Genetic and Environmental Influences on Hearing in Older Women

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Background. This study examined the relative contribution of genetic and environmental effects on the air-conducted hearing threshold level (0.5–4 kHz) and speech recognition threshold level of the better ear as well as self-reported hearing in older women.

Methods. Hearing was measured as a part of the Finnish Twin Study on Aging in 103 monozygotic (MZ) and 114 dizygotic (DZ) female twin pairs aged 63–76 years. Audiometric measured hearing was tested using standardized methods in soundproof conditions. Self-reported hearing was assessed by a structured question. Quantitative genetic modeling was used for data analyses.

Results. No significant differences in age, exposure to noise, hearing-aid use, auditory diseases or accidents, or number of self-reported chronic conditions or prescription medicines were observed between the MZ and DZ twins. A genetic component in common accounted for 75% (95% confidence interval [CI], 67%–81%) of the variance in the better ear’s hearing threshold level and 54% (95% CI, 43%–64%) in the better ear’s speech recognition threshold level, according to a bivariate genetic analysis. In addition, 10% (95% CI, 4%–15%) of the variance in the better ear’s speech recognition threshold level was explained by its specific genetic component.

Conclusion. Individual differences in audiometrically measured air-conducted hearing threshold level (0.5–4 kHz) and speech recognition threshold level in the better ear were largely accounted for by genetic differences between individuals. In contrast, self-reported hearing appears to be accounted for solely by environmental factors.

About every third 65-year-old and two-thirds of people aged 75 years have at least mild hearing impairment (1,2). Age-related hearing loss, presbycusis, is most often the underlying cause of deterioration. However, the etiology of presbycusis is not well understood. Various noxious environmental and genetic factors have been put forward as contributors to the process. The best known environmental factor affecting hearing loss is exposure to noise. However, the fact that people exposed to the same amount of noise do not suffer the same degree of hearing loss (3) suggests that individual susceptibility plays a significant role in this process. Ototoxic medication, chemicals, head trauma, tobacco smoking, and alcohol abuse have also been reported to cause hearing impairments as have medical risks such as elevated blood pressure, altered lipid metabolism, diabetes mellitus, and rheumatoid arthritis. For a review, see Fransen and colleagues (4).

In the Framingham Heart Study of families, the heritability (the proportion of the overall variance that is attributed to genetic factors) of high-frequency hearing loss was 35%–55% and of flat hearing loss 25%–42%. Heritability estimates were higher in women than in men (5,6). In a Swedish study of 78 male twin pairs in the age group 65 years and older, the primary, correlation-based heritability estimate of hearing in the high-frequency ranges (3–8 kHz) was 47% (7). In a Danish study of 866 male and female twin pairs, additive genetic effects accounted for 40% of the age- and sex-adjusted variation in self-reported reduced hearing in the age group 70 years and older (8). These studies provide preliminary evidence that, in part, hearing loss is linked to genetic susceptibility.

The purpose of this study was to examine genetic and environmental effects on hearing at the frequencies most crucial to overall hearing ability and understanding speech in social situations. In this analysis we used the hearing threshold level of the better ear at 0.5–4 kHz, the speech recognition threshold level of the better ear, and self-rated hearing.

Methods

Participants
This study forms part of the Finnish Twin Study on Aging (FITSA), a broader project on the contribution of genetic and environmental factors to the disablement process in older women. The participants were recruited from the nationwide Finnish Twin Cohort, which comprises all same-sex twin pairs born before 1958 with both co-twins alive in 1975 (9,10). An invitation to participate in the FITSA was sent to 414 twin pairs aged 63–76 years drawn on the basis of age and zygosity. Zygosity was ascertained by a battery of highly polymorphic gene markers for every FITSA
participant using DNA extracted from a venous blood sample. After the DNA ascertainment, the final sample consisted of 103 monozygotic (MZ) and 114 dizygotic (DZ) twin pairs. The main reasons for nonparticipation were refusal, poor health status, or death of one or both twin sisters after vital status had been updated for all cohort members. The recruitment process and participation have been described in more detail elsewhere (9–12).

The most common self-reported auditory disease of the participants was otosclerosis. As otosclerosis is an inheritable disorder (13) and might confuse the results, we excluded all persons with otosclerosis (one MZ individual and two DZ twin pairs) from our analysis.

### Procedures

Twin pairs arrived at the research center from all over Finland. Audiometric measurements were conducted as a part of a 5-hour laboratory test battery including a physician’s examination and multiple clinical tests of health and functional capacity.

One experienced audiologist performed all audiometric measurements in a soundproof booth using a clinical audiometer Madsen OB 822, equipped with TDH 39 headphones (Madsen Electronics, Denmark) and a cassette player (NAD 6140; NAD, Japan). Before the measurements, the equipment was calibrated according to International Organization for Standardization (ISO) 389 (14).

Air-conduction pure-tone hearing thresholds were measured at the frequencies of 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz for each ear separately according to ISO 8253-1 (15). In the analysis, the better ear hearing threshold level (BEHL) was used and defined as a pure-tone average of thresholds at 0.5–4 kHz in the better ear. The cut-off value between normal hearing and hearing impairment was set at 21 dB. A person was defined as having at least a mild hearing impairment if the BEHL was ≥ 21 dB. Classifications of BEHL and hearing impairments (Table 1) are based on European Union-recommended values and are in common use in the field of audiology [Stephens (16)].

The speech discrimination test was carried out using the national, phonetically balanced Finnish word lists (17). All the words in the lists were bisyllabic and were presented through earphones from a cassette player. The first volume presented was calculated as the mean of the air-conduction pure-tone thresholds at 0.5–2 kHz plus 10 dB rounded off to the nearest 5. The words were given in five-word groups at each volume. The volume was decreased in 5-dB steps until it reached the level at which all responses were incorrect or the respondent announced that she could not hear the words. The speech recognition threshold level was calculated by subtracting the number of correctly recognized words from the starting volume rounded off to the nearest five. The better ear speech recognition threshold level (BESRL) was defined as the better ear according to BEHL, meaning that the results of the BESRL and BEHL are from the same ear. The maximum word recognition score of the better ear according to BEHL was not analyzed further because only 28 persons of the 426 misrecognized 2 or more words. Due to lack of variation in the score, twin comparisons could not be performed.

Self-reported hearing was assessed according to the question “How is your hearing ability?” Response options were: good (no problems), slightly reduced, or substantially reduced. For the analysis, we dichotomized self-reported
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The variables were examined for normality and distribution. We transformed the BEHL and BESRL by the square root of the inverse, \( f(x) = 1/\sqrt{BEHL} \), \( f(x) = 1/\sqrt{BESRL} \). After the transformation, the absolute values of skewness and kurtosis were acceptable. In further analyses we used these transformed values multiplied by 10 to avoid difficulties arising from small variable values. The equalities of the means and distributions of the categorical variables between the MZ and DZ twins were calculated and tested using an adjusted Wald test to take into account the within-pair dependence of twin individuals. The equality of the variances was tested using the variance ratio test. Intraclass correlation coefficients (ICC) for continuous variables and tetrachoric correlations for binary variables were calculated separately for both zygosity groups. These correlations provide indicative estimates of the importance of genetic and environmental influences on the trait. The polyserial correlation coefficient was used to describe the association between audiometric measurements and self-rated hearing.

Twin similarity for presence of hearing impairment was summarized separately for both MZ and DZ pairs by estimates of probandwise concordance and its 95% confidence intervals (CI). The probandwise concordance rate is the probability that the co-twin of the affected twin will also be affected. Probandwise concordance is calculated with the formula \( 2 \times \text{concordant pairs}/(2 \times \text{concordant pairs} + \text{discordant pairs}) \) (19).

On the basis of comparison of the similarity between the MZ and DZ twins, the twin study aims to differentiate the sources of the variation in the phenotype of interest. Phenotypic variation can be decomposed into additive genetic effects (A), nonadditive, dominant, genetic effects (D), shared environmental effects (C), and nonshared environmental effects (E). The genetic modeling is based on the fact that MZ twins share all of their genes and DZ twins share on average only half of their segregating genes. Twin models assume that the environmental effects within MZ and DZ twin pairs are approximately the same. The greater similarity between MZ twins compared with DZ twins provides evidence for genetic influence on the trait (20).

Genetic and environmental influences contributing to BEHL and BESRL were estimated first with univariate models. The strong phenotypic correlation between the hearing test results suggested that same genetic and environmental effects may influence both BEHL and BESRL, and this was estimated with a bivariate Cholesky decomposition model. The aim of the genetic modeling is to find a model which provides a theoretically meaningful interpretation, fits the data well, and has as few explanatory parameters as possible. In the present study, the fit of the hierarchical submodels (AE, DE, E) against the full model (ADE) were assessed with the –2 log likelihood–difference tests (20). In all the models, age was included as a covariate.

Data were analyzed with the PRELIS version 2.51 module of LISREL (21), SPSS version 12.01 (22), and STATA version 8.0 (23). Genetic modeling was done with Mx using full information maximum likelihood with raw data input (24).

RESULTS

The variances of BEHL and of BESRL and the means of BEHL between MZ and DZ twin individuals did not differ (Table 1). The average BESRL was 4 dB better for DZ than for MZ twins, and the difference was significant. In addition, more DZ twins than MZ twins rated their hearing as good. Prevalence of hearing impairment (BEHL \( \geq 21 \) dB), exposure to noise, hearing-aid use, auditory diseases, and accidents did not differ between the zygosity groups. The mean age of MZ (68.3 years) and DZ twins (68.9 years) did not differ, but the variance of age was significantly larger for MZ twins than for DZ twins (14.1 vs 9.5, \( r = .004 \)). For the number of chronic diseases (mean = 2.0, standard deviation (SD) 1.5), number of prescription medicines (mean = 2.0, SD 2.0), BMI (mean = 28.0, SD 4.8), or MMSE scores (mean = 26.9, SD 2.3) no differences by zygosity in means or variances were observed. There were also no differences between the zygosity groups in the prevalence of current smoking (5%), cardiovascular diseases (55%), rheumatoid arthritis (4%), or diabetes (6%).

Probandwise concordance and tetrachoric correlation for hearing impairment (BEHL \( \geq 21 \) dB) was much higher for MZ than for DZ twin pairs (Table 2), suggesting a major genetic component. For self-rated hearing problems, the probandwise concordances were almost the same for MZ and DZ twins, and DZ pairs showed higher tetrachoric correlations than MZ pairs. These results suggest that environmental influences alone underlie individual differences. No further genetic analyses were carried out for self-reported hearing.

Self-rated hearing and audiometric measurements correlated moderately. Polyserial correlation between self-rated hearing and BEHL was –0.482 and between self-rated hearing and BESRL –0.398. Correlations were negative due the inverse transformation of the audiometric variables.

The ICCs for BEHL and BESRL, were approximately twice as high for the MZ compared with DZ twin pairs \( (r_{MZ} = 0.80 \text{ vs } r_{DZ} = 0.42 \text{ and } r_{MZ} = 0.71 \text{ vs } r_{DZ} = 0.30, \text{ respectively}) \), which suggested a genetic contribution to the variances and justified the use of ADE models.

The results of the univariate genetic models are shown in Table 3. For BEHL and BESRL, the AE model showed the best fit with the data. Additive genetic effects accounted for
DISCUSSION

According to our study among older female twins, individual differences in audiometrically measured hearing were predominantly explained by genetic influences. Over 75% (95% CI, 67%–81%) of the total variance in BEHL and 66% (95% CI, 55%–74%) of the total variance in BESRL. The remaining variance in both variables was due to nonshared environmental effects. The effect of age explained 9% in the variance of the BEHL and 6% in the variance of the BESRL.

Figure 1 summarizes the results of the bivariate genetic modeling. The AE model was selected on the basis of its best fit with the data and its theoretical acceptability. In the model, BEHL and BESRL shared an additive genetic component in common (Ac) which explained 75% (95% CI, 67%–81%) of the variance in BEHL and 54% (95% CI, 43%–64%) of the variance in BESRL. An individual environmental factor in common with the two traits (Ec) accounted for 25% (95% CI, 19%–33%) of the variance in BEHL and 17% (95% CI, 10%–27%) of the variance in BESRL. In addition, BESRL had its own additive genetic and individual environmental factors which explained the remaining variance. All in all, the results showed that the majority of the individual differences in BEHL and BESRL were explained by the same additive genetic effects.

Previous studies have indicated that age-related hearing loss is a complex trait and influenced by interplay between the environment and genetics (5–8). First, genetic factors may underlie the rate of change in hearing loss. Second, some evidence suggests that genetic factors may determine how vulnerable the inner ear is to risk factors for hearing loss (such as noise exposure), thereby making some people more prone or resistant to hearing loss (25–27). According to animal studies, there seems to be a gene (Ahl gene in mice) which affects both age-related and noise-induced hearing loss, making individuals with a particular Ahl genotype more susceptible to noise damage (25–27). Noise exposure may lead to cochlear damage in genetically susceptible persons even at levels that are not damaging to normally susceptible ears (26). According to our results, 25%–36% of the variance in hearing was explained by environmental factors. Assuming that all of the environmental variance in hearing acuity in our study was explained

Table 3. Univariate Genetic Models for Better Ear Hearing Threshold Level (BEHL) and Better Ear Speech Recognition Threshold Level (BESRL)

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Fit</th>
<th>Model Comparisons</th>
<th>Standardized Estimates % (95% CI)</th>
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<tr>
<td></td>
<td>–2 LL</td>
<td>df</td>
<td>Δ–2 LL</td>
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<tr>
<td>BEHL: Age: Regr = −0.0590</td>
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<td></td>
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<tr>
<td>ADE</td>
<td>721.020</td>
<td>424</td>
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<tr>
<td>AE</td>
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<tr>
<td>E</td>
<td>832.488</td>
<td>426</td>
<td>111.468</td>
</tr>
<tr>
<td>BESRL: Age: Regr = −0.0524</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ADE</td>
<td>807.716</td>
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<tr>
<td>E</td>
<td>880.942</td>
<td>423</td>
<td>73.226</td>
</tr>
</tbody>
</table>

Notes: The best-fitting model is in bold.
Regr = regression coefficient; a² = additive genetic effects; d² = dominant genetic effects; e² = nonshared environmental effects; –2 LL = –2 times log-likelihood; df = degrees of freedom; Δ–2 LL = difference between –2 LL of ADE model and the fitted model; Δdf = difference of degrees of freedom, AIC = Akaike’s information criterion; CI = confidence interval.
by noise exposure, that is the same magnitude, approximately a quarter, as observed in field studies concerning the etiology of noise-induced hearing loss (28). In this study we demonstrated that age-related hearing loss, previously ascribed predominantly to environmental factors, appears to be largely accounted for by genetic factors.

Research using contemporary molecular tools has provided insights into the genetic factors involved in the deterioration of hearing, but so far no individual gene has been identified as lying behind age-related hearing loss. Recently, DeStefano and colleagues (6) published a genome-wide linkage analysis of presbycusis in humans. About one third of the age- and sex-adjusted variance in the pure tone average at the low and middle frequencies was accounted for by genetic factors, with suggestive evidence of a linkage in chromosomes 10, 11, 14, and 18. Further studies need to replicate the suggestive linkage results and identify the underlying genes. Our results showing that a significant part of age-related hearing loss in the population at large is linked to genetic susceptibility underline the need for further genetic studies.

The heritability of hearing observed here was significantly higher than expected on the basis of a previous study of self-rated hearing (8). However, self-rated hearing and auditory tests differ from each other, and the results of these two measures may be complementary rather than being two measures of the same trait (29–31). In our data, self-reported and audiometrically measured hearing correlated only moderately. It can be assumed that auditory tests reflect auditory impairments, whereas self-rated hearing gives information about the limitation on activity from hearing impairments.

According to our results, the BEHL and the BESRL were accounted for mainly by the same genetic and environmental effects, but there was also a specific genetic and a specific environmental effect affecting speech recognition. Trait-specific effects of BESRL may be explained by the different, more demanding cognitive and neural processing required for speech recognition than for detecting signals in pure-tone audiometry.

The strengths of the current study were that the group of the participants formed a population-based, genetically informative sample of older women. The sample was also composed of nonclinical participants, allowing both good and poor hearing ability to contribute to the results. The audiometric measurements were performed in standardized conditions by one experienced audiologist. The validity of the results is supported by the fact that the prevalence of audiometrically measured hearing problems in our sample was similar to that in previous studies (1,2). However, heritability is always a population-specific and gender-specific estimate (32), and the results of this study cannot be directly generalized to other populations.

Summary

People with a family-history of age-related hearing loss may genetically be more predisposed to hearing problems. Such people, especially, may benefit from protection from environmental exposures and early fitting of hearing aids. Our study indicates that genes play a more important role in determining hearing ability than previous studies have suggested and provides a basis for genetic studies aiming at the identification of the genes causing age-related hearing loss.

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