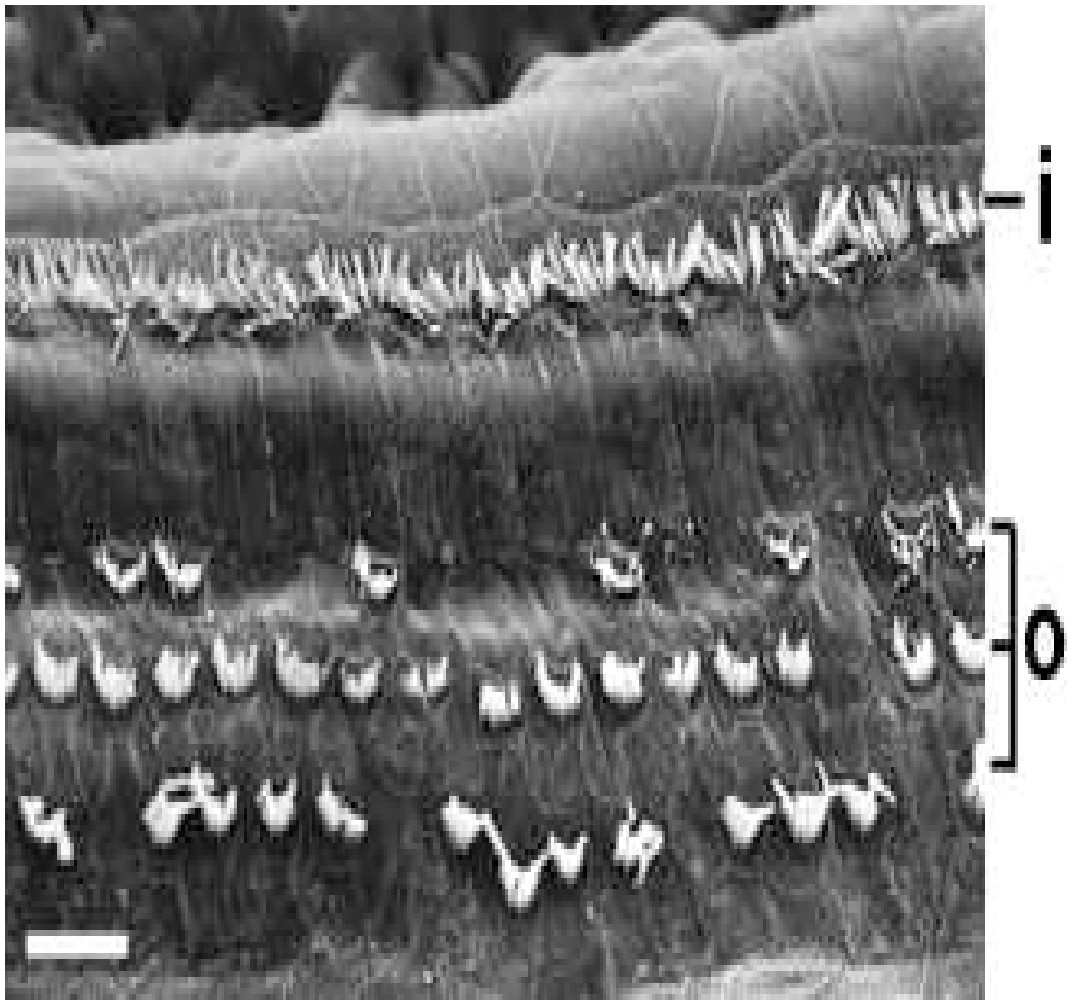
Introduction

- Conflicting views on the prevalence and nature of otoacoustic emission [OAE] abnormalities in ARNSHL families (Morell et al, 1998; Cohn & Kelley, 1999).
- Detailed study of OAEs in greater number of families +/- cx26 mutations.
- Elucidate prevalence of OAE anomalies and any specificity to this molecular group.

Fig 2. EM scan of permanent selective OHC damage.



- Majority of hereditary hearing loss is sensory.
- Involves abnormal development of the receptor cells (hair cells) of the inner ear.
- OAEs are a sensitive measure of sub-clinical auditory dysfunction.

Otoacoustic emissions [OAEs]:

- Widely used in human and animal studies to assess integrity of cochlear function.
- Also asses the effects of the efferent system on the dynamics of the cochlear processing [Kemp & Chum, 1980].
- Utilises a non-invasive technique.
- Main application in Universal Neonatal Hearing Loss Screening.
- Genetic factors are thought to have a role in the generation of OAEs [Hood, 1998].

Fig 3. Outer Hair-cell [OHC] Electromechanical Transduction.

- OHC activity with electro-mechanical coupling leading to transduction.
- Fast + slow electromotility generates active cochlear echoes [Kemp, 1978].

Fig 4. Modulation of OHC activity via MOCB efferent auditory pathways [Kemp & Chum, 1980]:

Study objectives:

1. To compare the prevalence of abnormal OAEs in carriers and controls.
2. To explore the possible association between any OAE anomalies and the presence of mutations in the *GJB2* gene.
3. To assess the value of OAEs as a clinical tool to identify carriers of ARNSHL.

Subject inclusion criteria (age range 25-45 years) :

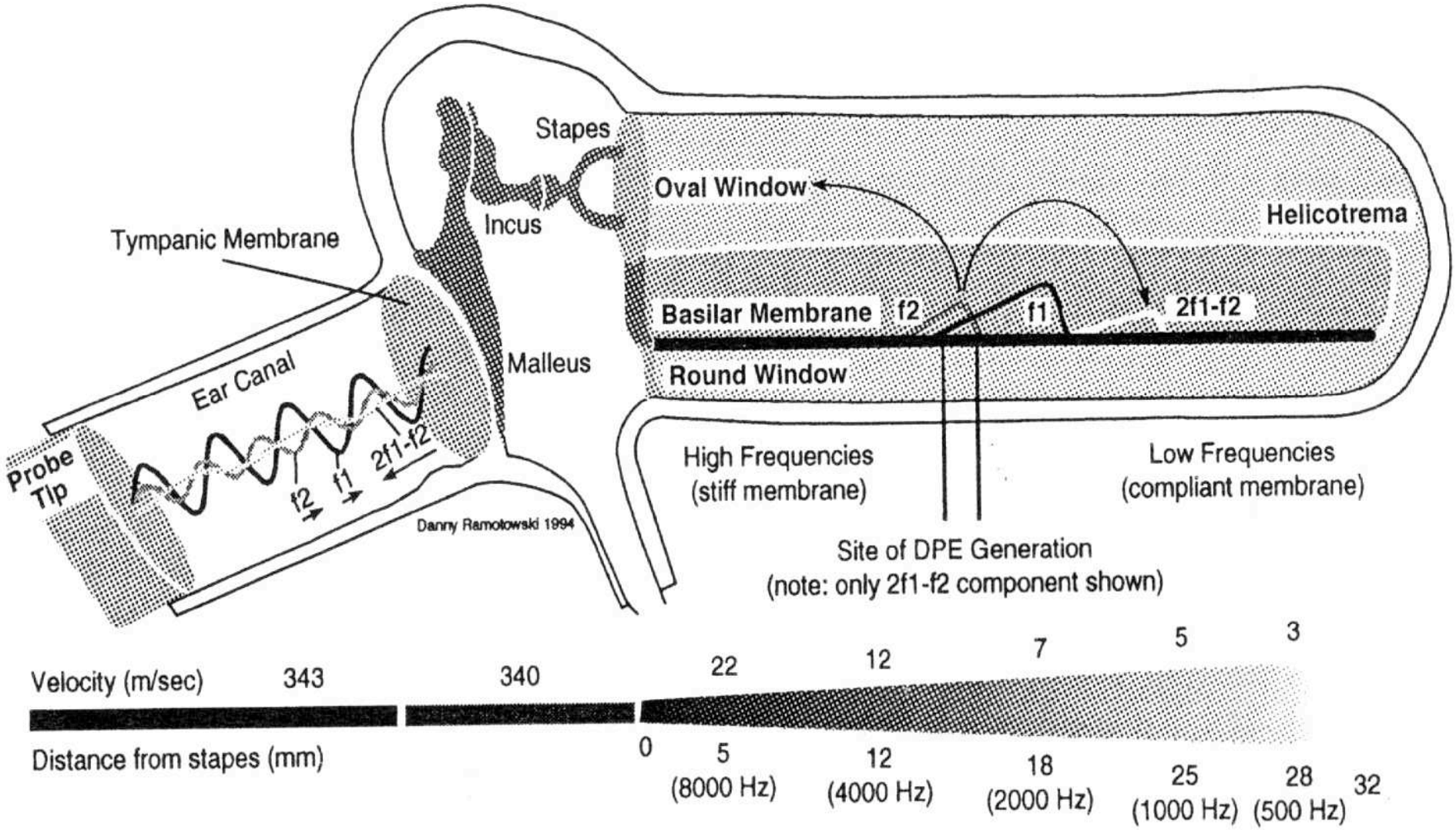
- Ten (5 parent pairs) normal hearing parents who had at least one hearing impaired child, found to have 2 pathogenic mutations in the *GJB2* gene (mean age: 38.5) >> ***cx26 +ve group***
- Ten (5 parent pairs) normal hearing parents who had at least 2 hearing impaired children, or consanguineous marriages with at least 1 hearing impaired child but did not exhibit mutations in the *GJB2* gene (mean age: 38) >> ***cx26 –ve group.***
- 5 male & 5 female control subjects (mean age: 37.5) >> ***controls***

Audiometric Investigations:

- *Pure-tone Audiometry*
- *Tympanometry*
- *OAE measurements:*

1. *Transient evoked otoacoustic emissions (TEOAEs)* [N: at least >3 dBSPL + > 50% reproducibility].
2. *Distortion Product otoacoustic emissions (DPOAEs)* [N: at least 6dBSPL above 'noise floor' level].
3. *Medial olivo-cochlear bundle (MOCB) efferent suppression test* [N: suppression effect at least > 1dB] [Ceranic et al, 1998].

Fig 5. Cochlea unrolled to show site of generation of DPOAE:



Genetic screening:

- *GJB2* screening consisted of DHPLC of exon 2 and sequencing of heteroduplexes.
- Heterozygotes for *GJB2* deletion and

–3170G>A splice site mutation.

- Mutation detection sensitivity detect at least 96% of mutations affecting the *GJB2* gene.

Fig 6. No statistical differences in mean pure-tone thresholds in carriers and controls at 6 Octave frequencies (t-test, P=0.1).

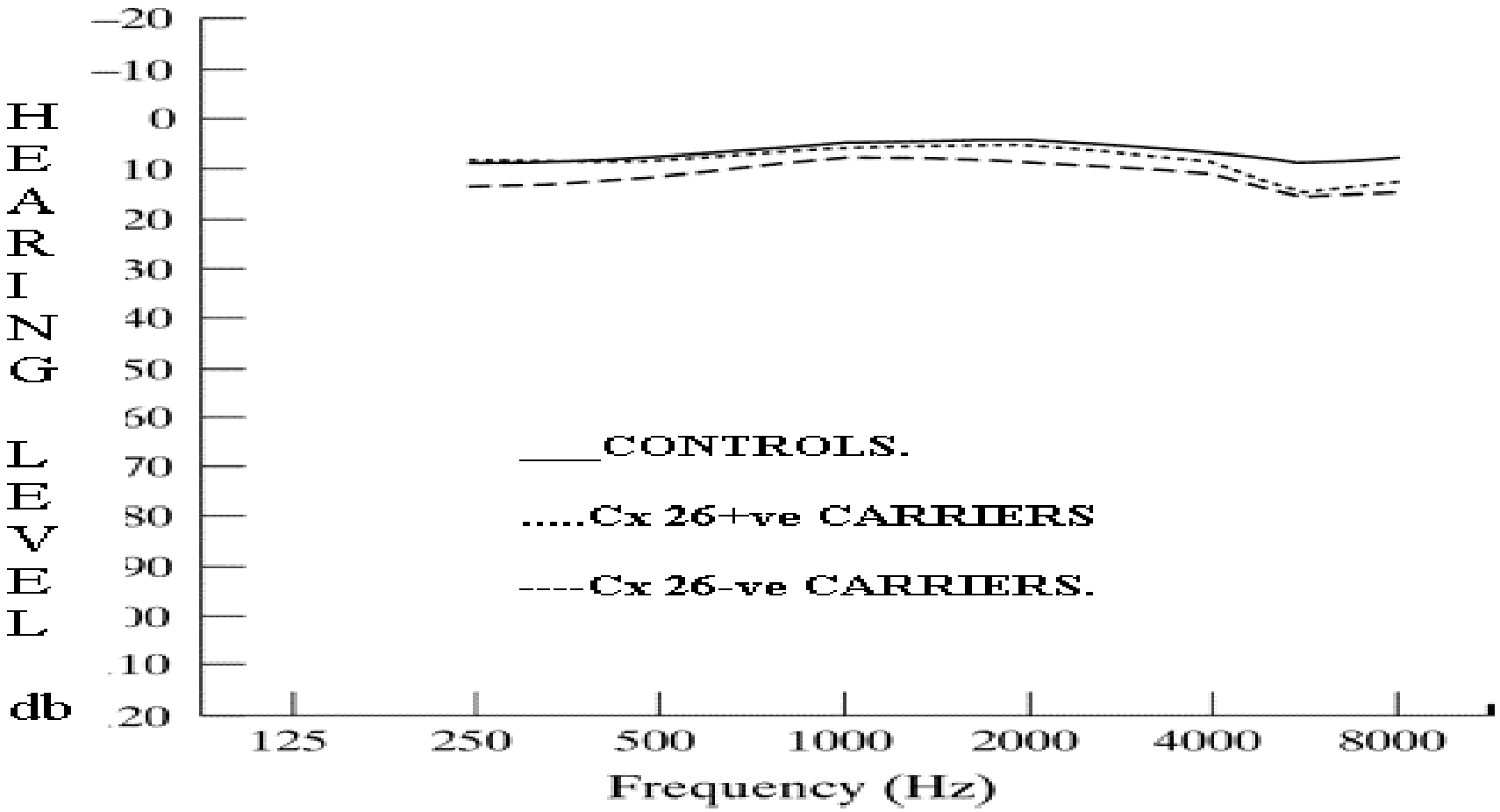
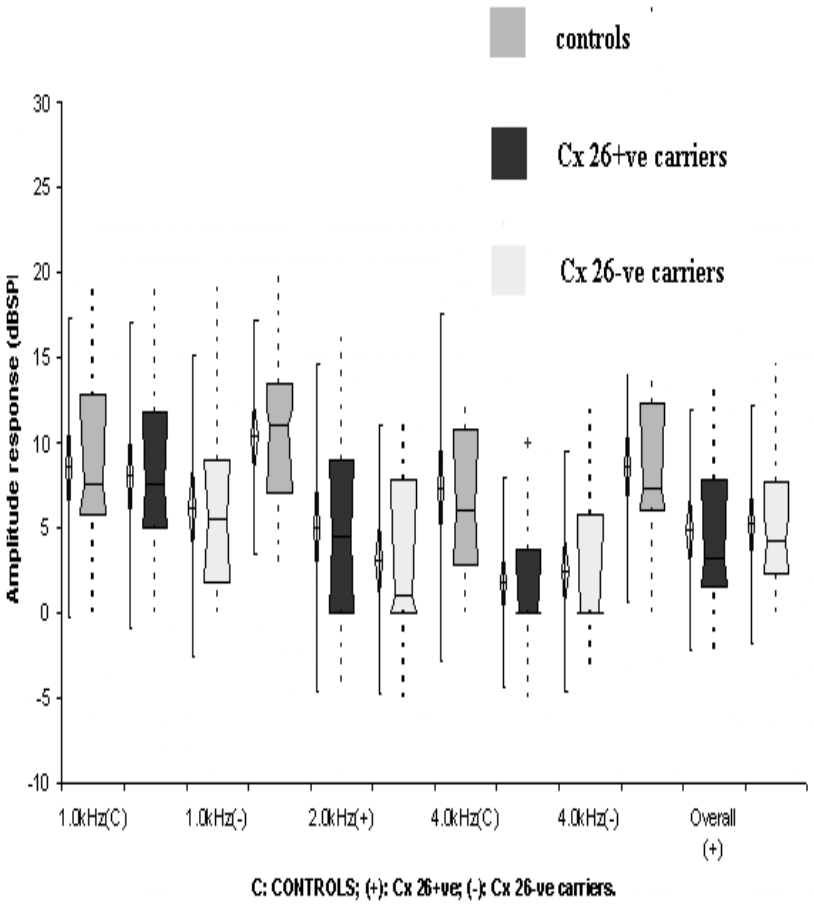
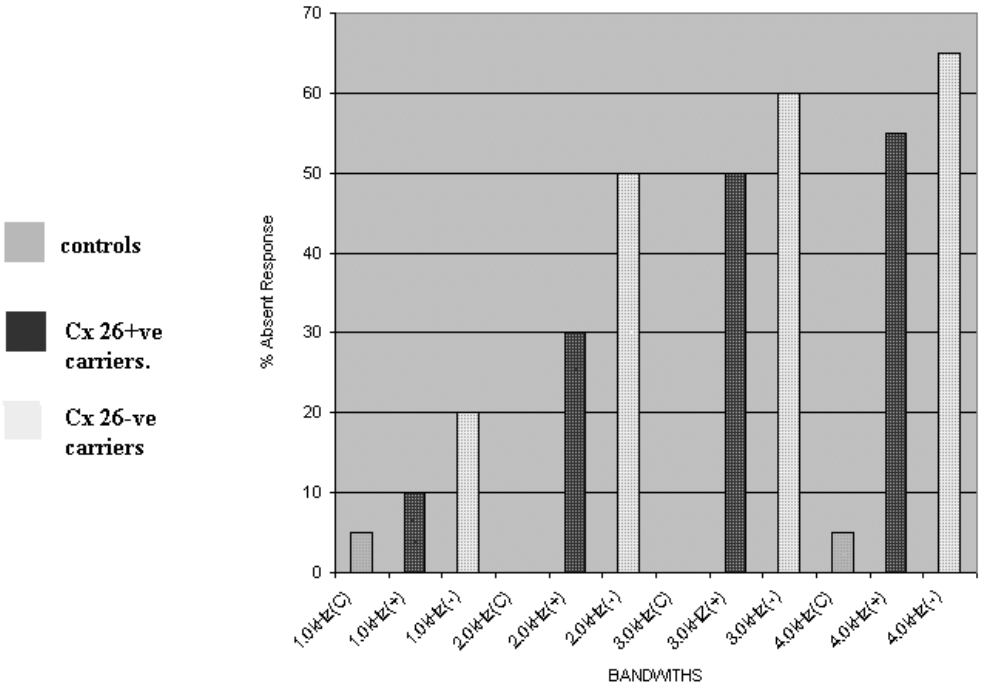


Fig 7. 95% CI for overall and frequency dispersive mean [blue] and median TEOAE amplitudes in carriers and controls:



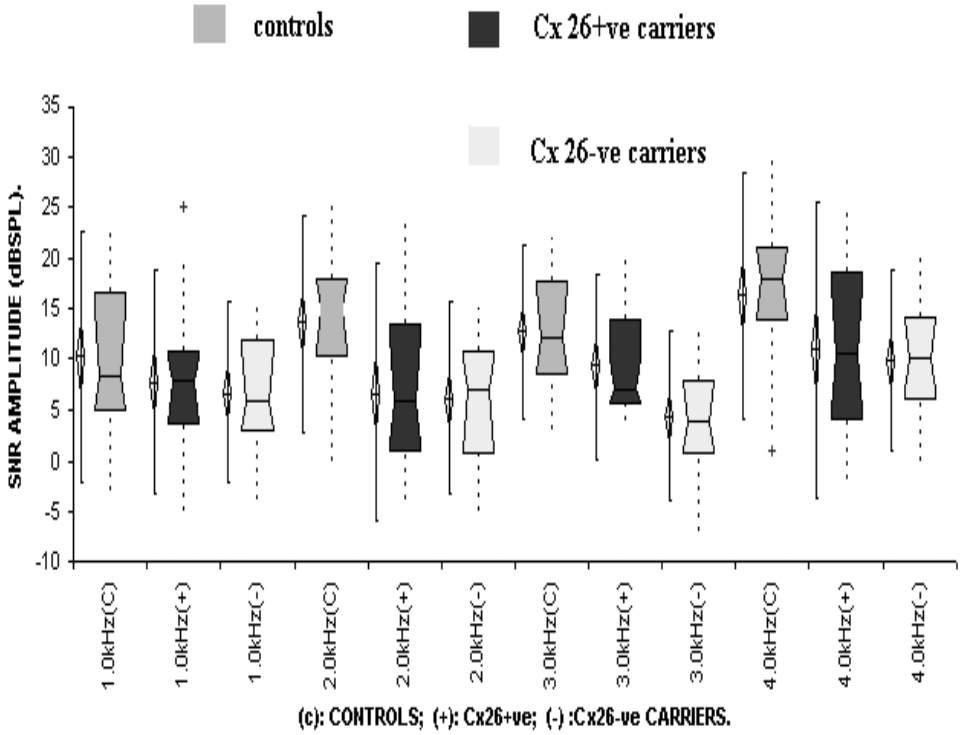
- Overall amplitude responses were significantly lower in the recessive groups (p=0.0018, two-tailed t-test).
- Spectral analysis showed significantly lower responses for both carrier groups in the 2.0 (p=0.04) & 4.0kHz (p=0.02) bands.

Fig 8. The percentage of absent TEOAE responses at each spectral band in ears of controls, cx26 +ve & cx26 –ve carriers.



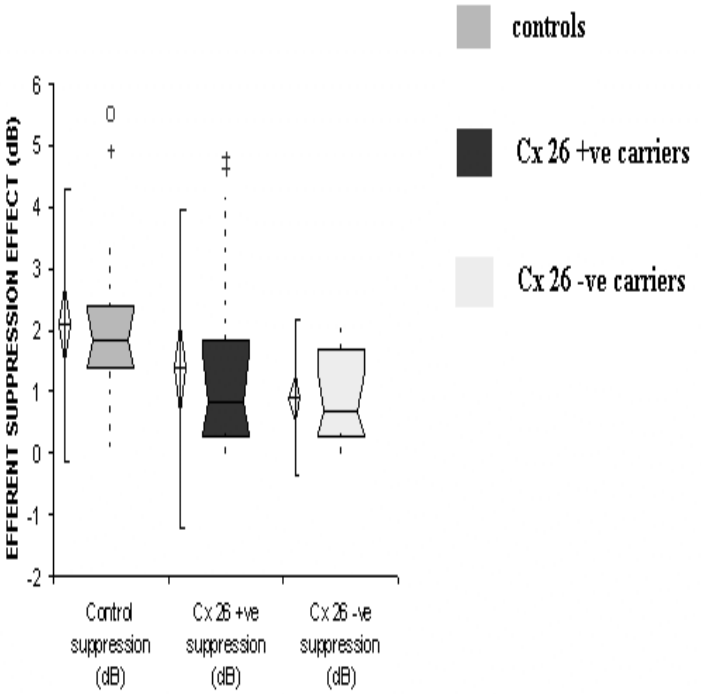
- Absent responses in 70% of cx26 –ve carriers, especially in bands >2.0 kHz.
- None of controls had absent TEOAE in the 2.0/3.0 kHz spectral bands.

Fig 9. 95% CI for mean [blue] and median DPOAE data for controls vs. carrier groups.



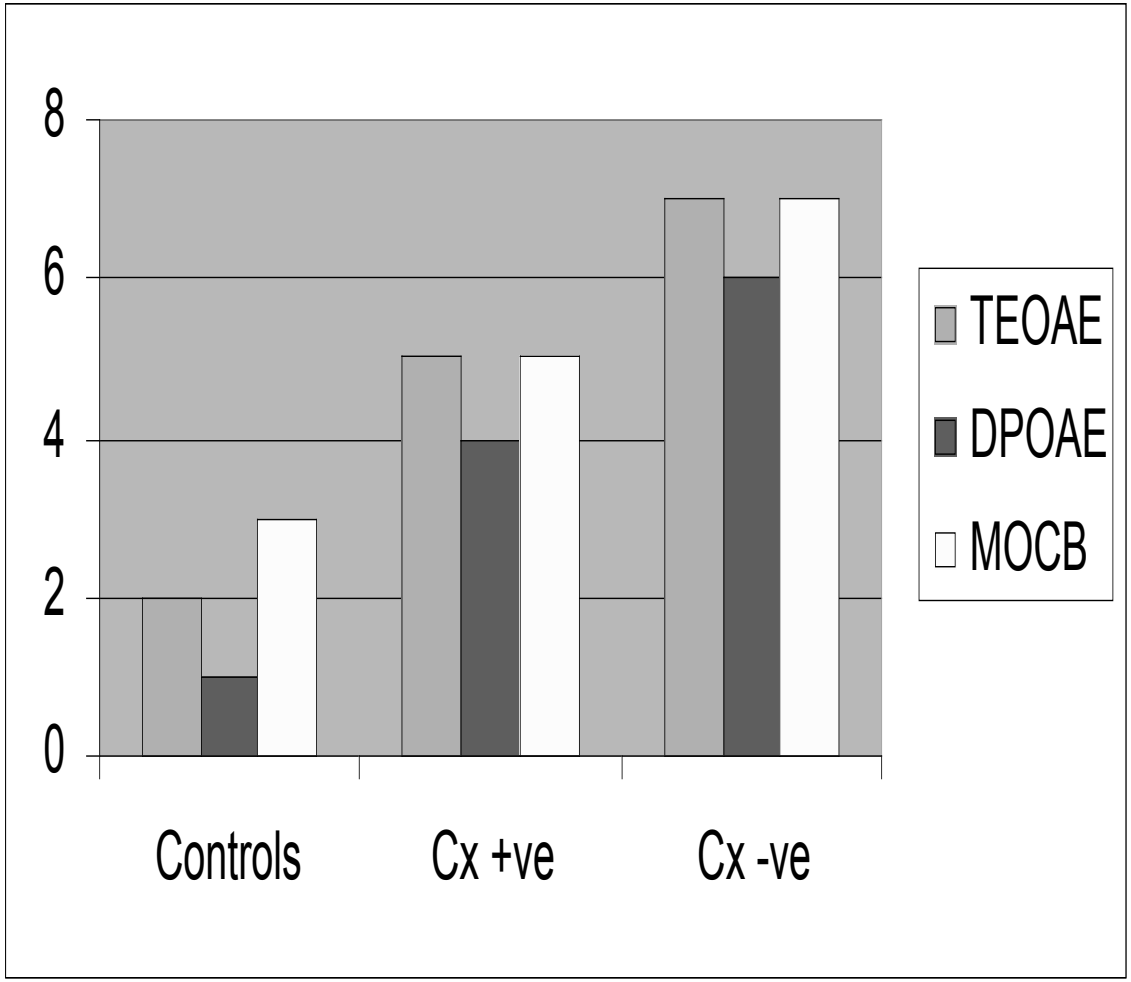
- DPOAE amplitudes were significantly reduced in recessive carriers ($p=0.001$, two-tailed t-test).
- Abnormalities were particularly prevalent in the cx26 –ve carriers in the mid- & high- spectral bands ($p<0.05$).

Fig 10. Boxplot of mean (blue) & median MOCB suppression effect in ears of controls, Cx +ve and Cx –ve groups.



- Significantly smaller suppression effect in carrier as whole group (p=0.014).
- Mean efferent suppression effect of 0.91dB was lower in the Cx –ve group (p=0.002, two-tailed test).

Fig 11. Number of subjects in each group with abnormal TEOAEs, DPOAEs or MOCB suppression test.



- The highest proportion of OAE abnormalities, either unilateral or bilateral, were found in the cx26 –ve carriers.

Summary of cardinal findings:

- TEOAE & DPOAE amplitudes were significantly lower in ears of carriers than controls.
- The mean amplitudes of TEOAEs & DPOAEs were lowest in ears of the Cx –ve group.
- The TEOAE abnormalities were found primarily in the 2-4 kHz band.
- Significantly reduced MOCB suppression effect was found in the cx26 –ve carriers only.

Conclusions:

- The study provides further evidence for the value of OAEs in unveiling subclinical cochlear dysfunction in carriers of ARNSHL.
- The proportion of greatest abnormalities was detected in the cx26 –ve carriers.
- The feature of high TEOAE absent responses at 2.0 & 4.0 kHz bands shows susceptibility of the mid-high frequency regions to genetic factors, particularly as it was not encountered in any of the controls.

Conclusions:

- The mid-frequency abnormalities are not sufficiently specific as a clinical tool to detect ARNSHL carriers as:
  1. The OAE abnormalities were not distinctive,
  2. The abnormalities were particularly prevalent in the cx-ve group, assumed to be highly heterogeneous genetically.

Conclusions:

- The finding of reduced MOCB efferent suppression effect in cx –ve carriers may reflect a different transduction mechanism to that proposed for the genetically homogeneous cx +ve carriers, with altered endocochlear K+ ion recirculation [Kelsell et al., 1998].

References:

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