation between microtia grade and external auditory canal atresia. N=142 ears.

<table>
<thead>
<tr>
<th></th>
<th>Marx I</th>
<th>Marx II</th>
<th>Marx III</th>
</tr>
</thead>
<tbody>
<tr>
<td>External auditory canal atretic,%</td>
<td>42</td>
<td>67</td>
<td>91</td>
</tr>
</tbody>
</table>
The reported prevalence of syndromic microtia is 15-75%. If no other anomalies are found, the microtia is interpreted as being "isolated" (Castilla and Orioli, 1986; Shaw et al. 2004). The defects most frequently associated with microtia are mandibular hypoplasia, cardiac defects, orofacial clefts, facial nerve palsy, anophthalmia or microphthalmia, limb defects, urinary tract and kidney defects and brain anomalies (Celia et al. 1989; Mastroiacovo et al. 1995; Harris et al. 1996; Forrester and Merz, 2005).

2.3.7. Syndromes

Oculo-auriculo-vertebral spectrum (OAVS) is a cluster of clinical findings characterized by facial asymmetry, microtia, ear and facial skin tags, epibulbar dermoids in the eyes, microphthalmia, and occasionally macrostomia. Hemifacial microsomia (HFM) and Goldenhar syndrome can be considered to represent different degrees of this spectrum. OAVS is likely to have heterogeneous etiology and most cases seem to be sporadic, but familial cases have also been reported (Vendramini-Pittoli et al. 2009). Craniofacial findings of OAVS are thought to be caused by failure in the development of the first and second branchial arch derivatives (Tasse et al. 2005). Extracranial features include renal, cardiac, and vertebral anomalies (Digilio et al. 2008). Some authors classify isolated microtia as the mildest form of OAVS. Tasse et al. (2005) suggest that even a preauricular tag or pit in a family member of the microtia patient is a diagnostic basis for OAVS, as coincidental finding is unlikely.

A syndrome can be defined as a combination of signs and symptoms that are indicative of a particular disease or disorder (Collin’s English Dictionary, 2003). Contrary to a syndrome, a spectrum is defined as a broad range of varied but related objects that form a continuous series or sequence (Random House Kernerman Webster's College Dictionary, 2010). In the mildest form of OAVS there can be only one clinical finding, microtia (or preauricular tag/pit). On the other end of the spectrum, the most severe cases of OAVS (Goldenhar) fulfill the criteria for a syndrome. Thus spectrum is the most inclusive and applicable term to describe OAVS.

In addition to OAVS, microtia is associated with a huge variety of rare syndromes. Roughly 10% of microtia patients have a known syndrome (excluding OAVS that was discussed...
of which Treacher Collins is perhaps the most widely known example. CHARGE, Nager, Klippel-Feil, Branchio-Oto-Renal syndrome are the other syndromes most frequently mentioned in the literature.

2.3.8. Genetics

There are no individual genes identified as causing isolated microtia. However, several genes have been identified as being associated with syndromic microtia.

**Homeoboxes (HOX)** are DNA sequences that are associated with cell differentiation and are important in embryogenesis. In animal studies HOXA1, HOXA2 and HOXB1 are found to be involved in the development of craniofacial structures. Mutations in these genes may result in failure to form the neural crest cell streams needed in the development of the 2nd pharyngeal arch. This in turn results in deficiencies in forming both 2nd arch and pouch derived tissues, as well as 1st arch and 3rd pouch derivatives (Rossel et al. 1999). In humans, inner ear malformations and deafness are frequently caused by HOXA1 mutations, with external ear malformations being less frequent (Bosley et al. 2008). A mutation in the HOXA2 homeobox gene has recently been identified in an Iranian family with grade II microtia and partial palatal cleft (Alasti et al. 2009).

**Treacher Collins syndrome (TCS)** is a craniofacial disorder that follows autosomal dominant inheritance. The TCOF1 (Treacher Collins-Franceschetti 1) gene encodes a protein called Treacle. In animal studies, the miscoding of Treacle has led to down-regulation of neural crest cell proliferation and high level of apoptosis. A reduction of the number of these cells at a critical time in embryogenesis leads to the malformations typical for TCS. In about 80% of human patients, TCS is caused by heterozygous mutations of the TCOF1 gene. The phenotype typically includes bilateral microtia and hypoplasia of the facial bones, especially the mandible and zygomatic complex. In the eyes, downward slanting of the palpebral fissures with notching of the lower eyelids is also very typical. Palatal cleft is present in about 28% of cases. The phenotype varies, ranging from mild occasionally unaffected mutation carriers, to severe forms leading to intrauterine death (Dixon et al. 1991; Edwards et al. 1997; Trainor et al. 2009; Beygoa et al. 2011).
Branchio-oto-renal syndrome (BOR) is an autosomal dominant disorder characterized by branchial cleft abnormalities, otic developmental defects and renal malformations. The associated EYA1 (Eyes absent 1) gene codes the corresponding protein. EYA1 is required for normal pre-placodal ectoderm and placodal neuron formation. EYA1 mutations may result in malformation of the otic placode and inner ear dysfunction. External ear findings are mild, mostly prominent or cup ears (Li et al. 2010). Microtia as such has not been reported, but is suspected (Gupta and Patton, 1995).

Mutations in the SALL1 (sal-like 1) gene may lead to the rare Townes-Brocks Syndrome (TBS) with anal, auricular and thumb malformations. External auricular anomalies in TBS typically include small ears with an overfolded superior helix and a small antihelix, with preauricular tags. Middle ear abnormalities are reported, but hearing loss is predominantly sensorineural (Powell and Michaelis, 1999).

Chromosomal abnormalities associated with microtia are also detected, such as trisomy of chromosomes 13, 18 and 22. Rearrangements, microdeletions and hereditary genomic copy number variants have also been found along with microtia (Alasti and van Kamp, 2009).

2.4. Microtia, the middle ear and hearing

2.4.1. Hearing impairment in microtia

Conductive hearing loss

External auditory canal atresia and middle ear anomalies are frequently (80-90%) associated with microtia causing conductive hearing loss in the affected ear (Llano-Rivas et al. 1999; Kelley and Scholes, 2007). If the ear canal is atretic, the soundwaves cannot enter the middle ear normally. On the other hand, the vibrating elements (the ear drum and ossicles) may be abnormal and soundwaves are hindered while entering the inner ear. Hearing evaluation with audiometry is an important part of assessing a patient with
microtia. Hearing thresholds are typically between 55-65 dB HL, while a normal level is 0-20 dB HL. Ishimoto et al. (2007) evaluated the relationship between hearing level and temporal bone abnormalities in patients with microtia. As a conclusion, the hearing level in microtic ears correlated with the formation of oval/round windows and ossicular development, but not with the degree of middle ear aeration, or severity of microtia. Even mild microtia with mild external auditory canal stenosis can be associated with severe conductive hearing loss due to ossicular anomalies.

Sensorineural hearing loss

All of the inner ear derivatives build up from ectodermal otic placode and develop separately from the external and middle ear structures. Thus, the prevalence of sensorineural hearing loss (SNHL) is rather infrequent among microtia patients. In a series by Carvalho et al. (1999), SNHL was present in 11% of the children with hemifacial microsomia. It is significantly higher than the 0.1% to 0.4% incidence of congenital SNHL or the 3% to 4% incidence of sensorineural hearing loss seen in patients with other craniofacial syndromes (Carvalho et al. 1999). In two other studies, the proportion of SNHL among microtia patients was 3.4-5.6 % (Eavey, 1995; Llano-Rivas et al. 1999). Bisdas et al. studied inner ear abnormalities among 14 Goldenhar syndrome patients and found 5 patients (36%) with sensorineural hearing loss (Bisdas et al. 2005).

2.4.2. Middle ear findings in microtia and aural atresia

The same embryological origin and timing during embryogenesis is a sensible explanation for coincidental malformation of the external and middle ear. The availability and accuracy of imaging, especially HRCT has made it possible to investigate middle ear findings among microtia patients.

Mayer et al. (1997) studied 184 temporal bones of 92 children with microtia. They found that the malleus or incus were dysplastic in half of the cases among patients with microtia (Marx) grade I-II, and 98% of the Marx grade III patients. The stapes was dysplastic or absent in 52% of grade I-II patients and in 71% of grade III patients. The oval window was occluded in 36-41% of cases and there was no correlation with microtia grade. Middle ear
space is typically reduced in microtia. The course of the facial nerve may be abnormal. The tympanic segment may be located caudally and the mastoid segment may be located anteriorly compared to the normal course (Mayer et al. 1997; Ishimoto et al. 2005).

2.4.3. Candidacy for hearing restoration surgery

Jahrsdoerfer et al. (1992) published an important and widely cited report called “Grading system for the selection of patients with congenital aural atresia”. The goal of the grading system is to select those patients who have the greatest chance of success in atresia and middle ear surgery, where success is defined as a postoperative speech reception threshold of 15 to 25 dB HL. The grading scheme is based on the preoperative temporal bone CT scan and the appearance of the external ear. Patients get a score consisting of points between 1 and 10. The objects that correspond to the points are presented in **Table 4**.

**Table 4.** Grading Scale Score for Congenital Aural Atresia by Jahrsdoerfer et al. (1992).

<table>
<thead>
<tr>
<th>Anatomical structure</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stapes bone</td>
<td>2</td>
</tr>
<tr>
<td>Oval window open</td>
<td>1</td>
</tr>
<tr>
<td>Middle ear space</td>
<td>1</td>
</tr>
<tr>
<td>Facial nerve</td>
<td>1</td>
</tr>
<tr>
<td>Malleus-incus complex</td>
<td>1</td>
</tr>
<tr>
<td>Mastoid pneumatization</td>
<td>1</td>
</tr>
<tr>
<td>Incus-stapes connection</td>
<td>1</td>
</tr>
<tr>
<td>Round window</td>
<td>1</td>
</tr>
<tr>
<td>External ear</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>
The better developed the external ear, the better developed the middle ear. This is the conclusion made by Stilianos et al. (1995) when they analyzed 199 ears with microtia and aural atresia, and 25 patients with aural stenosis without microtia. The average Jahrsdoerfer atresia score was 8.5 with Marx grade I microtia, 7.2 with grade II microtia and 5.9 with grade III microtia. In cases with canal stenosis without microtia, the average atresia score was 8.3.

To determine the predictive ability of the Jahrsdoerfer score in congenital aural atresia surgery, Shonka et al. (2008) evaluated 108 patients with aural atresia (116 ears). They compared the preoperative Jahrsdoerfer score (1-10 points) with the postoperative pure-tone averages and speech reception thresholds. Ears scoring 6 or less had a 45% chance of achieving a postoperative speech reception threshold of 30 dB HL or better, while ears scoring 7 or higher had an 89% chance. They also found that lack of middle ear aeration was the only anatomical factor predictive of a poor audiometric outcome. They state that the Jahrsdoerfer grading scale is an invaluable tool in the preoperative evaluation of patients with congenital aural atresia (Shonka et al. 2008).

2.4.4. Hearing aids and microtia

The typical hearing impairment in microtia is conductive. The inner ear itself is usually normal. Thus an appropriate sound amplification technique gives good audiologic outcomes.

Air conduction hearing aids

If there is only stenosis of the external auditory canal, the conventional air conduction hearing aid may be usable if the required anatomy of the external ear is present. The two main divisions are behind-the ear (BTE) and in-the-ear (ITE) hearing aids. The fitting has to be made on an anatomic and audiologic basis. In the overall rehabilitation, concept a
Bone conduction hearing aids

In most microtia patients, the external auditory canal is atretic and the anatomy of the pinna is so obscure that a conventional air conduction hearing aid cannot be used. As such, one of the three bone conduction hearing aid systems may be an option: 1. conventional: the bone conduction oscillator is compressed against the skin with a headband or with the earpiece of the patient’s eyeglasses, 2. transcutaneous: a magnetic plate is implanted in the temporal bone under the skin and a second magnet holds a transmitter in place on the outside of the skin, and 3. percutaneous: a titanium screw is fixed in the skull and it permanently penetrates the skin. An oscillator is then attached to the end of the screw (bone anchored hearing aid). The simplified structure of these devices includes a microphone, a sound amplifier and a transducer (bone conduction oscillator) (Paula et al. 2007). The microphone picks up the sound and converts the mechanical vibration into an electric signal and after modulation and amplification, the transducer converts the electric signal into bone vibration.

Bone-anchored hearing aid

The percutaneous model is also called bone-anchored hearing aid and is the most widely used apparatus among microtia/atresia patients. A percutaneously bone-anchored hearing aid has good compliance and audiologic results. The implantation site of the bone-anchored hearing aid is the temporo-occipital bone behind the pinna. This is both cosmetically and audiologically an appropriate area. In children the limiting factor is often the thickness of dense cortical bone in the temporo-occipital region and patients that are less than two years of age have been held as contraindication (Textbook of Audiological Medicine, 2011). According to the FDA, bone-anchored hearing aid is specifically used for patients over five years of age in the United States. However, even 14 months old children have been successfully implanted with a bone-anchored hearing aid. Davids et al. (2007) studied 20 children under 5 years of age implanted with bone-anchored hearing aid and compared them to 20 implanted children older than 5 years. They conclude that 2-stage...
implantation of bone-anchored hearing aid is safe and successful in younger children and has comparable audiologic outcomes and traumatic device failures and/or revisions to what is achieved in older children. There should be an appropriate delay between the titanium fixture implantation and the hearing-aid placement to allow for good osseointegration.

A bone-anchored hearing aid has several advantages over other bone-conduction hearing aids, such as the elimination of audio feedback, headband pressure and the instability of vibrator positioning. Additional benefits include improvement in high-frequency response and reduced distortion. The complication rate is low and patient satisfaction is high among bone-anchored hearing aid users in general. (Dutt et al. 2002; Badran et al. 2006; Davids et al. 2007).

Other hearing devices

There are also other hearing devices suitable for microtia patients. Middle ear implants, such as a Vibrant Soundbridge® (Med-El), have given satisfactory results. The floating mass transducer (FMT) of this device can be attached to the long process of the incus or round window, where it converts electric signal into vibration. When planning for a middle ear implant, the status of the middle ear should be carefully examined with HRCT (Roman et al. 2012).

New applications of old inventions are also introduced. Bonebridge™ (Med-El) is a transcutaneous implantable device, where an external audio processor is held in place directly above the implant by a magnet. The sound is converted into an electric signal, which is then transferred through the skin to the implant embedded in the temporal bone. The implant converts the signal into mechanical vibration, which is then conducted to the inner ear. Also, other devices based on bone conduction without a skin-penetrating abutment are available and have shown promising results in the pediatric population (Håkansson et al. 2008; Doshi et al. 2012).
2.5. Surgical reconstruction of microtia

According to the literature, an Italian surgeon Tagliacozzi described and illustrated repairing ear deformities with skin flaps from behind the auricle as early as 1597 (Tagliacozzi, 1597). The first mention of costal cartilage use in ear reconstruction is in 1919. This publication by H. D. Gillies (1920) is mostly based on selected cases of war injuries of the face. Gillies also repaired over 30 microtic ears with rib cartilage harvested from the patient’s mother. These allografts were found to progressively resorb (Gillies, 1937; Converse, 1977).

2.5.1. Autologous costal cartilage reconstruction

The established method of choice in microtia reconstruction is based on the autologous costal cartilage graft procedure introduced by RC Tanzer in 1959. His method has been the basis for the later and most widely used methods published by Burt Brent and Satoru Nagata (Tanzer, 1959; Brent, 1980; Brent, 1992; Nagata, 1993).

Brent has developed a reconstruction method consisting of 4 stages as follows: 1. harvesting the rib cartilage, sculpturing the pinna framework and inserting the cartilage beneath the auricular skin, 2. lobulus transposition, 3. elevation of the framework and covering of the posterior surface by a skin graft taken from the hip region and 4. tragus construction. The time interval between these stages is several months.

Nagata uses a two-stage procedure in which the first stage involves the harvesting of the costal cartilage, the fabrication of the 3-dimensional frame and the insertion of the frame under the skin to its terminal position. The second stage consists of the elevation of the pinna and the insertion of a cartilage block to support this protrusion. Instead of a free skin graft, Nagata uses a split-thickness temporoparietal fascia flap to cover the exposed posterior area of the pinna (Nagata, 1993). In addition to Brent and Nagata, many other surgeons have made several modifications of these operative techniques.

The appropriate age for microtia reconstruction varies, but certain physical and psychological factors should be considered. There is usually sufficient rib cartilage
available for reconstruction by the age of six if the surgeon uses the Brent technique. The patient should be aware of the problems and the surgical solution and thus be prepared for good co-operation. The most typical age to begin the surgery is 6-7 years for Brent (Brent, 1992). The auricle has almost reached adult size around 10 years of age. In Japan 10 year is the recommended age to start the surgery. The amount of costal cartilage in the Nagata technique should be sufficient at that age (Nagata in the book: Plastic Surgery: Indications, Operations, and Outcome, 2000). As live tissue, a reconstructed ear will propably grow after the implantation (DellaCroce, 2001).

2.5.2. Alloplastic reconstruction

In addition to autologous materials, alloplastic materials have also been used in auricular frameworks.

Silicone seems like an ideal material for auricular reconstruction. However, it is too sensitive for minor traumas, causing skin erosion, necrosis and extrusions of the frame. Thus, the use of silicone for auricular frameworks has been abandoned.

A high-density porous polyethylene framework (Medpor®) has been used for 20 years in ear reconstruction. With improved implant design and complete coverage of the implant with adequate skin and fascia flaps, the complication rate has diminished and long-term results are acceptable (Romo 3rd and Reitzen, 2008; Reinish and Levin, 2009). In addition to the auricle, Medpor® is widely used in the craniofacial area, such as the nose, maxilla and orbita (Cenzi et al. 2005). The porous material becomes vascularized and collagen is deposited on the surfaces. Porous polyethylene may provoke inflammation, but according to the literature the major complication rate is acceptable and equals that of costal cartilage reconstruction. Donor site morbidity, such as pain and a visible skin scar are avoided by using alloplastic material. With synthetic material, surgical time may be reduced and material fabrication is easier and more standardized. Some clinics prefer costal cartilage, while others accept synthetic materials, mainly Medpor®, as a good alternative (Williams et al. 1997; Zhao et al. 2009). Prospective studies, with independent evaluation of the results could not be found.
2.5.3. Ear epithesis

A missing auricle or part of the auricle can be substituted by a prosthesis (epithesis). The prosthesis is not an intracorporeal implant and it is not vulnerable to bioincompatibility factors. Thus, the materials of the prosthesis can be chosen on the basis of manageability and durability. Silicone, acrylate compounds and polyurethane are the commonly used materials. Silicone is the main corpus of the prosthesis and other materials are added to give support for the integration and coating that enhances durability. Ear prostheses can be attached by adhesives or titanium osseo-integrated implants. The adhesives may be troublesome in a hot and humid climate, when the patient has an oily skin type and when there is a lot of hair in the area of installment. Titanium implants require surgery and follow up. The lifespan of the prosthesis is currently a few years due to color fading, delamination of the lining and possible accidental cracks. One advantage of a prosthetic ear is a good anatomic replication of the normal ear. Surgery is rather straightforward: it is single-stage and the complication rate is small (Tollefson, 2006; Wagenblast et al., 2008; Fini et al., 2011).

An important decision to be made is whether to reconstruct an ear with cartilage or implant an epithesis. Unsuccessful ear reconstruction with cartilage graft can almost always be converted into a prosthesis repair (Katzbach et al. 2006). However, osseo-integration of the titanium bridge for ear epithesis causes scarring and may hinder future reconstruction with cartilage and skin/fascia flaps. In treatment centers with extensive experience in rib cartilage ear reconstruction, a prosthesis implantation with osseo-integration is often only a secondary choice (Thorne et al. 2001).

Westin et al. (2009) studied the safety and quality of osseointegrated epitheses. Ninety-nine Swedish patients, of which 8 were bilateral (107 prosthetic ears), were followed for a period ranging from 1 to 12 years. The incidence of significant skin reaction was only 3%. They concluded that the surgical technique for auricular prostheses is simple and is associated with a low rate of perioperative and late complications. Aesthetic satisfaction was high and 95% of the patients were wearing their prosthesis every day, in most cases over 10 hours per day.
2.5.4. Tissue-engineering

Tissue engineering aims to use a combination of living cells, engineered materials, and suitable biochemical factors to produce biological materials that are used to replace missing or damaged tissues. As an example, cartilage cells harvested from the auricle can be cultured in an appropriate cell culture media with growth factors and be supported by an ear shaped biocompatible polymer scaffold.

Kamil et al. (2004) succeeded in creating a tissue-engineered human-sized auricle of normal anatomic definition in an immunocompetent animal model using a mold technique. Mixtures of autogenous chondrocytes and biodegradable polymers were used inside a perforated, auricle shaped hollow gold mold. These molds were implanted subcutaneously in the abdominal area of 10 animals (pigs and sheeps). The constructs were then removed after 8 to 20 weeks for a gross morphology and histology analysis. They concluded that the technique appears promising for potential use in patients with microtia.

In a recent study by Reiffel et al. (2013), three-dimensional (3D) photogrammetry was utilized to create a copy of the human auricle. This 3D mold was then copied and filled with bovine chondrocytes, culturing media and a collagen type I scaffold. After a few days of culturing, these constructs were implanted in the dorsum of athymic nude mice. The implantation constructs were harvested and surveyed 1 to 3 months later. The histological and biomechanical properties were examined. As a conclusion, they created a biocompatible and anatomically patient-specific construct with appropriate biomechanical properties. Before the use of patient-specific chondrocytes or mesenchymal stem cells can be in clinical use, a lot of research has to be done. In their study, the new findings established that the use of 3D photogrammetry and collagen type I as a scaffold material was a promising development.

Yanaga et al. (2009) have developed a multilayer chondrocyte culture technique and have successfully generated human ears. In their culture system, fibroblast growth factor-2 (FGF2) has been added to the culture medium to make cells multiply and expand. In two-stage implantation, the cultured chondrocytes are injection-implanted into the lower abdomen of the patient, where the cells grow into a larger cartilage block in 6 months. This
grown and matured cartilage is harvested surgically. Thereafter it can be sculptured into an auricular framework and be used the same way as the costal cartilage. In the first series they reported auricular reconstruction for four microtia patients using this technique (Yanaga et al. 2009). In a recent report, Yanaga et al. (2012) explained their culturing and implantation method in more detail. When the multilayered chondrocytes are transplanted into the abdominal subcutaneous tissue, the neocartilage and neoperichondrium of elastic cartilage origin are regenerated within 6 months after the transplantation. In dynamic measurements, the regenerated cartilage had the same viscoelasticity as normal auricular cartilage. So far, 12 microtia patients have been implanted with an auricular framework made of tissue-engineered neocartilage. In the 6 year period of postoperative monitoring, the neocartilage has maintained a good shape. No absorption has been noticed. They suppose that this culturing and implanting technique can have many applications in reconstructive and craniofacial surgery where cartilage is needed as a support or defect substitute (Yanaga et al. 2012).
3. Aims of the study

1. Characterization of microtia in the Finnish population and comparisons to other populations.

2. To study the inheritance of microtia in the Finnish population and compare possible phenotypic differences between sporadic and familial microtia patients.

3. Analysis of the learning curve and patient satisfaction with reconstructive surgery for microtia.

4. Detection of correlations between auricular malformations and cleft lip and/or palate in Finnish cleft patients.
4. Materials and methods

This thesis constitutes an entirety that assesses and discusses microtia in the Finnish population and as a medical condition in general. The characterization, inheritance and surgical treatment of microtia are reported in three (I-III) original studies. The association of microtia and other external ear malformations with orofacial clefting is the main focus of the fourth original paper (IV). In this section, the general design and implementation of each study are explained. The Roman numerals in the brackets (I-IV) indicate a connection to a particular study.

4.1. Patients

The first step was to evaluate the clinical data of 200 microtia patients referred to the Cleft and Craniofacial Center of the Department of Plastic Surgery at Helsinki University Central Hospital between 1980-2005. In order to study isolated microtia, patients with chromosomal abnormalities and syndromic patients were excluded, thus leaving us with 190 microtia patients. Hospital records from the Cleft and Craniofacial Center and central hospitals in Finland for 190 patients, facial photographs for 162 patients and audiograms for 70 patients constituted the data used for analysis.

A detailed questionnaire was sent to all 190 patients. It concerned questions on physical and mental health, number of relatives, birthplaces of grandparents/parents, relatives with microtia or other malformations of the facial or auricular region. 109 patients (or parents) (57%) replied to the questionnaire. The hospital records and patient questionnaire derived data constituted the basis for studies I and II.

The inclusion criteria for the third (III) study were: unilateral, non-syndromic, Marx grade III (lobulus type) microtia. In addition, postoperative photographs were essential because surgical results were assessed by a panel and by patients themselves. All auricular reconstructions were performed by a single surgeon. Following these criteria, the study population consisted of 51 patients with a reconstructed auricle. The majority of these 51 patients are also included in the studies I and II.
The vast majority of the treatment of patients with cleft lip or cleft palate in Finland is centralized in the Cleft and Craniofacial Centre at the Helsinki University Central Hospital. As well, the majority of patients with other craniofacial malformations, including ears, are treated and examined in this institution.

The Cleft and Craniofacial Centre at the Helsinki University Central Hospital has collected prospective data on cleft patients since 1995 and retrospective data since 1950. From this register consisting of almost 8200 cleft patients, we searched for all patients with an external ear malformation and either cleft lip with or without cleft palate (CL±P) or cleft palate (CP). The hospital records were examined and altogether 100 patients were identified for further analyses in the fourth (IV) study. 66 patients had CP and 34 CL+/−P. There were 43 cleft patients with microtia and unlike in studies I-III, syndromic patients were also included. Other 57 patient had preauricular skin tags, prominent ears or miscellaneous ear malformation.

4.2. Study design

The 190 microtia patients were assessed for laterality, sex distribution, aural atresia or stenosis, and preauricular sinuses or tags. The hearing results for these patients were also registered. Patients were also classified according to Marx’s and Tasse’s classifications and the results of the classification scores were compared to identify correlation between these classification systems.

The Finnish Register of Congenital Malformations (RCM) was the source for identifying the prevalence, laterality and sex distribution of microtia in the Finnish population in general. The register is national and population-based. Stillbirths of 22 weeks of gestation or 500 g or more are registered. Statistics from 1993 to 2005, consisting of 771 425 births, were available to our study.

The information obtained from RCM was compared to the other population based register reports based on literature searches (I).

We surveyed individuals who reported a relative with microtia or preauricular tag. These individuals were classified as representing familial microtia (n=22). The phenotypic data of
these familial cases was compared against patients with no known relatives with microtia or preauricular tags (n=80). All the familial patients (or parents) were telephone interviewed. Familial patients (or parents) were also asked about the birthplace of their grandparents to identify regional clustering and a possible founder effect. If the birthplace of the grandparents were not known, parents were used instead (II).

The outcome of the microtia reconstruction was evaluated by the panel made up of three ear, nose and throat specialists and three reconstructive surgeons. Postoperative photographs (Figure 5) were shown to the panel in randomized, nonchronologic order and six panel members assessed the result using a scale of 1 to 10. The ratings of the panel were merged to generate the learning curve of a single reconstructive surgeon (III). In addition to the panel, 22 patients responded to a questionnaire based on their feelings about their reconstructed ear on a scale of 1 to 10. These patients formed the self-assessment group.

In the study concerning clefts and ear malformations (IV), we collected data concerning gender, birthplace, birthweight and length, gestational weeks, gestation problems, type of cleft, site of cleft, type and severity of ear malformation, audiometrics, imaging, chromosomal analyses, other anomalies or diseases, cleft operations, number of siblings, and anomalies among family members. Facial or lateral photographs of 62/100 patients were available for the analysis. According to the severity of the cleft, patients were divided into the subgroups: 1. CL+/-P: cleft lip, cleft lip and alveolus, cleft lip and palate, 2. CP: soft palate, soft and hard palate, submucous palatal cleft.

4.3. Statistical methods

The independent samples t-test is used to compare the means of two independent samples. In particular, it was used in the comparison of the phenotypes of familial and sporadic microtia patients (II).

To test whether independently chosen panel members are sufficiently able to form a reliable assessment group, intraclass correlations (ICC) were calculated (Shrout et al. 1979) (III). The panel results were plotted and moving averages were calculated. In addition, these panel results were split into 5 groups, the mean and the variability of each
group was calculated. The analysis was done by repeated measures ANOVA (III). A paired \( t \)-test was used to compare the self-assessment group and the panel. A two-sample test was used to evaluate the influence of age and gender on the self-assessment group (III). Cross-tabling and chi-square tests were used in the comparison of the external ear anomalies and orofacial clefts (IV).

4.4 Ethical perspectives

All the studies were approved by the Ethics Committee of the Helsinki University Central Hospital.
Figure 5. Example of the postoperative photographs assessed by the panel.
5. Results

5.1. Characterization of microtia (I)

5.1.1. Hospital and patient based characteristics

The severity of microtia was classified according to Marx and the proportions were: Marx grade I (8.4%), grade II (32.5%), grade III (57.6%) and grade IV (1.5%). The median birth weight was 3450 g (range 2050—4600 g, average 3459 g) and the median gestational age was 40 weeks (range 33—42, average 39.6 weeks). 4.6% of children were born preterm and 2.8% had a birth weight of under 2500 g. Congenital heart defects were present in 10.9% and 4.6% had anomalies of the extremities. 23% reported skeletal abnormalities, with scoliosis being the most frequently present. The patients spoke their first single words at the mean age of 13.2 months (range 6-36 months), and they walked unaided at the mean age of 12.2 months (range 8-54 months). A psychomotor developmental delay was reported to be present in 5.5% of the patients. The main characteristics are summarized in Table 5.

Adequate audiometric data was available for 70 patients. Conductive hearing loss was present in 96.1% and sensorineural hearing loss was found in 9.0% of the affected ears. All ears with normal auricles had normal hearing. The detailed hearing results are presented in Table 6.
Table 5. The patient based characteristics of Finnish microtia patients.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>190</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>58 % male</td>
</tr>
<tr>
<td><strong>Unilateral</strong></td>
<td>88.4 %</td>
</tr>
<tr>
<td><strong>Bilateral</strong></td>
<td>11.6 %</td>
</tr>
<tr>
<td><strong>Side of the defect</strong></td>
<td>59.5 % right</td>
</tr>
<tr>
<td><strong>Aural atresia or stenosis</strong></td>
<td>93 %</td>
</tr>
<tr>
<td><strong>Preauricular sinus/tag</strong></td>
<td>33.5 % (22.2 % ipsi, 7.2% contra and 4.2 % bilateral)</td>
</tr>
<tr>
<td><strong>Hearing loss in the affected ear</strong></td>
<td>Conductive 96.1 %</td>
</tr>
<tr>
<td></td>
<td>Sensorineural 9.0 %</td>
</tr>
</tbody>
</table>

Table 6. Hearing loss (PTA) in the affected ears. Classification by the American Speech-Language-Hearing Association. PTA = average hearing threshold for pure tones at 0.5, 1, 2 and 4 kHz.

<table>
<thead>
<tr>
<th>Degree of hearing loss (dB HL)</th>
<th>Proportion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to slightly disabled hearing (0-25)</td>
<td>3.9</td>
</tr>
<tr>
<td>Mild (26-40)</td>
<td>1.3</td>
</tr>
<tr>
<td>Moderate (41-55)</td>
<td>13.2</td>
</tr>
<tr>
<td>Moderate-severe (56-70)</td>
<td>59.2</td>
</tr>
<tr>
<td>Severe (71-90)</td>
<td>21.1</td>
</tr>
<tr>
<td>Profound (91 and more)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

5.1.2. Population-based results

Data obtained from the Finnish Register for Congenital Malformations included 335 microtia patients among 771 425 births (live + stillbirths). This corresponds to a prevalence of 4.3/10 000. Detailed register data is presented in Table 7.
Table 7. Population-based characteristics of microtia in Finland.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>4.3 / 10 000</td>
</tr>
<tr>
<td>Sex</td>
<td>60.9 % male</td>
</tr>
<tr>
<td>Unilateral</td>
<td>84.8 %</td>
</tr>
<tr>
<td>Bilateral</td>
<td>9.0 %</td>
</tr>
<tr>
<td>Side of the defect</td>
<td>63 % right</td>
</tr>
</tbody>
</table>

5.2 Inheritance of microtia (II)

Twenty-two patients of out of 109 had a relative with microtia or a preauricular tag. These patients were classified as familial. In addition, seven patients reported relatives with other craniofacial deformities. No regional clustering indicating a founder effect was detected when the birthplaces of parents or grandparents were analyzed. The proportion of familial microtia was 22/102 (approximately 22 %). The pattern of inheritance seemed to be autosomal dominant with incomplete penetrance.

One-hundred and two (102) patients were included for phenotypic comparison. The familial and sporadic patients did not differ in gestational age, birth weight, psychomotor development, sex distribution or laterality of the affected ear. There was no difference in problems during pregnancy. Scoliosis or congenital heart problems were equally present in both groups. The distribution of the severity of microtia based on Marx classification was relatively equal. Urinary system anomalies were statistically more prevalent among familial patients (p< 0.01).
5.3. Reconstructive surgery for microtia (III)

The objective was to create a learning curve for a single surgeon performing microtia reconstruction. The results were assessed by a panel consisting of six physicians and a self-assessment group of 22 patients.

To test the reliability of the assessment panel, the intraclass correlation (ICC) was calculated. The ICC addresses the uniformity of the panel. The ICC for three ENT specialists was 0.75 and it was 0.86 for the three plastic surgeons. The ICC for all six was 0.90. The target level is 0.80 and thus the reliability of the assessment panel can be considered to be high in this study.

The average number of assessment points given by the self-assessment group was 6.91 and the average number of assessment points given by the panel was 6.59 (scale 1-10). This difference was statistically insignificant. Postoperative patient satisfaction was also evaluated. Females seemed to be more critical (n=6, range 1.0-8.0, mean 5.2, median 5) than males (n=16, range 5-10, mean 7.6, median 8). This difference is statistically significant (p mean = 0.014, p median = 0.025). Patients who were operated under 10 and over 13 years of age did not have a statistically significant difference in their assessment points.

The learning curve of microtia surgery was studied. A single surgeon performed 51 auricular reconstructions. The learning curve created by 51 consecutive moving averages is demonstrated in Figure 6. The moving average is the mean of consecutive means. In this study, five consecutive means were calculated. The moving average smooths out high fluctuation and makes the visual interpretation of the results easier.

In addition to the moving average, 51 patients were split into 5 groups of ten (11 in the last group). The mean number of points in each group was calculated and the results are presented in Table 8. There was a highly significant increasing trend in learning (p=0.000001). This learning trend did not rise constantly. Some improvement was still going on between the last two groups.
**Figure 6.** An example of the learning curve consisting of a continuum of 5 consecutive means for points given by the assessment panel.
Table 8. The mean number of points for groups assessed by the panel.

<table>
<thead>
<tr>
<th>Group No</th>
<th>Mean of points ( SE 0.20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.95</td>
</tr>
<tr>
<td>2</td>
<td>6.83</td>
</tr>
<tr>
<td>3</td>
<td>6.25</td>
</tr>
<tr>
<td>4</td>
<td>6.08</td>
</tr>
<tr>
<td>5</td>
<td>7.41</td>
</tr>
</tbody>
</table>
5.4. The relationships of cleft lip and/or palate and auricular malformations (IV)

Auricular malformations of one hundred patients with cleft lip or palate were studied. The proportion of cleft palate (CP) was 66 % and cleft lip+/-palate (CL+/-P) was 34 %. There was no difference in sex distribution between these groups and this is consistent with the whole Finnish cleft register. There were 48 males and 52 females in the study group.

The ear malformation was bilateral in 47 % (31/66) of the CP patients and 35 % (12/34) of the CL+/-P patients. Cleft lip and unilateral ear malformation occurred on the ipsilateral side in 88% (30/34) of the patients and on the contralateral side in 12% (4/34) of the patients. In 45/100 cases (45%) the combination of cleft and ear malformation was related to a syndrome.

Microtia is almost equally prevalent in both CP and CL+/-P. Skin tags seem to be associated with CL (Figure 7) and especially with CL+/-A (cleft lip with or without cleft alveolus). Prominent ears seem to be associated with isolated CP (Figure 8). The prevalence of microtia seems to increase with the severity of CL+/-P, but there is not a similar association between microtia and CP (Figures 9 and 10). In addition to microtia, skin tag and prominent ears, there were 19 miscellaneous ear malformations, such as macrotia, malposition of the pinna, missing lobulus or cup ear.

The combination of microtia and cleft lip +/- cleft palate was frequently found in both oculo-auriculo-vertebral sequence (OAVS) and Treacher Collins syndrome (TCS). In OAVS, CP is slightly more common than CL+/-P. Of the seven Treacher Collins patients, six had CP and only one patient had cleft lip.

Also other known syndromes were represented in the study population including 22q11.2 deletion syndrome (CATCH22), Klippel-Feil, Pallister-Killian, Pierre Robin sequence, FAS and Turner. In addition, a few patients with syndromic features without definitive diagnosis were included.
**Figure 7.** Proportion (%) of skin tags among all cleft patients (N=100).

**Figure 8.** Proportion (%) of prominent ears among all cleft patients (N=100).
Figure 9. Proportion (%) of microtia among cleft lip patients (N=34).

Figure 10. Proportion (%) of microtia among cleft palate patients (N=66).
6. Discussion

The treatment and careful inspection of a patient with microtia is beneficial. A reconstructive surgeon, an otologist, a pediatrician, a genetic counselor, an audiologist, an orthodontist and a psychological counselor are all often needed at different stages of the treatment. The treatment varies globally because economic conditions, health care arrangements, attitudes and agreed-on habits have influence on how medical conditions are taken care of. Non-life-threatening and rare diseases are not given special focus when resources in health care are allocated. Therefore, applied and basic research are the imperative foundation for decision making.

We have probably 1000-2000 microtia patients in Finland with the total population of 5.4 million. The treatment of microtia and associated conditions is emphasized during the first two decades of life and approximately 400 microtia patients are actively in a follow-up situation. Increased knowledge gives health care professionals and patients better tools to cope with this congenital condition. The target is to establish adequate practices for the treatment and examination of the microtia patient.

The population in Finland is relatively small and has been genetically isolated. This has led to unique genetic characteristics. An example is the Finnish disease heritage: some genetic diseases are only found in Finland and conversely, diseases that are rather common in other parts of the world are not found in Finland. In addition to inherited diseases, this random genetic drift is likely to have an effect on the special features of genotypes and diseases in the Finnish population. Thus, the characteristics of malformations reported abroad cannot be compared directly to Finland.

Our aim was to define the overall picture of microtia in Finland. Characterization, heredity, surgical treatment and its outcomes, and the association of auricular malformations with orofacial clefts were the focused areas of interest in this thesis. In addition, treatment options for auricular reconstruction, hearing restoration surgery, audiological aspects and the role of imaging are discussed.
6.1. Characteristics of microtia

6.1.1 Patient-based studies

Patient-based studies on the characteristics of microtia are numerous. The number of patients in these studies range from 53 (Tasse et al., 2005) to 592 (Okajima et al., 1996). This range of study size seems to be sufficient enough to define the integral features of microtia. State of the art imaging, particularly HRCT, has also specified the overall assessment of microtia. (Calzolari et al. 1999, Takegoshi and Kaga, 2003).

All 190 patients in our study concerning the characterization of microtia were referred for surgical correction of the auricle. This probably results in underreporting of the mildest forms of microtia. Also an unknown but probably rather small number of patients may in addition from microtia suffer from other more severe conditions and are never even referred to the reconstructive surgeon. This might be the case particularly in syndromes with profound phenotypic expression. It is supposed that neither our patient material nor the other patient-based reports represent the true characteristics of microtia in the general population. However, this information can be utilized in planning treatment protocols and multi-professional approaches.

In our study based on hospital records, male predominance (58%) and right-sidedness (59.5%) are in concordance with most hospital patient-based studies (Eavey et al., 1995; Okajima et al., 1996; Llano-Rivas et al. 1999). These features are supposed to be true because they are consistently present in the literature. The explanation for these manifestations is not clear. Twenty-two (11.5%) of the patients in our study had bilateral microtia with varying severity and asymmetry. In the literature, the range is from 9.1% (Okajima et al., 1996) to 50.9% (Tasse et al., 2005). In the latter report, skin tag on one side and microtia on the other side was classified as bilateral. In our material, microtia was associated with atresia or stenosis of the external auditory canal in 93% of cases. According to the literature, atresia is associated with microtia in 55-92% of cases (Llano-Rivas et al.1999, Okajima et al. 1996, Castilla et al. 1986). There are also reports without comments on atresia or stenosis of the external auditory canal and only a few reports focusing on the degree of atresia (Kountakis et al. 1995, Ishimoto et al. 2005).
In our study, patient questionnaires concerning physical health were replied to by 109 patients (or their parents). This data obtained through self-reporting should be interpreted with caution. The incidence of preterm (2.8%) and low birth weight (4.6%) in our material was not significantly higher than in the Finnish population in general (preterm 5.8% and low birth weight 4.4%). Structural heart defects were seen in more than 10% of our patients. Thus, the possibility of cardiovascular malformations should be remembered when examining a child with microtia.

6.1.2 Population-based register studies

There are several population-based registers providing epidemiologic information on congenital anomalies. The variation in classification systems, assessment, nomenclature and reporting of microtia sets up challenges for the precise characterization of microtia. Luquetti et al. (2011) debated these challenges comprehensively. They evaluated 92 surveillance programs covering almost 9 000 cases of microtia-anotia. They state in their review that existing data on the prevalence of microtia should be examined critically. In addition, they hope for a coding system that enables complete phenotype characterization of microtia, including severity and laterality.

The high variation in birth prevalence of microtia ranging from approximately 0.8-17.4 / 10 000 births can be partly due to the registration artefacts. However, the twenty-fold difference is so huge that it is likely to be caused by real biological factors (environmental and genetic). In populations living at high altitudes, the birth prevalence of microtia is substantially higher than in general. In Quito, La Paz and Bogota, which are located between 2600-4100 m above sea level, the prevalence of microtia, oral clefts, heart defects and limb defects were higher than at lower living areas (Castilla et al. 1999, González-Andrade et al. 2010). High altitude is one factor that those defects have in common, but nutrition may be unique at higher altitudes and ethnicity may bring bias as well. There is no clear evidence that high altitude is an independent cause of microtia.

The prevalence of microtia is 2.35/10 000 births in Sweden (Harris et al. 1996) and 4.34/10 000 births in Finland. The environmental factors are rather similar in both countries, but heredity is likely to be different. The prevalence of microtia in Finland may be two times higher than the global overall prevalence, which is 2.06/10 000. The
assessment of microtia patients and other factors mentioned above challenge the reasons and exactness of these findings. As we were not able to analyse the actual cases in the register there may be overreporting by physicians not familiar with auricular deformities and the numbers obtained from Finnish Malformation Register have to be treated with caution.

6.2 Inheritance of microtia

In our study on the inheritance of non-syndromic microtia in the Finnish population, we concluded that the prevalence of familial microtia is over 20 %. This finding was based on the patient questionnaire. The majority of the relatives were not examined by the author(s). As microtia is very visible and confusing, information given by the patients or their parents can be considered true. Minimally abnormal ears, such as skin tags and Marx grade I microtia, may be overlooked and thus the actual proportion of familial microtia may be even greater.

The majority of previous reports suggest that there is a hereditary form of microtia with an autosomal dominant mode of inheritance with variable expression and incomplete penetrance (Mastroiacovo et al. 1995, Chafai Elalaoui et al. 2010). In addition, autosomal recessive modes have been scarcely reported (Konigsmark et al. 1972, Llano-Rivas et al. 1999).

In most studies, the possibility of multigenic inheritance is suggested. A single gene mutation causing microtia has not been identified, though microtia is a clinical finding in many known single gene syndromes or disorders. It is possible that a gene or some genes interact with environmental factors and that this co-operative action causes microtia.

As with other populations, the mode of inheritance of microtia in the Finnish population seems to be autosomal dominant with incomplete penetrance in the majority of the families. Some typical features of autosomal dominant inheritance are present: fairly even expression of microtia in men and women, frequent expression in siblings and frequent expression in successive generations. In our study, multigenic inheritance cannot be excluded.
The genetic isolation and genetic bottlenecks of the Finnish population have led to a unique “genetic pool”. Bottleneck can be described as a remarkable reduction in the size of a population. The result is a decrease in the gene pool of the population. War, starvation and environmental catastrophes may cause genetic bottlenecks, for instance. A founder effect occurs when a small subset of a large population has been genetically isolated. This new small “founder” population has less genetic variation than the original population leading to enrichment of some alleles and lack of others. This is demonstrated by the Finnish disease heritage: some genetic diseases are enriched in Finland and others are extremely rare in the Finnish population due to the genetic features of the Finnish founder population. A common distant ancestor is often shared with regard to the diseases of Finnish heritage. We tried to identify a founder effect by analyzing the birthplaces of grandparents of microtia patients. Concentration around particular places would have suggested the presence of a common ancestor. In our study the birthplaces of parents or grandparents of familial and sporadic microtia patients were rather evenly distributed. No founder effect was identified. This can be due to genetic heterogeneity or an ancestor so distant that it could not be identified.

In our study, we compared the phenotypic differences between the familial and sporadic microtia patients. In the statistical analysis there were no significant differences, except for that familial microtia patients had more urinary tract anomalies than sporadic cases. This difference was statistically significant (P=0.01), but the sample size was small (3/22 versus 0/79) and the finding must be interpreted with caution.

The knowledge of the gross proportion of familial, non-syndromic microtia cases in Finland is valuable information for the patients and their parents. Microtia is definitely a dramatic condition and questions concerning the hereditary nature of this condition are important. On the basis of this study, we can estimate the gross magnitude of familial microtia in Finland.

6.3 Surgical reconstruction of the auricle

In most studies concerning the reconstruction of the auricle, the procedure is characterized by the words challenging, difficult or complex. The process through which you have to create a three-dimensional, immunocompetent, aesthetically acceptable and durable auricle deserves those definitions.
The term “learning curve” is used to describe a phenomenon where repetition of a task leads to improvement in performance over time. If the task is rather simple, such as myringotomy, improvement is supposed to be fast in the beginning and a steady state is reached quickly. If the task is complex, like auricular reconstruction, improvement is supposed to be slow and steady outcomes may be reached within many years. In addition, if the surgical procedure is complex, there may be evolution of the procedure and therefore the learning may occur more rapidly or begin to slow down.

We studied the learning curve of a single surgeon performing the reconstruction of the auricle. The object of the learning process was the aesthetic result and this was evaluated by a panel consisting of six physicians. In the same study, patient satisfaction was evaluated. All 51 patients in the study were non-syndromic, their microtia grade was Marx III and all cases were unilateral. These inclusion criteria enabled us to study patient material that was as coherent as possible. For example, syndromic facial features or severe hemifacial microsomia would have distorted reliable evaluation of the aesthetic result. In Marx grade III (lobulus-type) microtia, a customized style of reconstruction is required and it is supposed to have a specific learning curve. Unilaterality was one criterion that made comparison between the result and the unaffected auricle possible.

According to our study, the learning curve in microtia surgery is long and gentle. This is consistent with the hypothesis that in complex surgery, an extended training period is required. It is not just the total scope of the operation, but also the frequency that is supposed to have an influence on learning. The surgeon who made all the ear reconstructions in our study had done less than 10 operations per year in the beginning and handled 20 new cases a year in the later period in the studied time sequence, which was from 1998 to 2006. There was a statistical plateau in the outcomes from operation 20 to 40. Thereafter, a new period of improvement started and at the endpoint of the study there still seemed to be a trend towards improvement in the outcomes. The possible explanation for this improvement is the increase in the frequency of the operations. Including all ear reconstructions the overall volume was 124 during the studied period of time. This volume plus other soft-tissue surgery are supposed to have positive effect on learning.
The first stage was done according to the basic Nagata technique. The cartilage was taken from sixth to eighth rib. In the first stage, the costal cartilage was harvested, the auricular frame was constructed and then placed under the skin flaps. In early cases the subcutaneous pedicle in the concha region was omitted, but as skin edge necrosis at the distal edge of the flap was common, the pedicle was used in later cases. In the second stage, the cartilage graft that was used as a wedge was placed behind the pinna to give support to the protrusion. This cartilage was covered with a retroauricular fascial flap and a split skin graft taken from the scalp with dermatome.

The assessment of the surgical results was done by the panel of six physicians and the patient’s self-assessment group. The findings that support the reliability of the evaluation method used in our study are: 1. high intraclass correlation (0.90) and 2. the mean of points given by the self-assessment group (6.91) and the mean given by the physicians for the corresponding patients (6.59) were rather similar. Twenty-two patients did a self-evaluation of their reconstructed auricle. Female patients were more critical and gave fewer points than males. This difference was statistically significant. The age of the patient did not affect the evaluation. This self-assessment group is rather small and the results should be interpreted with caution.

There are previous learning curve studies where rather objective variables are measured. Moffat et al. (1996) studied facial nerve outcome in 300 patients undergoing vestibular schwannoma surgery. They found major improvement between the first and second series of 50 patients. Aural atresia surgery has been studied and the main outcomes were hearing results and complication rate (Patel and Shelton 2007). Hearing results have been the measured objective in a learning curve study concerning stapedotomy (Sargent 2002). Operation time, complication rate and hearing results are key objectives to be measured. According to our study, the outcomes of aesthetic surgery can also be assessed reliably using reasonable technical arrangements.

Microtia reconstruction with the use of autogenous rib cartilage is difficult. Learning and perfecting the procedure happens over the long-term and it may be accelerated by increasing the frequency with which operations are performed. Based on this finding, I would dare to suggest that auricle reconstruction should be performed from a centralized location in order to secure acceptable quality. In addition, an apprentice should be recruited well in advance if continuity of the reconstructive surgery of the auricle is an
issue. Microtia reconstructions are predominantly performed by a plastic surgeon in Finland. Both otologic surgeons and plastic surgeons do microtia operations worldwide. Good soft-tissue fingering and sense of aesthetics are valuable properties regardless of the background of the surgeon. Visits to and co-work with an experienced colleague may be helpful in the learning process. The surgeon in our study was in collaboration with a high-volume surgeon F. Firmin and gained good basic training in the beginning of his learning curve (Firmin, 1998). As with surgery in general, preoperative patient information is important and criticism by females may be useful for the surgeon to know when planning auricular reconstruction.

### 6.4 Treatment options in auricular reconstruction

Auricular reconstruction with autogenous rib cartilage is a widely accepted and preferred method. The patient’s own tissue is definitely biocompatible and a successfully reconstructed auricle is durable. Yet there are still some drawbacks, such as scarring and temporary pain in the donor site. Difficult and multi-stage surgery that is connected with a long learning curve is also a relative drawback of this well-established technique. There are alternative solutions to the rib cartilage technique.

The Medpor™ is a high-density porous polyethylene (PPE) material that has been used in craniofacial surgery since the 1990’s. Auricular prosthesis made of PPE has been used worldwide and nowadays the complication rate may be acceptably low in experienced hands (Romo T 3rd et al. 2009, Reinisch et al. 2009). Advantages of the Medpor™ include the ability to operate on a younger child so that rib cartilage growth does not have to be waited for, avoidance of chest incision, decreased operation time and ease of use compared to meticulous sculpturing of the cartilage. A possible negative reaction to foreign material, sensitivity to infections and the durability of the implant are debatable drawbacks. Reinisch et al. (2009) have a large amount of patient material and long follow up cases spanning up to 18 years. The problems they had in the early years, like fractures of the frame and exposures, were minimized through the evolution of the procedure. The frame design has undergone design changes and is stronger nowadays. In addition, the covering of the frame with temporoparietal fascia (TPF) and the underlying subgaleal fascia (SGF) has diminished the rate of frame exposures. They have also started to do single stage procedures. Their total amount of auricular reconstruction with Medpor™ has been 786, as reported in 2009. Rheinish states that the presence of an ipsilateral bone-anchored
hearing aid or previous failed auricular reconstruction are not obstacles for the success of their technique based on PPE frame and TPF+SGF covering.

Ear epithesis (or synonymously prosthesis) is another choice instead of rib cartilage reconstruction. The best practice is the use of osseointegration of the epithesis. Fixation with adhesives is less secure and more messy. There is a long tradition and extensive experience with the use of ear epitheses in Sweden. A. Tjellström is a pioneer in this area and he has been using osseointegration for over three decades (Tjellström et al. 1981). In their studies, high patient satisfaction and low complication rates have been achieved (Westin et al. 1999). In addition to the surgeon successfully implanting the titanium fixation into the skull, a skilled artist called an anaplastologist is needed. The coloring of the epithesis should be appropriate and must be adjusted to the surrounding skin. The role of a skilled Anaplastologist is important and such a professional should be available when planning the implantation of an ear epithesis.

The indications for autogenous rib cartilage reconstruction versus epithesis are outlined in a comprehensive and inclusive report by Thorne et al. (2001). They gathered the following relative indications for prosthetic reconstruction based on their experience: 1. failed previous cartilage reconstruction, 2. severe soft-tissue and/or skeletal hypoplasia, for example serious hemifacial microsomia, 3. a low or unfavorable hairline and, 4. posttraumatic or ablative auricular defects. The disadvantages of the prosthesis include: replacement of the prosthesis every 2 to 5 years for life, attention of the transcutaneous abutment, the patient must remember to put the prosthesis in place every day, and the possibility of breakage or loss. They conclude that the primary indication for prosthetic reconstruction is an acquired auricular defect, generally in an adult patient.

It can be concluded that autogenous rib cartilage reconstruction is the preferred method over ear epithesis. However, the advantages and disadvantages of both methods should be discussed with the patient and their parents.

Replacement of damaged or missing structures of the human body by biological tissue-engineered materials is possible nowadays. Auricular cartilage can be manufactured by means of tissue-engineering. The desirable advantages of tissue-engineering could be avoidance of donor site morbidity in the rib cartilage area and avoidance of challenging
and time consuming sculpting of the auricular frame. The method that is used by Yanaga et al. (2009) includes: 1. the surgical harvesting of the tissue-engineered cartilage block from the abdominal subcutis, 2. sculpturing of the auricular frame from that block. Thus, in their method, neither of the advantages are actualized. The fabrication of the auricular frame is an important step that may have an influence on the look of the reconstructed ear. In addition, just like with a PPE frame, the handling of the skin flaps and fascias may significantly affect the final appearance.

Adipose-derived stem-cells are used for regenerative purposes, in particular following surgery for breast cancer. Some authors suggest that tissue-engineered grafting procedures may predispose the patient to the recurrence of breast cancer (Chandler et al. 2012). This possible risk is worth recognizing even though the breast cancer prone humans are not directly comparable with microtia patients and the use of cartilage for reconstruction. Tissue-engineered auricular cartilage may be a good choice in the future if the manufacturing process could be done without surgery and hand sculpting of the frame. In addition, the safety with regards to the possibility of neoplasia should be confirmed. So far, reconstruction with human rib cartilage is superior.

6.5 Auricular malformations and orofacial clefts

The incidence of auricular malformations among patients with cleft lip or cleft palate are reported to be 0.6-2 % (Hartung et al. 1973, Lilius 1992). There is only a small amount of reported data on the association of these malformations. The lips and the palate are derived from the first pair of pharyngeal arches. As well, the external and middle ear arise mainly from the first and second pharyngeal arches and the pharyngeal clefts and pouches are in between them. Differentiation of these structures begins in the 5th and 6th gestational week. Due to embryogenesis, it is supposed that orofacial clefts may be concurrently expressed with malformations of the external and the middle ear. We conducted detailed and systematic research on these possibly coincidental malformations.

We found one hundred patients with cleft lip or palate and a malformed auricle. One focus was whether there is a specific auricular malformation associated with a certain cleft type. In our cleft patient material, the prevalence of microtia increased as the severity of cleft increased from cleft lip through cleft lip and alvelous to cleft lip and palate. This trend was
not present among patients with cleft palate only. Microtia was present in 43% of the cleft patients and it seems to be the most common ear malformation and skin tag was present in 15% of the patients. Some bias may be present because the diagnosis of microtia is definite, while skin tags may be overlooked and underreported. In addition, there is no objective and evident line between protruding and normal auricles. The prevalence of microtia among cleft patients is approximately 5/1000, which is significantly more than the prevalence of microtia in the whole Finnish population (4.3/10000). This is not surprising, because the orofacial structures are derivatives of the first pharyngeal arches and the auricles arise from the first and the second pharyngeal arches. However, the exact pathogenesis of these malformations remains unknown.

Some limitations were present in our analyses. Informative photographs of the auricles were available for 62% (62/100) of the patients. In the remaining 38 patients, our classification of the ear malformation was based on written explanations of ear deformities. To avoid misconceptions, only unequivocal cases were included in this study. In the beginning of the study, we had 122 patients, but 22 patients were excluded on the basis of unclear or missing information in the hospital charts. In addition, the subgrouping of clefts and ear deformities was essential, but it resulted in small sample sizes and statistical strength was diminished. The number of observations in each group was too small to prove the differences statistically.

Even if our material constituted the largest report on associations of auricular malformations and clefts, the findings were not statistically significant and we could not affirm the hypothesis that the severity of the cleft correlates with the severity of the ear malformation. Almost all cleft patients are included in the cleft register and it is impossible to arrange a more inclusive study in Finland. To test the increasing prevalence of microtia in relation to the severity of cleft, an international multi-center study with a larger amount of patient material should be conducted.

6.6 The role of imaging

The value of routine imaging with HRCT or MRI (magnetic resonance imaging) is debatable. However, imaging can reveal anomalies of great importance when planning middle ear and external ear canal surgery in microtia patients.
If the external ear canal is atretic, abnormal skin growth into the middle ear or mastoid area is not assumable and the development of cholesteatoma is hindered. In our material, only two patients of 190 were reported to have cholesteatoma. It is possible that all cholesteatomas were not reported, but still it seems to be infrequent. Cole et al. (1990) reviewed over 600 patients with major congenital ear malformations. In their material, 50 patients (8.3%) had congenital aural stenosis. In patients 12 years and older with a stenosis of 2 mm or less, cholesteatoma was present in 91% percent of their ears. In this study, cholesteatoma seemed to appear slowly and was particularly associated with ear canal stenosis.

On the basis of the literature and our own patient material, imaging on a routine basis should be avoided and used only when necessary for the diagnosis or treatment of the disease. Those microtia patients with external auditory canal stenosis should be placed in follow up and cholesteatoma should be suspected if typical symptoms or signs are present, such as pain and recurrent external ear canal discharge. In suspicious cases, HRCT is recommended.

6.7 Hearing restoration surgery

In bilateral microtia hearing restoration by surgery should be considered. The decision is mainly based on the Jahrsdoerfer grade (1992). With a Jahrsdoerfer atresia score of seven or more (on a scale of 1-10), the chance of successful surgical hearing restoration is good. Stilianos et al. (1995) stated that in Marx grade III microtia, the atresia score is 5.9 on average. Patel et al. (2007) retrospectively studied 64 aural atresia patients and stated that a learning curve of at least 48 operations was required to reach stable long-term (>1 year) hearing results. The mean long-term postoperative air-bone gap (ABG) was 26.7 dB HL. All the operations were done during a ten-year period at a tertiary referral center. In the entire group 38% of patients achieved good hearing (speech reception treshold of < 30 dB, speech discrimination score > 70%). In the last group of 16 operation the percentage was 56, which means improvement in hearing results.

In our material, the proportion of Marx grade III is almost 60%. With 11.5% bilaterality and based on this, only 5% of microtia patients in Finland would be candidates for hearing restoration surgery. This leaves us with one or two patients per year, which strongly
supports national centralization of auricular surgery in Finland. Systematic review of the hearing results of the hearing restoration surgery in Finland is not available and it should be organized.

An interesting question is whether to operate on ears with unilateral conductive hearing loss and if so, what is a sensible target level of reception thresholds. In a study by Lieu (2004), school-age children with unilateral hearing loss (UHL) appear to have increased rates of grade failures. They also needed additional educational assistance and they were seen as having behavioral difficulties in the classroom. Speech and language delays may occur in some children with UHL, but it can be temporary. In a recent study by Lieu et al. (2012), children with UHL demonstrated improvement in oral language verbal skills over time during follow-up, but did not demonstrate improvements in school performance. They recommended individual education plans as a solution. Unilateral hearing preservation surgery (or hearing aid) was not mentioned in the conclusion.

Hearing restoration surgery for reasons other than atresia of the external ear canal is easier to justify for anatomic reasons. Stapes surgery or standard tympanoplasty are also performed on a regular basis with unilateral conductive hearing loss. With a normal external ear canal and a mostly normal middle ear, achieving satisfactory postoperative hearing results is realistic. It is also likely that regular and frequent ear surgery yields better results. Because of the low frequency of operations and long learning curve, hearing restoration surgery should be avoided in aural atresia if contralateral hearing is normal. This conception is supported by the low frequency of good hearing results (38-56%) in a high-volume center (Patel et al., 2007).

Bilateral microtia is a challenge because these patients require both reconstruction of the auricle and rehabilitation of hearing. If hearing restoration surgery is planned, it is recommended to be done after the auricular reconstruction. The main reason is scarring of the soft tissues that may make the reconstruction more difficult. However, patients with bilateral microtia and hearing impairment cannot wait until the age of nine to ten. Three possibilities are available: 1. a conventional air conduction hearing aid, if the anatomy is favorable, 2. a bone conduction hearing aid without bone anchoring, 3. a bone-anchored hearing aid that is fixed 6-7 cm behind the pinna. A bone-anchored hearing aid that is fixed was recommended in a small study by Bajaj et al. (2005).
Alternative hearing devices without a skin-penetrating material are also available. These transcutaneous applications may cause less scarring and could be a choice for microtia patients even before the reconstruction of the auricle.

6.8 Audiological aspects

Otoacoustic emissions and auditory brainstem responses are used for newborn hearing screening. If the test result is normal for the non-affected ear of a newborn with microtia, no additional testing is routinely carried out.

The auricle and the external ear canal are usually abnormal in microtia and the use of a conventional hearing aid is impossible. Instead, percutaneous bone-anchored hearing aids are practical.

A hearing aid is justifiable in bilateral microtia, but debatable in unilateral microtia. There are several studies with pros and cons. A bone-anchored hearing device (or BAHA®, bone-anchored hearing aid, registered trademark is owned by Cochlear) head band is a valuable tool for preoperative evaluation. It is like a tennis player’s sweatband that slightly compresses the device against the skull. Kunst et al. (2008) studied 20 patients with congenital unilateral conductive hearing impairment. They conclude that some patients have good directional hearing and speech-in-noise scores even without a BAHA®. Six of the patients did not show any significant improvement after a hearing device implantation. However, compliance with BAHA® use in the whole patient group was high. The proportion of patients using a bone-anchored hearing device 4-7 days/week was 80% and 7 days/week 55%. In the consensus statement on the bone-anchored hearing device by Snik et al. (2005), it was advised to provide the patient with a head band for a trial period of at least 2 weeks when planning a BAHA® fitting for the patients with unilateral conductive hearing loss. A positive reaction to the trial BAHA® is the most valuable prognostic factor during the preoperative workup. They also conclude that bone-anchored hearing device results are superior to those obtained with conventional bone conduction devices. The bone-anchored hearing system should be seen as the first choice when a bone conduction device is the right solution. In bilateral cases, audiological results are better with a bilateral fitting. It is recommended to implant one bone-anchored hearing device and pretest the second with a head band before possible surgery. If a bone-anchored system is assembled, the operation should be done after the auricular reconstruction or the bone-anchoring should be fixed 6-7 cm behind the pinna. A bone-
anchored hearing device is applicable for both conductive and sensorineural hearing impairment.

In our material, all patients with a BAHA® had bilateral microtia (not reported in our original publication). One patient is using a BAHA® bilaterally. Referring to the literature, we could more actively consider bilateral implantation of bone-anchored hearing device. Both in unilateral and bilateral microtia, pretesting with a head band is recommended. This pretesting mode is also applied at Helsinki University Hospital. The new innovations of transcutaneous devices, which can be used through the intact skin, have been introduced recently and can be utilized among microtia patients.
7. Conclusions

There is variation in the prevalence and characteristics of microtia in different populations. The register based prevalence of microtia in Finland is almost double compared to the overall global prevalence.

The prevalence of familial microtia in the Finnish population is higher than 20%. The sporadic and familial microtia patients do not differ significantly. The pattern of inheritance seems to be autosomal dominant with incomplete penetrance.

The learning curve with microtia reconstruction surgery is long. Surgical centralization and long-term trainee arrangements are advisable. The results of reconstructive surgery and aesthetic results can reliably be rated by an evaluation panel.

Microtia seems to be the most common auricular malformation among cleft patients. The prevalence of microtia seems to increase as the severity of cleft lip increases, whereas in isolated cleft palate, microtia seems to occur independently from the grade of cleft.
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Samuli Suutarla
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Appendix
The patient questionnaire, which constituted the basis for the patient based information in studies I and II.

Ulkokorvan kehityshäiriöt – tietoa tutkimuksesta

Otamme teihin yhteyttä, koska Teitä / lastanne on tutkittu HYKSin Huul- ja suulahalkokeskuksessa (HUSUKE) ulkokorvan kehityshäiriön vuoksi. HUSUKE:ssa ja HYKSin Korvaklinikalla on vuonna 2006 alkanut tutkimus, jonka tavoitteena on selvittää ulkokorvan kehityshäiröiden syntymekanismeja, ominaispiirteitä ja perinnöllisyyttä.


Vastatessanne tähän kyselyyn, annatte samalla suostumuksen tutkimukseen osallistumisesta. Vastatkaa kyselyyn mahdollisimman tarkasti, käyttäen selkeää käsitteää. Mikäli ette tiedä vastausta johonkin kysymykseen niin jättää kyseisen kohta tyhjääksi. Palauttakaa kyselykaavake oheisessa palautuskuorassa. Mikäli teillä on kysyttävää tutkimuksen osalta voitte ottaa meihin yhteyttä puheilmitse tai sähköpostitse:

Lääkärin laakto, HYKS HUSUKE
Lääkärin laakto, HYKS Korvaklinikka

Ulkokorvan kehityshäiriöt – Kyselykaavake

NIMI:__________________________________________________________________________
SYNTYMÄAIIKA:________________________________________________________________

1) Syntymäpainonne?_________________________________________________________ En tiedä

2) Syntymäviikot (ts. täysiaikainen vai keskonen)?______________________________ En tiedä

3) Oliko äidillänne raskauskaikana ongelmia? Kyllä Ei En tiedä
(Esim. raskaudenaikainen sokeritauti, raskausmyrkytys, vakavia tulehduksia)?

Mikäli kyllä, mitä? _______________________________________________________________

4) Nykyinen pituus: ___________________________ paino: ___________________________

5) Oliko lapsuutena/nuoruutena kasvu ja kehitys normaali? Kyllä  Ei  En tiedä

6) Minkä ikäisenä tuli ensimmäiset sanat: ____________, kävely: ________________

7) Normaali kansa- / peruskoulu? Kyllä  Ei  Erityisluokka? Kyllä  Ei

8) Onko teillä sydänsairauksia tai sydämen kehityshäiriöitä? Kyllä  Ei

Mikäli kyllä, mikä? _____________________________________________________________

Onko jollakin suvussanne sama sairaus?  Kyllä, kenellä?____________________________

9) Onko teillä ihon sairauksia? Kyllä  Ei

Mikäli kyllä, mikä? _____________________________________________________________

Onko jollakin suvussanne sama sairaus?  Kyllä, kenellä?____________________________

10) Onko teillä hengityselinten/keuhkojen sairauksia? Kyllä  Ei

Mikäli kyllä, mikä? _____________________________________________________________

Onko jollakin suvussanne sama sairaus?  Kyllä, kenellä?____________________________

11) Onko teillä munuaisten, virtsateiden tai sukuelinten sairauksia? Kyllä  Ei

Mikäli kyllä, mikä? _____________________________________________________________

Onko jollakin suvussanne sama sairaus?  Kyllä, kenellä?____________________________

12) Onko teillä raajojen sairauksia tai kehityshäiriöitä? Kyllä  Ei

Mikäli kyllä, mikä? _____________________________________________________________

Onko jollakin suvussanne sama sairaus?  Kyllä, kenellä?____________________________

13) Onko teillä kuuston, nivelten tai selkärangank kehityshäiriöitä? Kyllä  Ei

Mikäli kyllä, mikä? _____________________________________________________________

Onko jollakin suvussanne sama sairaus?  Kyllä, kenellä?____________________________

14) Onko teillä hiukset, kynsien tai hampaiden sairauksia? Kyllä  Ei

Mikäli kyllä, mikä? _____________________________________________________________

Onko jollakin suvussanne sama sairaus?  Kyllä, kenellä?____________________________
15) Onko teillä silmien, aivojen tai hermoston sairauksia?  
Kyllä  
Ei
Mikäli kyllä, mikä?  
Onko jollakin suvussanne sama sairaus?  
Kyllä, kenellä?

16) Onko teillä sisäelinten tai ruuansulatuskanavan sairauksia?  
Kyllä  
Ei
Mikäli kyllä, mikä?  
Onko jollakin suvussanne sama sairaus?  
Kyllä, kenellä?

17) Onko teillä psykkisiä sairauksia (esim. masennus)?  
Kyllä  
Ei
Mikäli kyllä, mikä?  
Onko jollakin suvussanne sama sairaus?  
Kyllä, kenellä?

18) Onko teillä hormoni / aineenvaihdunnan sairauksia?  
Kyllä  
Ei
Mikäli kyllä, mikä?  
Onko jollakin suvussanne sama sairaus?  
Kyllä, kenellä?

19) Onko teillä jokin muu sairaus/kehityshäiriö?  
Kyllä  
Ei
Mikäli kyllä, mikä?  
Onko jollakin suvussanne sama sairaus?  
Kyllä, kenellä?

20) Onko teillä jokin säännöllinen lääkitys?  
Kyllä  
Ei
Mikäli kyllä, mikä?

21) Onko jollakin suvussanne teidän lisäksenne korvahiden kehityshäiriö?  
Kyllä
(Esim. epänormaali tai puuttuva korvahed)
Mikäli kyllä, kenellä?

22) Onko jollakin suvussanne korvan lähialueen/kasvojen kehityshäiriö?  
Kyllä
(Esim. poikkeava ihon aukko tai poimu, huuli- suulakihalkio)
Mikäli kyllä, kenellä?

23) Onko suvussanne jokin perinnöllinen sairaus?  
Kyllä  
Ei
Mikäli kyllä, mikä?

24) Onko teillä sisaruksia?  
Kyllä. Veljä ________ kpl, siskoja ________ kpl

25) Onko teillä lapsia?  
Kyllä. Poikia ________ kpl, tyttöjä ________ kpl
26) Onko vanhemmillanne sisaruksia?
   Kyllä. Äidin siskoja ___, äidin veljii ___, isän siskoja ___, isän veljiä _____

27) Onko teitä tutkinut korvan kehityshäiriön vuoksi
   Korvalääkäri? Kyllä Ei En tiedä
   Mikäli kyllä, missä? __________________________________________
   Lastenlääkäri? Kyllä Ei En tiedä
   Mikäli kyllä, missä? __________________________________________
   Perinnöllisyyslääkäri? Kyllä Ei En tiedä
   Mikäli kyllä, missä? __________________________________________

28) Onko teille tehty kuvantamistutkimuksia (esim. röntgen, ultraääni, magneettitutkimus)?
   Korvien/ pään tietokonekuvaus? Kyllä, missä? __________________________
   Kasvojen tai hampaiden röntgen? Kyllä, missä? __________________________
   Muita tutkimuksia? Mikä ja missä? ________________________________

29) Saammeko pyytää sairauskertomustietojanne muista sairaaloista, terveyskeskuksista yms.?  
   Kyllä Ei

30) Arvioi leikatun korvasi ulkonäkö käyttäen pisteytystä 1-10 (1 täysin kelvoton – 10 täydellinen):  
    __________ pistettä. Jos korvaa ei ole leikattu jätä kohta tyhjäksi.

31) Saammeko ottaa teihin yhteyttä mahdollisten lisääksymysten tai jatkotutkimuksien osalta?
    Kyllä Ei
    Puhelimitse, nro ______________________, klo ______________________
    Sähköpostitse, osoitteeseen ________________________________

   ___________________________ ________________________________
   Päiväys Allekirjoitus (tarvittaessa huoltajan)

   ___________________________ ________________________________
   Nimenselvennys
Original publications