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 assess 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]:

![Image of auditory pathways](image-url)
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 \textit{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].
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