

## Research Article

# Prevalence and Nature of Hearing Loss in 22q11.2 Deletion Syndrome

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**Purpose:** The purpose of this study was to clarify the prevalence, type, severity, and age-dependency of hearing loss in 22q11.2 deletion syndrome.

**Method:** Extensive audiological measurements were conducted in 40 persons with proven 22q11.2 deletion (aged 6–36 years). Besides air and bone conduction thresholds in the frequency range between 0.125 and 8.000 kHz, high-frequency thresholds up to 16.000 kHz were determined and tympanometry, acoustic reflex (AR) measurement, and distortion product otoacoustic emission (DPOAE) testing were performed.

**Results:** Hearing loss was identified in 59% of the tested ears and was mainly conductive in nature. In addition, a

high-frequency sensorineural hearing loss with down-sloping curve was found in the majority of patients. Aberrant tympanometric results were recorded in 39% of the ears. In 85% of ears with a Type A or C tympanometric peak, ARs were absent. A DPOAE response in at least 6 frequencies was present in only 23% of the ears with a hearing threshold  $\leq 30$  dB HL. In patients above 14 years of age, there was a significantly lower percentage of measurable DPOAEs.

**Conclusion:** Hearing loss in 22q11.2 deletion syndrome is highly prevalent and both conductive and high-frequency sensorineural in nature. The age-dependent absence of DPOAEs in 22q11.2 deletion syndrome suggests cochlear damage underlying the high-frequency hearing loss.

The 22q11.2 deletion syndrome (22q11DS), also known as Shprintzen syndrome, velocardiofacial syndrome, or Di George syndrome, is one of the most common chromosomal microdeletion syndromes with an estimated incidence of one in every 4,000 births (Devriendt, Fryns, Mortier, van Thienen, & Keymolen, 1998). It results from a hemizygous deletion at the 22q11.2 locus of usually 3 megabases (MB) in size, though atypical shorter deletions are present in about 15% of patients. The typical 3 MB deleted region encompasses about 45 different genes, of which mainly the *TBX1* gene has been linked to the phenotypical features of 22q11DS (Kobrynski & Sullivan, 2007). 22q11DS has an autosomal dominant inheritance, but most cases (>90%) result from de novo events, with both parents unaffected (McDonald-McGinn & Zackai, 2008). Since 1992, submicroscopic 22q11.2 deletions can be diagnosed

by fluorescent in situ hybridization (FISH). More recent techniques, such as genome-wide microarray-based tests and multiplex ligation-dependent probe amplification, also allow detection of atypical 22q11.2 deletions that do not include the target sequences of the common FISH probes (Bassett et al., 2011), and are gradually replacing diagnosis by FISH.

Phenotypically, 22q11DS is associated with a large range of anomalies in different organ systems, but symptoms vary widely across patients. The most frequent clinical manifestations are developmental and/or learning difficulties, behavioral issues, congenital conotruncal cardiac anomalies, immunodeficiency, a (submucous) cleft palate, velopharyngeal insufficiency, a characteristic facial appearance, psychiatric illness, and hypocalcaemia (Kobrynski & Sullivan, 2007; Vantrappen et al., 1999).

Hearing loss is a common feature in patients with 22q11DS, with a reported prevalence of 40%–65% (Digilio et al., 1999; Persson, Friman, Óskarsdóttir, & Jönsson, 2012; Reyes, LeBlanc, & Bassila, 1999; Zarchi et al., 2011). In particular, during childhood, patients with 22q11DS are known to have a high prevalence of middle ear effusion and recurrent acute middle ear infections, resulting in conductive hearing loss (Digilio et al., 1999; Reyes et al., 1999). Dysfunction of the Eustachian tube due to the abnormal

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craniofacial and palatal anatomy may contribute to the frequent middle ear problems, which is supported by recent work in mouse models of 22q11DS (*Df1/+* and *Tbx1<sup>+/-</sup>*), showing a correlation between the presence of otitis media with effusion and hypoplastic levator veli palatini muscles (Fuchs, Linden, Baldini, & Tucker, 2015; Fuchs et al., 2013). Another factor that may increase the likelihood of middle ear problems in 22q11DS is the associated immunodeficiency. Although this is classically described as cell-mediated (thymus hypoplasia and resulting deficits in T-cell numbers), alterations in the humoral compartment (deficiencies of IgA, IgM, IgG, or specific antibodies) have been reported in these patients, which seem to be significantly correlated with recurrent (middle ear) infections (Finocchi et al., 2006; McLean-Tooke, Spickett, & Gennery, 2007). Besides conductive hearing loss, sensorineural hearing loss is also reported in 22q11DS, though data on its prevalence vary widely, ranging from 7% to 47% of patients in different studies (Digilio et al., 1999; Dyce et al., 2002; Persson et al., 2012; Reyes et al., 1999; Zarchi et al., 2011). Zarchi et al. (2011) found the sensorineural hearing loss to be most pronounced in the high frequencies up to 8 kHz and positively correlated with age.

Speech and language difficulties are among the most distressing problems that children with 22q11DS and their parents face (Lima, Folling, Eiklid, Natvig, & Abrahamsen, 2010). They are caused by different factors. The onset and development of language is often delayed (Solot et al., 2001). Palatal abnormalities and velopharyngeal insufficiency may hamper intelligibility, even after corrective surgery (Spruijt, ReijmanHinze, Hens, Vander Poorten, & Mink van der Molen, 2012). Voice problems, with or without structural laryngeal anomaly, may also contribute to the problems with speech and language (Leopold et al., 2012). Last, hearing loss is associated with an increased prevalence of speech delay in children with 22q11DS and has a deleterious impact on intelligibility into adulthood (Digilio et al., 1999; Persson et al., 2012; Reyes et al., 1999). Though the relative contribution of hearing loss on speech and language difficulties in 22q11DS needs to be further studied, an optimal management of hearing loss is without doubt important in these patients who have a multifactorial vulnerability for speech and language difficulties. To explore the prevalence, the severity, the type, and the prognosis of hearing loss in 22q11DS, we performed extensive audiological tests in patients with 22q11DS of different ages.

## Materials and Methods

### Participants

Eighty-two participants with 22q11DS with a minimum age of 6 years were identified using the database of the Centre of Human Genetics and ENT Department, University Hospitals Leuven and were invited to participate in the study, of which 40 agreed to undergo extensive audiological testing. The age of the participants ranged between 6 and 36 years (mean age 15 years) and the male/female

ratio was 24/16. The study was approved by the local ethical committee of the hospital. All participants or their parents gave written informed consent.

### Procedure

From all patients or their parents, a detailed otological history was obtained and otomicroscopy was performed by an otorhinolaryngologist to identify outer or middle ear problems. The audiological protocol included the following measurements: standard pure-tone audiometry (frequency range from 0.125 to 8.000 kHz), high-frequency audiometry (frequency range 8 to 16 kHz), 226 Hz tympanometry, acoustic reflex (AR) testing and otoacoustic emissions (DPOAE) measurement. All tests were carried out by an experienced audiologist in our tertiary medical center.

The thresholds of an individual's hearing sensitivity for calibrated pure tones were measured using standard pure-tone audiometry (0.125–8.000 kHz) and high-frequency audiometry (8–16 kHz). The measurements were conducted in a sound-attenuated room with a Madsen Astera or a Madsen Orbiter 922 v.2 audiometer (Otometrics, Taastrup, Denmark), both similarly calibrated. Both air conduction (AC) and bone conduction (BC) thresholds were determined to discriminate between conductive and sensorineural hearing loss. AC thresholds were measured at the frequencies 0.125, 0.250, 0.500, 1.000, 2.000, 4.000, 8.000, 9.000, 10.000, 11.200, 12.500, 14.000, and 16.000 kHz. BC thresholds were measured at the frequencies 0.25, 0.50, 1.00, 2.00, and 4.00 kHz. All thresholds are reported in dB HL. Masking was applied when necessary.

On the basis of these measurements, three pure-tone averages (PTAs) were calculated for each ear, representing the hearing thresholds at different frequency ranges: the standard PTA (PTA, the average of the thresholds at 0.5, 1.0, and 2.0 kHz), the high-frequency PTA (HF PTA, the average of the thresholds at 4 and 8 kHz), and the extended high-frequency PTA (EHF PTA, the average of the thresholds at 9.0, 10.0, and 11.2 kHz).

We made a first classification of the type of hearing loss on the basis of the standard PTA in AC and BC. The hearing was classified as normal when the AC PTA was  $\leq 15$  dB (Clark, 1981). An AC PTA above 15 dB was classified as a hearing loss. The hearing loss was considered to be conductive if the BC PTA was  $\leq 15$  dB and the air–bone gap (ABG) was  $\geq 10$  dB, sensorineural if the BC PTA was  $> 15$  dB and the ABG was  $< 10$  dB, and mixed if the BC PTA was  $> 15$  dB and the ABG was  $\geq 10$  dB. The severity of the hearing loss was classified according to Clark (1981): slight hearing loss (16–25 dB HL), mild hearing loss (26–40 dB HL), moderate hearing loss (41–55 dB HL), moderate-severe hearing loss (56–71 dB HL), and severe hearing loss ( $> 71$  dB HL).

Tympanometry and AR testing were performed using a Madsen Zodiac 901. Tympanometry measures the compliance of the tympanic membrane, providing information on tympanic membrane and middle ear functioning. The resulting tympanogram was classified as Type A, which is

normal (pressure peak between  $-105$  and  $25$  daPa), Type C, which represents a negative middle ear pressure (pressure peak less than  $-105$  daPa), or Type B (a flat curve, no measurable peak), representing a lack of mobility of the tympanic membrane (in case of middle ear effusion or tympanic membrane perforation; Alaerts, Luts, & Wouters, 2007).

ARs were measured when the tympanometric response showed a Type A or a Type C curve. The AR is a contraction of the stapedius and tensor tympani muscle in the middle ear as a response to high-intensity sound stimuli. It is a protective reflex, creating a stiffness of the ossicular chain and therefore reducing the sound transmission to the cochlea. Ipsilateral measurements were conducted at the frequencies  $0.5$ ,  $1.0$ , and  $2.0$  kHz. Absence of the AR was defined as a failure to elicit the response at the maximum stimulation intensity of  $105$  dB SPL.

DPOAEs were measured with the Otodynamics ILOv6 software (Otodynamics, Hatfield, United Kingdom). Sound is transmitted through a probe placed in the ear canal. At the same time the acoustic response generated by the outer hair cells is measured. The presence of measurable DPOAEs indicates a normal outer hair cell function in the cochlea. A DPOAE response was measured in the seven frequency bands— $1.0$ ,  $1.4$ ,  $2.0$ ,  $2.8$ ,  $4.0$ ,  $6.0$ , and  $8.0$  kHz—and was expressed in dB SPL. The DPOAEs were considered normal when the signal-to-noise ratio (SNR) was  $\geq 6$  dB in six or seven of the frequency bands. When a SNR  $\geq 6$  dB was reached in three to five frequency bands, the DPOAE response was regarded as weak. When a SNR  $\geq 6$  dB was found in fewer than three frequency bands, the DPOAEs were considered absent. To rule out outer and middle ear problems as causes of absent DPOAEs, DPOAEs were not measured in cases of otitis media with effusion, outer ear canal stenosis, presence of ventilation tubes, and tympanic membrane perforation, because these outer and middle ear problems weaken the signal that's being sent to and reflected by the cochlea, even when there is no outer hair cell damage. In outer hair cell pathology, only the reflected signal will be reduced or absent. For the same reason, only ears with a PTA better than  $30$  dB HL were included.

### Statistical Analysis

To compare percentages of normal versus abnormal otomicroscopies, tympanometries, ARs, and otoacoustic emissions in different age categories, we used the chi square ( $\chi^2$ ) test or the Fisher Exact test as appropriate. Correlations between age and hearing thresholds were analyzed using the Pearson correlation coefficient after normality checking. The significance level was set on  $p < .05$ .

## Results

### Otomicroscopic Examination

Otomicroscopy was performed in all participants. In  $55\%$  of ears, the outer ear and tympanic membrane were normal. Observed abnormalities included otitis media with effusion, tympanic membrane retraction, myringosclerosis,

auditory canal stenosis, otitis externa, presence of ventilation tubes, and tympanic membrane perforation. An overview is given in Table 1. There were significantly more abnormal otomicroscopic findings in the age group below  $15$  years of age ( $p < .001$ ,  $\chi^2$  test).

### Pure-Tone Audiometry

On the basis of the standard PTA,  $78\%$  of the participants presented with a unilateral ( $38\%$ ) or bilateral ( $40\%$ ) hearing loss. Interpreting these results per ear, we found a hearing loss in  $59\%$  of ears. The hearing loss was conductive in  $53\%$ , sensorineural in  $4\%$ , and mixed in  $2\%$  of ears. Figure 1 shows the mean AC and BC thresholds on the basis of the standard pure tone audiometry ( $0.125$ – $8.000$  kHz). The average standard audiogram in 22q11DS presents a mild conductive hearing loss with an ABG of  $20$ – $30$  dB. In Figure 2, mean AC thresholds for the high-frequency range ( $8$ – $16$  kHz) are shown. The average high-frequency audiogram in 22q11DS has a down-sloping curve, representing a high-frequency sensorineural component to the hearing loss.

In individuals with 22q11DS, hearing loss is both more prevalent and more severe in the high frequencies. Indeed, although  $59\%$  of ears present with a hearing loss on the basis of the PTA, this increases to  $65\%$  on the basis of the HF PTA, and further to  $79\%$  on the basis of the EHF PTA. And although the majority of patients presents with a slight or mild hearing loss in the standard PTA (mean  $20 \pm 12$  dB HL), the hearing loss is on average more severe in the higher frequencies, with a mean HF PTA of  $23 \pm 14$  dB HL and a mean EHF PTA of  $34 \pm 22$  dB HL. The distribution of tested ears according to the grade of severity of hearing loss in the three frequency ranges is presented in Figure 3. No significant age correlation was found for the PTA (Pearson  $r = .01$ ), the HF PTA (Pearson  $r = .039$ ), nor the EHF PTA (Pearson  $r = .211$ ).

### Tympanometry and Acoustic Reflex Measurement

A tympanometry was conducted in  $66$  of the  $80$  ears ( $83\%$ ). Fourteen ears could not be tested because of the presence of a perforation in the tympanic membrane, ventilation tubes, external otitis, auditory canal stenosis, or test rejection. Of the tested patients,  $61\%$  presented with a Type A tympanogram,  $12\%$  a Type B tympanogram, and  $27\%$  a Type C tympanogram. In  $30\%$  of ears exhibiting a conductive or mixed hearing loss, a Type A curve was nevertheless found on tympanometry. The difference of normal versus abnormal tympanometric responses in different age categories ( $6$ – $14$  years vs.  $15$ – $36$  years) was not significant ( $\chi^2$  test  $p = .37$ ).

An ipsilateral AR measurement was conducted in all ears with a Type A or Type C curve on tympanometry ( $n = 55$ ). In  $33\%$  of these ears, we found a response on at least one frequency. The difference in the percentage of absent ARs in different age categories ( $6$ – $14$  years vs.  $15$ – $36$  years) was not significant ( $\chi^2$  test  $p = .74$ ).

**Table 1.** Otomicroscopic findings.

Finding	All ears ( <i>n</i> = 80), No. (%)	Ears of patients <15 years of age ( <i>n</i> = 42), No. (%)	Ears of patients ≥15 years of age ( <i>n</i> = 38), No. (%)
Normal	44 (55)	16 (38)	28 (74)
Otitis media with effusion	3 (4)	2 (5)	1 (3)
Tympanic membrane retraction	4 (5)	1 (2)	3 (7)
Myringosclerosis	14 (18)	10 (24)	4 (10)
Auditory canal stenosis	1 (1)	0 (0)	1 (3)
External otitis	2 (2)	2 (5)	0 (0)
Ventilation tubes in situ	5 (6)	4 (10)	1 (3)
Tympanic membrane perforation	7 (9)	7 (17)	0 (0)

### DPOEA Measurement

Forty-four ears could be included for the measurement of DPOEAs (see Methodology). Within this group there was a high degree of absent or weak responses (77%). Only 9% of the ears showed a response at all seven frequencies. There was a significantly higher degree of absence in the age category 15–36 years (83%), compared to the younger patients (29%; Fisher’s exact test  $p < .001$ ; see Figure 4).

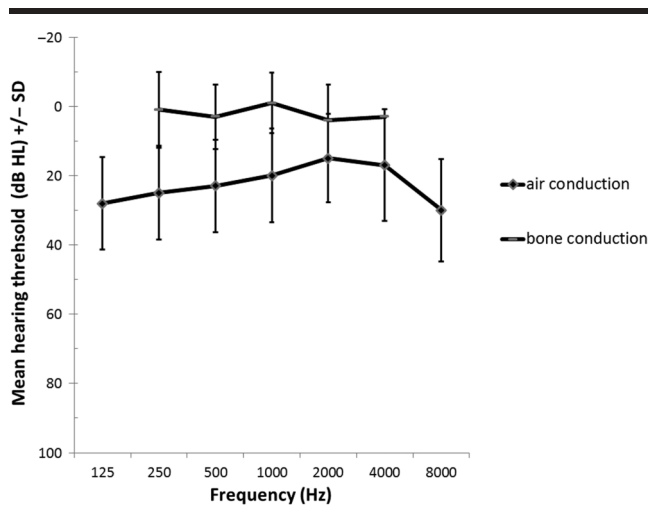
### Discussion

We found a hearing loss in at least one ear in 78% of participants with 22q11DS, on the basis of a standard PTA >15 dB HL. Bilateral hearing loss was found in 40% of patients. The prevalence of hearing loss in this study seems to exceed earlier reported prevalences of 40%–65% (Digilio et al., 1999; Persson et al., 2012; Reyes et al., 1999; Zarchi et al., 2011). There is, however, no uniformity in the criteria to define a hearing loss. Although most authors used the average of thresholds at 500, 1000, and 2000 Hz to calculate PTA, Reyes et al. (1999) also included the 4000 Hz frequency, and Zarchi et al. (2011) failed to report

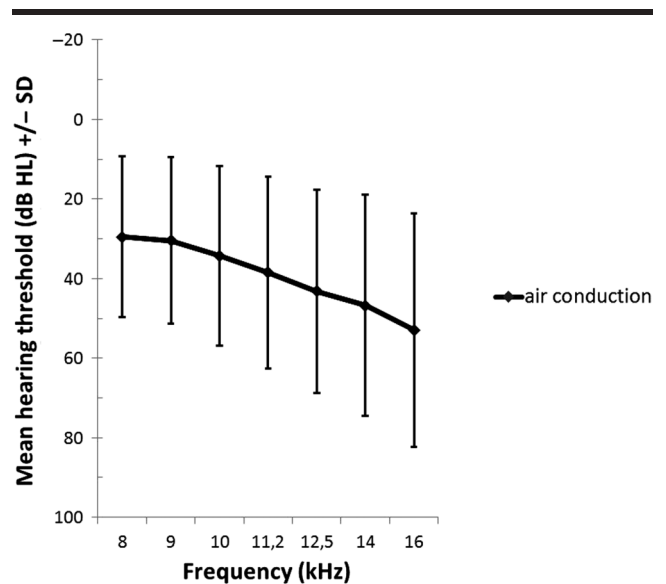
which average was used. In addition, we interpreted a mean standard PTA of >15 dB HL as a hearing loss in accordance with the classification of Clark (1981), whereas most authors used a threshold of >20 dB HL (Digilio et al., 1999; Persson et al., 2012; Reyes et al., 1999) or even >25 dB HL (Zarchi et al., 2011) to define hearing impairment. Reanalyzing our data, we find a prevalence of hearing loss (in at least one ear) of 60% using the criterion of >20 dB HL, which is in accordance with the previously reported data. The prevalence of hearing loss in persons with 22q11DS greatly exceeds the general prevalence of hearing loss found in large population-based surveys. For example, a PTA >15 dB HL is reported in about 15% of children between 6–19 years of age (Niskar et al., 1998), and 3%–5% of adults aged 20–40 years have a PTA ≥25 dB HL (Agrawal, Platz, & Niparko, 2008).

Two components contribute to the hearing loss in 22q11DS. In the lower frequencies (standard PTA), we found a hearing loss in 59% of ears, which is mostly conductive in nature and of slight to mild severity (see Figure 1 and

**Figure 1.** Mean AC and BC thresholds in the frequency range 0.125–8.000 kHz in 22q11DS (*n* = 80 ears, age 6–36 years).



**Figure 2.** Mean AC thresholds in the frequency range 8–16 kHz in 22q11DS (*n* = 76 ears, age 6–36 years).





**Figure 3.** Distribution of tested ears according to the grade of severity of hearing loss for each of the three frequency ranges: PTA, HF PTA, and EHF PTA.

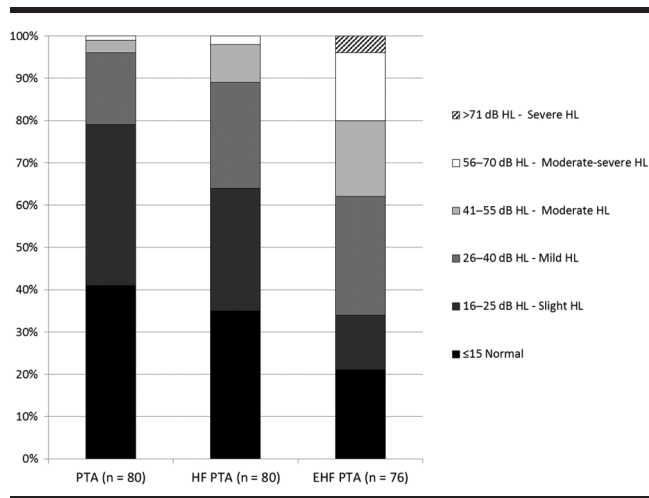
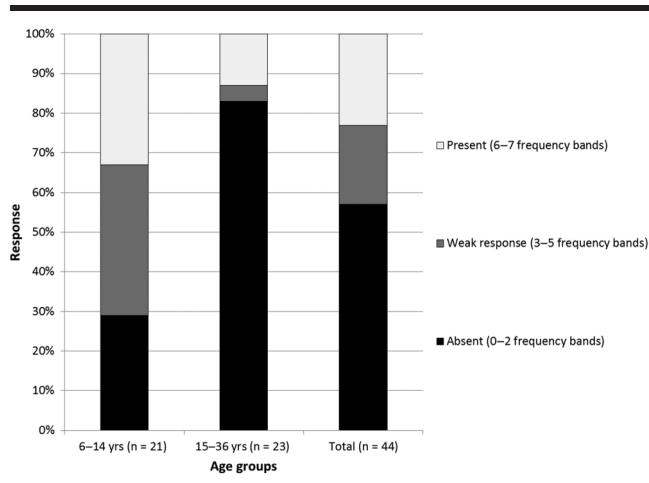


Figure 3). On top of the mild conductive component, the majority of participants presented with a high-frequency hearing loss, which can be assumed to be of sensorineural origin. Our study is the first to report on hearing thresholds in frequencies above 8 kHz in 22q11DS, clearly demonstrating a down-sloping curve in this frequency range on the audiogram (see Figure 2). Considering the EHF PTA (9.0, 10.0, and 11.2 kHz), we found a hearing loss in 79% of ears, which was mostly mild to moderate in severity (see Figure 3).

The conductive component of the hearing loss in 22q11DS is usually attributed to Eustachian tube dysfunction, otitis media with effusion, and recurrent middle ear infections in the pediatric 22q11DS population. In analogy with the cleft palate population, one would expect that Eustachian tube dysfunction caused by malfunctioning of the velar musculature would improve with age (Timmermans, Vander

**Figure 4.** Percentages of present, weak, and absent DPOAEs in patients with 22q11DS of different age groups.



Poorten, Desloovere, & Debruyne, 2006). However, although our study showed a significantly lower percentage of normal otomicroscopy findings in the age group from 6 to 14 years old versus the older participants (15–36 years old), the percentage of abnormal tympanometric results and the percentage of conductive hearing losses did not differ between the two groups. Moreover, the conductive hearing loss cannot fully be explained by Eustachian tube dysfunction, because 30% of ears with a conductive hearing loss demonstrated a Type A curve on tympanometry. On the other hand, congenital middle ear anomalies may explain part of the conductive losses seen in 22q11DS. Three cases of congenital ossicular chain anomalies are described in patients with 22q11DS (Cunningham et al., 2003; Devriendt, Swillen, Schatteman, Lemmerling, & Dhooze, 2004), and murine studies show a crucial role of *Tbx1* in the development of both middle and inner ear (Arnold et al., 2006). No large series of CT-scans of the petrosal bones in patients with 22q11DS are available, partly because of ethical considerations, and it is therefore currently not possible to estimate the true incidence of congenital middle ear malformations in 22q11DS. Another factor in the persistence of conductive hearing loss into adulthood in patients with 22q11DS, may be the development of tympanosclerotic middle ear changes due to chronic and acute otitis media in childhood. These sclerotic middle ear changes may also account for the high prevalence of absent ARs in 22q11DS as found by Zarchi et al. (2011) and as confirmed in our research. Other causes for malfunctioning of the ARs in 22q11DS may be congenital stapedia anomalies and the general muscular hypotonia found in these patients.

DPOEAs were absent in 57% of the ears with a PTA <30 dB HL in our study population, indicating malfunctioning of the outer hair cells and thus suggesting a cochlear origin of the high-tone sensorineural hearing loss. Several possible mechanisms may contribute to this hearing loss. Besides middle ear malformations, congenital inner ear anomalies have been described in 22q11DS, such as a Mondini-type cochlear malformation (Devriendt et al., 2004) or a common cavity between the vestibule and the lateral semicircular canal (Devriendt et al., 2004; Hopsu, Markkola, & Pitkäranta, 2007), which may be caused by the *Tbx1* hemizyosity (Arnold et al., 2006). On the other hand, middle ear inflammation can cause ototoxic damage via diffusion of inflammatory mediators through the round window membrane, affecting the hair cells in the basal cochlear duct and thus the high-frequency hearing thresholds (Joglekar et al., 2010; Margolis, Saly, & Hunter, 2000). In addition, Zarchi et al. (2011) postulated that the sensorineural hearing loss in 22q11DS may be noise-induced secondary to dysfunction of the protective ARs, but the relatively well-preserved hearing at the frequency of 4000 Hz makes this unlikely. Not one of the participants in our study presented with a typical noise-induced 4000-Hz threshold dip on their audiogram. In their study, there was a positive correlation between the severity of the high-frequency hearing loss and age, which was not significant in our study

cohort. We did, however, find that otoacoustic emissions were more frequently absent in older patients, favoring the hypothesis of cochlear damage due to middle ear effusion and infections. Congenital cochlear anomalies or immunological deficits in 22q11DS may cause the cochlea to be more vulnerable to permanent damage, resembling the cochlear fragility described in Williams syndrome (Barozzi et al., 2013). Longitudinal studies on hearing in 22q11DS, including DPOEA testing and high-frequency audiometry, would be informative in future.

In conclusion, hearing loss is highly prevalent in 22q11DS, and both conductive and high-tone sensorineural in nature. The decreased presence of DPOEAs in ears of older participants with 22q11DS suggests cochlear damage as the plausible mechanism for the development of the high-frequency hearing loss. Rigorous otological follow-up and prompt treatment of middle ear infections and effusion is advisable in this population at high risk for speech and language difficulties.

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