GENETICS AND PRESBYCUSIS – MONOGENIC FORM OF AGE RELATED HEARING IMPAIRMENT CAUSED BY *CDH23* MUTATIONS

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Abstract

Background: Presbycusis (age-related hearing impairment: ARHI) is believed to be a typical complex disorder associated with both genetic factors and environmental factors ("complex ARHI"). However, a small portion of patients with *CDH23* mutations exhibit an ARHI-like phenotype ("monogenic ARHI"). It is an interesting question as to the difference between the two types of ARHI from the clinical viewpoint as well as audiogram configurations.

Subjects and Methods: The detailed clinical courses of two cases of "monogenic ARHI" caused by *CDH23* mutations were evaluated. In addition, statistical classification of audiogram configurations was used to determine whether or not "monogenic ARHI" can be differentiated from the other clusters with high frequency involved hearing loss.

Results: Although onset age of the present two cases was somewhat earlier than commonly encountered in ARHI, clinical features were very similar to presbycusis, with slowly progressive high frequency involved hearing loss.

Conclusions: The present data strongly supports the view that there are at least two types of ARHI and a particular type of ARHI (late onset hereditary hearing loss) is monogenically inherited. It may be possible to differentiate those subtypes through statistical classification of audiogram configurations.

Keywords: age related hearing impairment • ARHI • presbycusis • *CDH23* • late onset • progressive • high frequency hearing loss • recessive • audiogram configuration

Background

Presbycusis (age-related hearing impairment: ARHI) is the most common sensorineural impairment in elderly people and in developed countries, more than 30% of people over 65 years old are affected. ARHI is believed to be a typical complex disorder associated with both genetic factors and environmental factors ("complex ARHI"). However, some hereditary hearing loss patients showed late-onset hearing loss similar to presbycusis ("monogenic ARHI"). Recently we reported 52 probands with *CDH23* mutations among 1396 SNHL patients (Miyagawa et al., 2012), the majority of the patients showed congenital, high frequency involved, progressive hearing loss. However, among them, we have found a small portion of patients with *CDH23* mutations exhibiting ARHI-like phenotype (Miyagawa et al., 2012). Three out of 52 probands had "late-onset" hearing loss. Interestingly, two of the three patients are associated with a particular *CDH23* mutation (p.R2029W), indicating that some particular mutations cause late onset progressive high frequency involved hearing loss. In this paper, we report the detailed clinical course of "monogenic ARHI" caused by *CDH23* mutations and discuss the difference between the two types of ARHI from the viewpoint of audiogram configurations.

Subjects and Methods

The detailed clinical courses of two cases of "monogenic ARHI" caused by *CDH23* mutations were evaluated. Audiogram configuration classification of high frequency involved hearing loss was carried out using 2846 patients (with ages ranging from 4 to 93 and an average age of 53.9) who visited the outpatient clinic of Shinshu University Hospital between 2001-2010. Using air conduction of seven frequencies, 0.125, 0.25, 0.5, 1, 2, 4, 8 kHz, K-means cluster analysis was conducted to classify the degree and shapes of pure tone audiometric data in SPSS v18 (SPSS Inc., Chicago IL). The cluster results were tested by ANOVA and the significance was estimated.

Results

Clinical courses of two cases of "monogenic ARHI" caused by *CDH23* mutations

As stated below, in these two cases, onset age was somewhat earlier than commonly encountered in ARHI, but their clinical features including late-onset and slowly progress nature of high frequency involved hearing loss were confirmed from the anamnestic evaluation and pronunciation, as well as pure tone audiogram.

Case 1 (#2806)

53 y.o. male.

The patient had not noticed any hearing loss in childhood and passed the annual school hearing screening (in Japan, mandatory hearing testing for 1000 Hz and 4000 Hz is performed annually in elementary and junior high school). However around age 40, his hearing loss was found in an annual company health check (in Japan, hearing testing for 1000 Hz and 4000 Hz is performed at most companies), and his hearing loss gradually progressed. The audiogram presented high frequency predominant hearing impairment (Figure 1). Incomplete pronunciation of consonants was not noted in this patient. He had tinnitus but did not have any vertigo nor any other associated symptoms. Caloric testing showed normal response. Mutation analysis identified homozygous for p.R2029W (p.[R2029W];[R2029W]) (Miyagawa et al., 2012).

Case 2 (#3255)

71 y.o. female.

The patient had not noticed any hearing problem in childhood and passed the annual school hearing screenings. However, she noticed her hearing loss around age 60, and it then gradually progressed. The audiogram presented high frequency predominant hearing impairment (Figure 1). She used hearing aids from age 70 due to progressiveness. Incomplete pronunciation of consonants was not noted in this patient. She had tinnitus but did not have any vertigo nor any other associated symptoms. Mutation analysis identified homozygous for p.R2029W (p.[R2029W];[R2029W]) (Miyagawa et al., 2012).

Audiogram configuration classification of high frequency involved hearing loss

Audiograms of the patients could be divided into 12 groups by clustering (Figure 2), and the two cases with *CDH23* mutations were compatible with belonging to cluster 2.

Discussion

"Complex ARHI" *vs.* "monogenic ARHI"

It has been thought that any type of hearing loss is caused by (either or both) genetic factors and environmental factors, though the ratio of genetic/environmental influence is variable (Figure 3). For example, congenital hereditary hearing impairment is nearly 100% genetically determined disease, though injury or viral infection is caused by predominantly environmental factors. ARHI is situated between, and believed to be a typical complex disorder associated with both genetic factors and environmental factors ("complex ARHI"). The accumulated external and internal factors lead to degeneration and age-related changes in the cochlea. These environmental factors, including exposure to noise for a long time, ear disease, ototoxic drugs, circulatory disease, and diabetes mellitus, play important causative roles in presbycusis. The effect on the development of presbycusis of smoking and alcohol is controversial. Previous studies indicated heritability of ARHI phenotypes is estimated to be 0.35–0.55 and SNPs (single nucleotide polymorphisms) of many genes are reported to be risk factors for ARHI (see Liu and Yan 2007, for review).

On the other hand, some hereditary hearing loss patients showed late-onset hearing loss similar to presbycusis ("monogenic ARHI") (Figure 1). The present data from two cases with *CDH23* mutations strongly supported the view that the particular type of ARHI (late onset hereditary hearing loss) is monogenically inherited.

CDH23 gene mutations are known to be responsible for both Usher syndrome type ID (USH1D) and non-syndromic hearing loss (DFNB12). Cadherin 23, part of the cadherin superfamily of cell surface adhesion proteins, conforms to the "Tip Link" structure of stereocilia important for hair-cell function. Therefore, it is conceivable that altered adhesion property or reduced stability of Cadherin 23 may confer susceptibility to ARHI.

Such late-onset phenotype is not surprising because a series of animal studies have shown that *Cdh23* mutation is involved in ARHI. C57BL/6 strain mice are known as

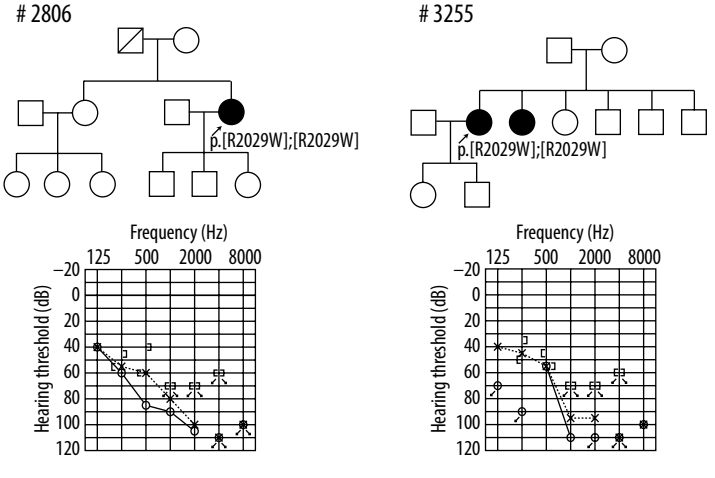

Figure 1. "Monogenic ARHI" caused by *CDH23* mutations. These two patients are associated with a particular *CDH23* mutation (p.R2029W). Some particular mutations cause "late-onset" hearing loss with residual hearing in low frequencies.

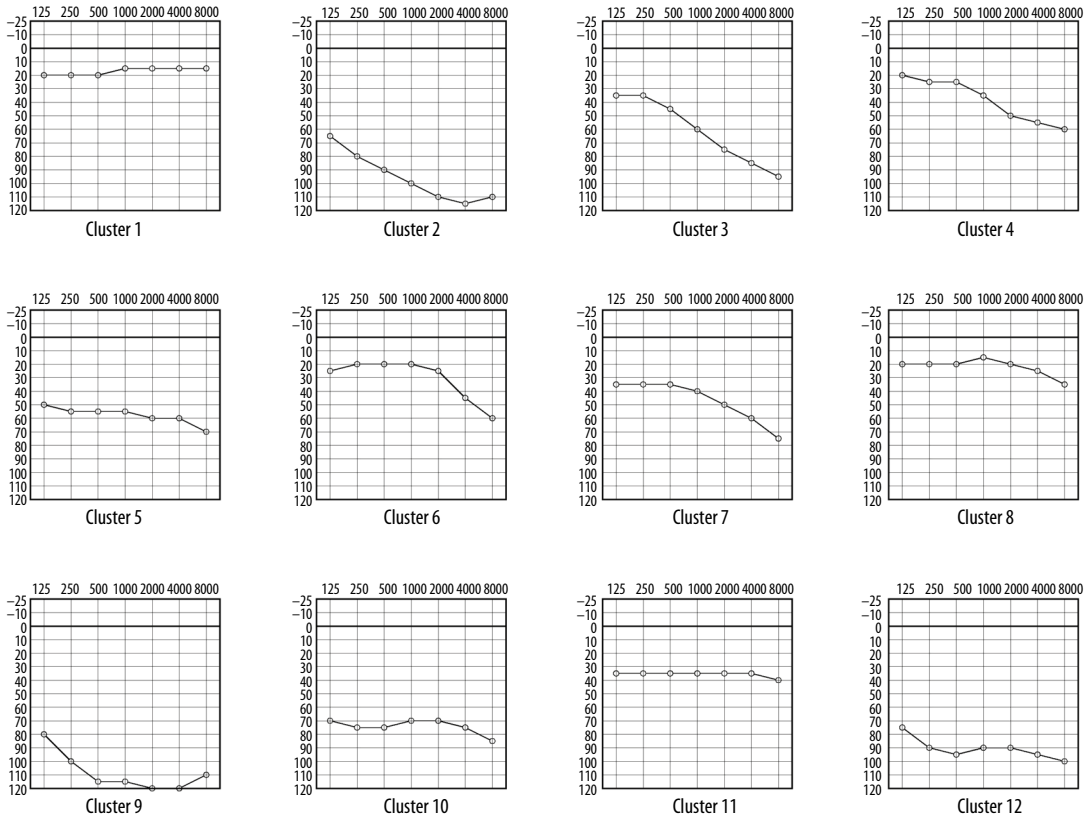

Figure 2. Audiogram configuration classification. Audiograms of the patients could be divided into 12 groups by clustering. Statistical analysis indicated that two cases with *CDH23* mutations ("monogenic ARHI") were compatible with belonging to cluster 2.

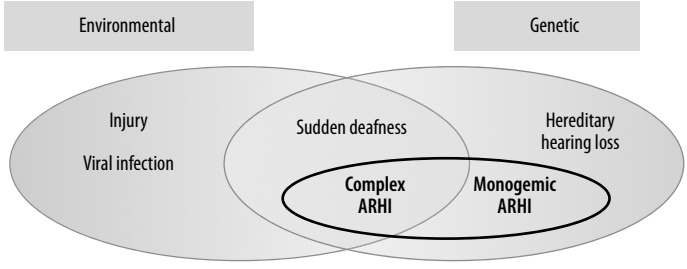

Figure 3. Etiology of presbycusis (age related hearing loss: ARHI). "Complex ARHI" is caused by both environmental and genetic factors, whereas "monogenic ARHI" is more genetically involved.

the most common model mice for ARHI. It has been reported that the 57BL/6 strain has *Ahl1* (Age-related hearing loss 1 gene) in chromosome 10 (Johnson et al., 1997). *Cadherin 23* was found to be the responsible gene at the *Ahl1* locus (Noben-Trauth et al., 2003).

Audiogram configuration classification of high frequency involved hearing loss

It would be an interesting question whether audiograms of "monogenic ARHI" caused by *CDH23* mutations could be distinguished from those of "complex ARHI", because certain correlations between audiogram configuration and etiology have been suggested. We have tried to classify audiogram shapes statistically and looked at whether the two groups would belong to the different clusters. Clusters 4, 5, 6, 7, and 8 had one peak around the 60–70's with regard to age distribution (data not shown), suggesting they may be the commonest ARHI type ("complex ARHI") of audiogram configuration, whereas the two cases with *CDH23* mutations belonged to cluster 2. The mean age (32.8 y.o.) of cluster 2 was comparatively young and age distribution of cluster 2 has a peak around 1–10 years old, indicating this cluster may be predominantly involved with genetic causes. The present objective classification based on audiogram configuration successfully distinguished "monogenic ARHI" from the other groups with high frequency involved hearing loss, suggesting that such a classification together with genetic testing is helpful for better understanding of etiology.

Future direction

High-throughput sequencing platforms using next generation sequencer have now been developed and are available for clinical study. With such new technologies, efforts to determine the genetic involvement for ARHL should be continued for clarifying the mechanism of ARHI, predicting individual risk, preventing progressiveness, and selecting suitable intervention.

Acknowledgements

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References:

1. Miyagawa M, Nishio S, Usami S: Prevalence and Clinical Features of Hearing Loss Patients with CDH23 Mutations: A Large Cohort Study. PLoS One, 2012; 7(8): e40366
2. Liu XZ, Yan D: Ageing and hearing loss. J Pathol, 2007; 211: 188–97
3. Johnson KR, Erway LC, Cook SA et al: A major gene affecting age-related hearing loss in C57BL/6J mice. Hear Res, 1997; 114: 83–92
4. Noben-Trauth K, Zheng QY, Johnson KR: Association of cadherin 23 with polygenic inheritance and genetic modification of sensorineural hearing loss. Nat Genet, 2003; 35: 21–23