INTRODUCTION

Hearing loss (HL) affects 3 per 1000 newborns, and the prevalence roughly doubles by age 4 (Nance and Morton, in press). In the U.S., by 60 years of age is affected by HL and the figure increases to more than 50% by age 85. At birth, genetic factors account for at least 50% to 70% of cases (Marazita et al. 1993). Syndromic deafness accounts for about 10% of cases, while genetic, for nonsyndromic HL explain the remaining 70%. Environmental or infectious etiologies are implicated in the remaining 30-50% of children with “non-genetic” HL (Marazita et al. 1993). In the past decade, over 100 genes for deafness have been identified. Without some estimates there will be over 300 genes, or 1% of the human genome, responsible for the mechanisms of auditory perception. Significant attention has been placed upon profound deafness, while milder forms of hearing loss have received less consideration, despite the fact that they affect a larger percentage of the population. Until the molecular bases of these forms of deafness are fully understood, gene therapy and other etiological, specific forms of treatment will not be possible. The current study examined the molecular basis of high frequency HL in probands ascertained from our national hereditary deafness DNA repository.

METHODS AND MATERIALS

We conducted a prospective clinical study of 39 subjects. We identified probands with high frequency hearing loss from our National Hereditary Deafness Repository. All probands had high frequency hearing loss, defined as hearing loss >25dB at 4kHz and above, with normal hearing below 4kHz. Clinical data and family history of HL were obtained on enrollment. Candidate deafness genes (Table 1) were screened either using direct sequencing (GJB2 and GJB6) or by single strand conformation polymorphism (SSCP), with mutation confirmation by sequencing. The 39 subjects ranged in age from 3 to 57 years old, (mean age at diagnosis of HL was 14.6 years). The population was of Caucasian (56%), African-American (30%), Hispanic (10%) and Asian (4%) origin. Family history of HL was noted in 27 subjects (73.0%). Sequence variants were present in 53.8%, but most were considered nonpathogenic.

RESULTS

Clinical: In our sample of 39 subjects, there was a roughly equal male to female ratio. Subjects ranged in age from 3 to 57 years old, while the mean age at enrollment into the repository was 13.9 years. The hearing loss affected both ears in 84.2% of the sample, and ranged in severity from moderate to severe (Figure 1). The population was of Caucasian (56%), African-American (30%), Hispanic (10%) and Asian (4%) origin. 27 subjects (73.0%) had a family history of HL. CT or MRI scans were available in 28% of the sample, with the majority (73%) read as normal. Molecular: Overall, sequence variants were present in 53.8% of the subjects for the candidate genes screened (Table 1). 23% of the probands (9/39) had GJB3 variants, all of them being characterized as silent mutations, with no change in amino acid sequence. In 20% (8/39) of the probands, sequence variants in the TECTA gene were identified, the majority being nonpathogenic mutations. Six probands (15%) had heterozygous sequence variants in the PDS gene, three subjects had heterozygous sequence variants in the COCH gene, and 2 silent mutations were detected in TECTA, all of which were nonpathogenic (Table 2). Clinically, one subject had Waardenburg syndrome. Notably, 8 subjects (20%) had changes in more than one gene.

CONCLUSIONS

A number of nonpathogenic sequence variants were identified in our subjects, with alterations in GJB3 being the most common. Gene-environmental interactions may contribute to the development of high frequency HL. Family history and genetic etiology should be explored in patients with high frequency HL.

REFERENCES