EUROPEAN WORKING GROUP ON GENETICS OF HEARING IMPAIRMENT

The second workshop of the European Concerted Action H.E.A.R. (of the European Working Group on Genetics of Hearing Impairment) was held during past 11-13 October 1996, in Milano, Italy at the CRS Amplifon Auditorium with the participation of 150 researchers from European countries and few from non-European countries.

The meeting was divided into two sections: a section reserved for the work of the groups that are involved in the different aspects of the research of the Concerted Action. In this phase of the project, the work of the groups was aimed to establish common terminology as well as common working protocols and the organisation of a Data Bank to coordinate exchange of data and findings from different groups (Audiologists, ENT specialists, Maxillo-facial specialists, Ophthalmologists, medical geneticists, molecular geneticists, etc.).

The second section of the Meeting was open to all interested researchers even if not members of H.E.A.R. The coordinators of the groups (Martini, Sthephens, Parving, Luxon, Calzolari, Cremers, Read) summarised in this section the outcome of the group work and presented as well results from their work. Their presentations along with that of: Karen Steel (Nottingham) "Genetics of deafness"; Peter Phelps (London) "Radiology of inner ear defects"; Ségolène Aymé (Villejuif) "Genetics of Cranio-facial malformations"; Guy van Camp (Antwerp) "Locating genes for hearing loss"; William Kimberling (Omaha) "Molecular approaches to mutation identification"; Richard Smith (Iowacity) "Homozygosity mapping applied to hereditary hearing impairment; localizing recessive deafness genes"; Christine Petit (Paris) "Physiopathology of Usher syndrome type IB" as well as all the other presentations mentioned in the program reported at the end of the present Infoletter, represent the state of the art in this field.

Furthermore, the informatic work that have been developed by Guy van Camp (Hereditary Hearing Homepage: http://dnalab-www.uia.ac.be/dnalab/hhh/) and Leopoldo Saggin & Manuela Mazzoli (Database of families with Non-syndromic hearing impairment, http://www-fog.bio.unipd.it/audiology/family.html, temporary address) is intended to become a common working platform and to be a useful tool for the researchers of the Concerted Action as well as source of information for anyone interested in this topic.

The meeting was the first official meeting of the European Working Group on Genetics of Hearing Impairment, after the approval of the European Committee Directorate XII as Concerted Action in the BIOMED 2 program.

The papers presented in Milano have been collected and will be published in a volume from a new series dedicated to the work of our Concerted Action by Whurr, London.
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This Infoletter is primarily intended to be a tool for rapid communication relating both participants in the HEAR project and to general activity in the field. All readers are invited to submit items and to announce related conferences and publications. Contributors are kindly invited, whenever possible, to send the material by E-mail to: Alessandro Martini at the above address.
1. STUDY GROUP ON TERMINOLOGY, DEFINITIONS, AND HEARING ASSESSMENT

Group Co-ordinator - Dafydd Stephens, (Cardiff, Wales)

This group has met three times so far, once prior to the formal inception of the Working Group, (Copenhagen February 1996) once during the International Congress of Audiology (Bari, June 1996) and at the Plenary work shop, (Milan, October 1996). The first meeting was attended by eleven members of the group, the second by nine and the third by seventeen. At each of these meeting we addressed all five targets and have been helped by relevant input from the other working groups, particularly the Epidemiology group, with which we have had two joint meetings.

In this report I shall discuss our progress in the context of the 5 targets listed in the project outline and in the context of the timescale proposed.

1. Definition of relevant genetic and audiological terms.

We have added to initial proposals a consideration of Epidemiological terms (in conjunction with Study group 2), terms related to balance tests and balance disorders (in conjunction with study group 3) and guidelines for audiologists wishing to collaborate with genetic laboratories (in conjunction with Study group 5). We are particularly grateful to the group leaders Agnete Parving, Linda Luxon and Andrew Read, together with Adrian Davis, Bob Mueller and Marcus Pembury in this context.

(a) Audiological Terms - The relevant terms have been agreed and are listed and defined as appendix 1.

(b) Genetic Terms - These have been agreed and are listed as appendix 2.

(c) Epidemiological Terms - These are shown as appendix 3.

(d) Vestibular terms - These are currently in preparation in conjunction with Study Group 3, and should be available and circulated by the end of the first year of the project.

(e) How to collaborate with genetic laboratories - Guidelines for audiologists are complete and presented as appendix 4.

This section of our work should thus be completed by the end of the first year of the Project as envisaged by the section on project milestones.

2. Definition of Phenotypes

Initial attempts in this respect resulted in considerable confusion because of the different formats and approaches to data presentation by the various researchers who had described the different phenotypes. It was therefore decided to produce a specific
format in which these should be defined. Furthermore it was later agreed that, initially this should be restricted to phenotypic descriptions of non-syndromal hearing impairment. At the time of writing, while only one gene responsible for non-syndromal hearing impairment has been identified, this and the other non-syndromal conditions in which the genes have been located should be targeted first. As information becomes available, the phenotypes related to specific mutations will be described.

This work is being carried out by Dafydd Stephens (Cardiff), Valerie Newton (Manchester) and Manuela Mazzoli (Ferrara) in conjunction with the data base approach to individual families being developed at Padova and Ferrara by Leopoldo Saggin and Manuela Mazzoli for the project as a whole. It is envisaged that the definition of phenotypes will constitute a subset of that database. The work will also relate closely to, and compliment the Hereditary Hearing Loss Home Page established by members of Working Group 5 at Antwerp on the Internet.

The current format for defining the phenotypes is as follow:

**Non-Syndromal Hearing Impairment**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>MIM No:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal Dominant/Autosomal Recessive/X-linked Dominant</td>
<td></td>
</tr>
<tr>
<td>X-linked Recessive/Mitochondrial/Polygenic</td>
<td></td>
</tr>
</tbody>
</table>

Gene Location: Gene Identification
Mutations identified:

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Geographical location of families:
Ethnic origins of families:

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Hearing Loss:

Percentage affected by age band and by gender
Pathology

Type: Conductive/cochlear/mixed/neural/central
Severity:
Configuration: (1)
Unilateral/bilateral
Age of onset: (2)
Progression: (3)
Vestibular involvement:
Interfamilial variability

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Source References for
1. Gene location & identification
2. Hearing loss descriptors
The timescale for the definition of Phenotypes is likely to extend throughout the 3 years of the project in view of the rapid advances currently taking place in the localisation and identification of genes responsible for non-syndromal hearing impairment. Currently it is envisaged that there are likely to be some 50 separate genes responsible for Non-Syndromal Autosomal Dominant genetic hearing impairment and a similar number for Non-Syndromal Autosomal Recessive hearing impairment, with smaller numbers resulting in X-linked and mitochondrial related conditions.

It is planned that a first list of the phenotypes will be produced by the end of the first year of the project.

3. Audiometric Investigation of Probands

This was approached in two ways in order to define an agreed minimal set of audiometric investigations which should be performed on probands with a genetic hearing loss. Firstly, a survey was conducted of those individuals within the groups 1 and 2 of the concerted action programme currently performing such testing, to determine which audiometric procedures are currently being used. These results were then discussed at the meeting in Copenhagen at which a minimal set of tests was defined together with a listing of other test procedures which were considered to merit further investigation.

The results of the survey of 18 departments is shown in figure 1. They comprised groups from Austria, Denmark, England (x4), Finland, France, Germany, Ireland, Italy (x3), Netherlands (x2), Portugal, Sweden and Wales. (Not all provided data on both probands and carriers, so the numbers in this figure are based on 16 returns).

From this it is apparent that the only tests invariably carried out in the great majority of departments were air and bone conduction audiometry, together with otoadmittance testing including tympanometry and acoustic reflex threshold determination.

It was recommended that the following should comprise a minimum set for children aged over 5 years and for adults.

3.1.1 Clinical Tests - Voice, tuning fork, Barany box.

3.1.3 Pure Tone Audiogram - Air conduction (with masking where indicated) - at least at octave frequencies 125 Hz-8kHz.
3.1.3 Bone Conduction - Always masked - to be performed except when hearing is normal at the low frequencies.

3.1.4 Békésy Audiometry (or Rapid Sweep Audioscan) 125Hz - 8 kHz, 2.5 dB/s attenuation, 45 or 60s/oct. This gives better information on the configuration of the audiogram, and should be performed in all cases with mild or moderate hearing impairment, and old enough to perform the test. If Békésy audiometry is not available, pure tone audiometry should be performed including the $\frac{1}{2}$ octave intervals (0.75, 1.5, 3 and 6 kHz).

3.1.5 Oto-admittance - 220-250 Hz probe tone, +200 to -400 daPa should be performed unless the tympanic membrane is perforated.

3.1.6 ARTs - 500-4000 Hz + WBN ipsilateral and contralateral with non-acoustic reflex thresholds measures if no responses are present with acoustical stimulation.

3.3 The following should be performed when clinically indicated.

   ABR.

3.4 The following are not in the minimum set.

3.5 Balance Tests will be defined by Study Group 3.

3.6 Children Under 5 years of age - As many as possible of the tests recommended for over 5s should be included. TOAEs and ABR should be performed when a full test battery is not possible. The other tests used will be age dependent but should include at least one test of low frequency threshold and one of high frequency threshold.

3.7 PROGRESSION - Full audiogram or Békésy audiometry should be performed after one year and subsequently at 2 year intervals unless there are any significant changes in the hearing level.

3.8 TINNITUS - It should be noted whether or not this symptom is present.

3.9 It was agreed that the following tests should be piloted:

   a. Extended High Frequency Audiometry - after some piloting following the initial meetings, it was agreed to discontinue this as the results were too inconsistent.

   b. Otoacoustic Emissions - A working group comprising Kunigunde Welzl-Müller (Innsbruck), Stavros Hatzopoulos (Ferrara), David Parker (Manchester) and Fei Zhao (Cardiff) has been established to define an appropriate protocol, particularly to identify retrocochlear causes of hearing impairments.

4. Audiometric Investigation of First Degree Relatives
Firstly current practice was surveyed in the same way as tests used with probands. We then defined a current minimal set for use and highlighted procedures of further investigation and evaluation.

The results of the survey of current practice are shown in figure 2 which summarises the responses from 17 centres. It may be seen that the only test regularly performed at a majority of centres was pure tone audiometry.

4.1 After considerable discussion the following conclusions were reached with regard to a **minimal set of tests**.

Tests should be applied to both parents, any children and all siblings of the proband. The aim is particularly to demonstrate any hearing loss which may be present.

1. All branches of the family should be followed as far as possible.
2. Clinical examination and tuning fork tests should be performed.
3. Békésy Audiometry 125 Hz-8kHz should be conducted to define the audiometric configuration, with pure tone audiometry at \( \frac{1}{2} \) octave intervals conducted where that is not available.

4.2 **The following tests would not normally be performed:**

4.2.1 Pure Tone Audiometry - Unless Békésy/Audioscan not available. If tested, it should be performed at \( \frac{1}{2} \) octave intervals.

4.2.2 Speech Audiometry - Speech in noise testing will be considered at a later stage (see Target 5).

4.2.3 ABR.

4.2.4 ARTs.

4.2.5 TOAEs - May be reconsidered lately.

4.2.6 Vestibular tests - unless abnormalities found in the proband.

4.3 It was agreed that the following tests should be further considered and investigated as at present there is considerable confusion arising from the use of different stimulus parameters and criteria for abnormalities. They should at present be restricted to obligate carriers whose hearing level is better than 20 dB PTA, with normal middle ear function, and no history of ear infection, head, noise or acoustic trauma or ototoxic drugs.

4.3.1 Audioscan Testing - Initial pilot studies had indicated considerable different results between centres and the reasons for some of these differences were highlighted by detailed analysis performed by Fei Zhao and Dafydd Stephens.

It was agreed that:
(a) Janjua (Manchester) Geneviève Lina Granade (Lyon) and Dafydd Stephens should agree a universal protocol.

(b) Large groups of controls of different ages should be tested once this protocol had been defined.

c) Patient testing should be restricted to those in whom at least the gene location had been identified.

4.3.4 **Distortion Product Otoacoustic Emissions**

The problems of stimulus parameters and quantification were discussed. It was agreed that these should be investigated further by the subgroup, looking at Otoacoustic Emissions in probands.

4.3.5 **Extended High Frequency Testing**

This was considered by the Group and investigated further by Martti Sorri (Oulu) who concluded that it was of little value in the detection of carriers.

5. **FUTURE AREAS**

These include Audioscan and Distortion product Otoacoustic Emissions which have been discussed under the testing of probands and Carriers.

Other areas currently being explored are:

a. Transient Otoacoustic Emissions  
b. Frequency Resolution  
c. Temporary Threshold Shift  
d. Speech in noise tests.

**Target 1: DRAFT AUDIOLOGICAL, EPIDEMIOLOGICAL & GENETIC DEFINITIONS**

**Appendices 1-4**

Dafydd Stephens, Adrian Davis & Andrew Read

*The Definitions outlined below are a somewhat pragmatic series of definitions produced with the aim of providing uniformity and coherence to studies on the genetics of hearing impairment.*

**REFERENCES**


APPENDIX 1

AUDIOLOGICAL TERMS
(Dafydd Stephens)

Pathology - An abnormality of structure. In the auditory system this may entail, for example, atrophy of the stria vascularis.

Impairment - Defective function of the auditory system which may be measured using psycho-acoustical or physiological techniques. The terms “Hearing Disability” and “Handicap”, or even “Hearing Handicap” are often loosely applied to hearing impaired people. These terms are not usually relevant to studies on genetic hearing impairment and should be avoided, except when used in the following contexts:
Disability - The auditory problems experienced and complained of by the individual, (e.g. difficulty hearing in a noisy place).
Handicap - The disadvantage resulting from an impairment or disability that prevents or limits the fulfilment of a role that is normal for the individual, (e.g. social isolation).

2. AUDIOMETRIC MEASURES (After Parving & Newton, 1995; Liu & Xu, 1994).

Deafness - This term has many different meanings in different contexts and should be avoided in the context of genetic hearing impairment.

Hearing Level - The level of hearing of the individual for pure tones compared with internationally agreed standards (ISO, 389, 1991).

Hearing Levels - Applied to the better hearing ear, averaged across 500, 1000, 2000 and 4000 Hz (Pure tone average, PTA). If these verbal descriptors are used. The actual hearing level should also be included.

Mild - over 20 dB and less than 40 dB
Moderate - over 40 dB and less than 70 dB
Severe - over 70 dB and less than 95 dB
Profound - equal to and over 95 dB

Frequency Ranges
Low - Up to and equal to 500 Hz
Mid - Over 500 Hz up to and equal to 2000 Hz
High - Over 2000 Hz and equal to 8000 Hz
Extended High - Over 8000 Hz
**Audiometric Configurations**

*Mid Frequency U-shaped* - $\geq 15$ dB difference between the poorest thresholds in the mid frequencies, and those at higher & lower frequencies.

*Low frequency Ascending* - $\geq 15$ dB from the poorer low frequency thresholds to the higher frequencies.

*Flat* - $< 15$ dB difference 125 - 8000 Hz

*High Frequency:*
  - *Gently Sloping* - 15-29 dB difference between the mean of 500 & 1000 Hz and the mean of 4000 & 8000 Hz.
  - *Steeply Sloping* - $\geq 30$ dB difference between the above frequencies.

**Unilateral Hearing Impairment** - One ear only has either $> 20$ dB Pure Tone Average or one frequency exceeding 50 dB, with the other ear better than or equal to 20 dB.

**Asymmetrical Hearing Impairment** - $> 10$ dB difference between the ears in at least two frequencies, with the pure tone average in the better ear exceeding 20 dB HL.

**Progressive Hearing Impairment** - A deterioration of $\geq 15$ dB in the Pure Tone Average within a 10 year period. Results in those aged over 50 years should be treated with some reservation. In all cases, the time scale and patient age should be specified.
3. TYPES OF HEARING IMPAIRMENT

**Conductive** - Related to disease or deformity of the outer/middle ears. Audiometrically there are normal bone conduction thresholds (< 20 dB) and an air-bone gap ≥ 15 dB averaged over 0.5, 1 and 2 kHz.

**Sensorineural** - Related to disease/deformity of the inner ear/cochlear nerve with an air/bone gap < 15 dB averaged over 0.5, 1 and 2 kHz.

**Mixed** - Related to combined involvement of the outer/middle ears and the inner ear/cochlear nerve. Audiometrically > 20 dB HL in the bone conduction threshold together with ≥ 15 dB air-bone gap averaged over 0.5, 1 and 2 kHz.

**Sensory** - A subdivision of sensorineural related to a disease or deformity in the cochlea.

**Neural** - A subdivision of sensorineural related to a disease or deformity in the cochlear nerve

**Central** - A sensorineural hearing loss related to a disease or deformity central nervous system nostral to the cochlear nerve.
APPENDIX 2

GLOSSARY OF GENETIC TERMS
(Andrew Read)

Allele One or several possible forms of a particular gene which may or may not be pathological.

Allelic heterogeneity - Allelic heterogeneity is seen when many different mutations at the same genetic locus can cause a disease. This is almost always the case - e.g. Waardenburg syndrome Type 1 is always caused by mutations at the PAX3 locus, but different families usually have different PAX3 mutations.

Association - co-occurrence at a frequency significantly different from statistical chance. Characters may be associated in a phenotype, or a genetic condition may be associated in population with a particular allele at a locus. Associations can be positive or negative.

Autosome - A chromosome other than a sex chromosome (X or Y).

Autosomal inheritance - The transmission of an allele carried on an autosome. Autosomal inheritance is suspected when a character can be transmitted by a parent of either sex to a child of either sex.

Autosomal dominant - The pedigree pattern seen when an allele at an autosomal locus causes a dominant character. *Pedigree description of autosomal dominant inheritance.* Both males and females can be affected. The disorder is transmitted from generation to generation and can be transmitted in all possible ways; female to female, female to male, male to female and male to male (this latter specifically distinguishes autosomal from X-linked inheritance). Formal segregation studies are not usually possible to be able to see that the ratio is 1:1 affected: non-affected in individual families. In small families the mode of inheritance can be difficult to determine, but transmission across three generations is good evidence for dominant inheritance. Many dominant conditions are variable (even within families) and may skip generations.

Autosomal recessive - The pedigree pattern seen when an allele at an autosomal locus causes a recessive character. *Pedigree description of autosomal recessive inheritance.* Both males and females can be affected. If the parents of affected individual(s) are consanguineous, then recessive inheritance is more likely, but not certain. Usually only individuals within one sibship are affected; parents and other relatives are usually unaffected. In most cases there is only one affected individual in the family, making the pedigree pattern hard to identify as autosomal recessive, but in large multiply inbred kindreds, affected individuals may be seen in several branches of the family.

Cousin - in genetics, the world “cousin” should be used only as part of the specific terms “first cousin”, “second cousin” etc., and not as a general term for “relative”. First
cousins are the offspring of sibs. Two people are second cousins if their parents are first cousins.

**Degree of relationship** - First-degree relatives are parents, offspring, sibs; these relatives share half their genes. Second-degree relatives are grandparents, grandchildren, uncles, aunts, nephews, nieces, half-sibs; these relatives share one quarter of their genes. Third-degree relatives share one eighth of their genes; first cousins are the main category ascertained in practice.

**Dominant** - A character which is manifest when present in the heterozygous state.

**Genotype** - The genetic constitution of a person. One can talk of the genotype at a single locus, or the overall genotype. Cf. **Phenotype**.

**Homozygous** - having two identical alleles at a locus

**Heterozygous** - having two different alleles at a locus

**Inbred** - A person is inbred whose parents are blood relatives (consanguineous). Since ultimately everybody is related, a practical working definition is that the parents are second cousins or closer relatives.

**Kindred** - an extended family.

**Locus** - The position that the gene occupies on a chromosome. Since people have a pair of each autosome, a person has two alleles (identical or different) at each autosomal locus.

**Locus heterogeneity** - locus heterogeneity is seen when indistinguishable mendelian disorders can be caused by mutations at more than one locus. This is a common finding in genetics, e.g. Usher Syndrome Type 1 can be caused by mutations at loci on the long arm of chromosome 14 (14q31), the long arm of chromosome 11 (11q13) or the short arm of chromosome 11 (11p13).

**Lod score** - the statistical outcome of linkage analysis. The logarithm of the odds of linkage versus no linkage. A lod score above +3 gives significant evidence for linkage, and a score below -2 gives significant evidence against linkage.

**Mitochondrial inheritance** - Each mitochondrial contains several copies of a small circular DNA molecule containing 37 genes concerned with mitochondrial function. Mitochondria are transmitted in the egg but not in the sperm. Whe a condition is caused by a mutation in the mitochondrial genome, mothers pass it on their children of both sexes, but fathers do not transmit it. Pathological mutations usually affect only a proportion of the mitochondria (heteroplasmy), and the consequences of inheriting a mitochondrial mutation can be very variable, both between individuals in a family and between different tissues in the same individual. Characteristically, mitochondrial disease affects more than one organ system, e.g. hearing impairment and diabetes.
Non-penetrance - describes the situation when a person carrying a gene for a dominant character does not manifest the character. This is because of the effects of other genes or of environmental factors.

Nuclear family - parents and their children; any larger family can be called a kindred.

Offspring - A person’s offspring are his or her children, regardless of their age.

Penetrance - the probability that a phenotype will be seen with a given genotype.

Phenotype - the observed characteristics of a person (including the result of clinical examination). Compare with Genotype.

Recessive - A character that is manifest only in the homozygous state, and not in heterozygotes.

Sibs (siblings) - brothers and sisters, regardless of sex.

Sibship - a set sibs.

Syndrome - the occurrence together of several features having a presumed common cause.

X-linked inheritance - X-linked inheritance is seen when a condition is caused by an allele located on the X chromosome. Pedigree description of X-linked inheritance. Many X-linked diseases are seen only or almost only in males; where females are affected they may be more mildly or more from his mother and never from his father, so male to male transmission rules out X-linked inheritance. The line of inheritance in a pedigree must go exclusively through females or affected males. All daughters of an affected male are carriers. The distinction between dominant and recessive is less clear-cut with X-linked than with autosomal conditions; however, female heterozygotes for most X-linked conditions are not obviously affected (even though testing may reveal sub-clinical signs of affections), so these conditions are X-linked recessive.
APPENDIX 3

EPIDEMIOLOGY
(Adrian Davis)

**Cohort** - the component of the population that is born during a particular period and identified by period of birth, so that its characteristics (e.g. prevalence of childhood hearing impairment, age at first hearing aid fitting) can be ascertained as it enters successive time and age periods.

**Cohort Study** - has now come to mean many things such as follow-up study, prospective study, longitudinal study. A cohort study is essential to understanding change over time and the impact of services for hearing impaired children. (A study of cases arriving at a clinic, e.g. in year 1996 is **not adequate** for giving an unbiased estimate of the effect of service provision etc).

**Incidence** - the number of new instances of a specific condition (e.g. hearing impairment from meningitis) occurring during a certain period in a specified population.

**Incidence rate** - is the rate at which this occurs per standard population, e.g. 10 new cases per year per 100,000 children.

**Odds Ratio** - (sometimes known as relative odds). The ratio of two odds. The term “odds” is defined differently, depending on what is under discussion. Consider the following concerning distribution of disease given exposure to a risk:

<table>
<thead>
<tr>
<th>Exposed</th>
<th>not exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>a</td>
</tr>
<tr>
<td>No disease</td>
<td>c</td>
</tr>
</tbody>
</table>

where a.....d are the numbers of people in each category, then the odds ratio is \((a * d)/(b * c)\).

The exposure odds ratio for a set of case control data is the ratio of the odds in favour of exposure among the cases \((a/b)\) to the odds in favour of exposure among the non-cases \((c/d)\) --> \(a*d/b*c\). For a rare disease (< 2% prevalence of incidence) this is a good estimate of the risk ratio.

**Odds Score** - is synonymous with odds ratio.

**Population Study** - the whole collection of units from which a sample may be drawn; not necessarily a population of people - it may be a collection of hearing aid clinics, schools for the deaf, etc. The sample is intended to give results that are representative of the population as a whole. Thus when attempting a prevalence study, if there are \(n\) children with hearing impairment in the study, and the whole population of children is \(N\), then the prevalence rate is \((n*100/N)\) percent. In this case we must be sure that the \(n\) hearing impaired children really come from all the birth cohorts of children represented by the population of \(N\), and that there is co-terminosity of \(n\) and \(N\), in terms of geographical boundaries. It is quite common to either underestimate \(n\)
(because not all children with a given condition have been found) or to confuse populations, e.g. because of migration of children into or out of particular districts. A population study is one in which the sample is carefully selected for representativeness of the whole population.

**Positive predictive value** (PPV) - The proportion of those who fail a screening test who have a specified condition.

**Prevalence** - the total number of instances of a specified condition (e.g. Pendred syndrome) in a given population at a specific time.

**Prevalence rate** - is the number who have the condition or attribute divided by the population at risk at a point in time (or midway through a period).

**Risk** - the probability that an event will occur, e.g. that a child will have a hearing impairment of 50 dB HL or greater.

**Risk Ratio** - is the ratio of two risks, e.g. the ratio of the probability that a child will be hearing impaired if there are two brothers with congenital hearing impairment to that of being hearing impaired if no relatives are congenitally hearing impaired.

**Risk Odds Ratio** - is the ratio of the odds in favour of getting a disease, if exposed, to the odds in favour of getting the disease if not exposed. The odds derived from a cohort study is an estimate of this.

**Sensitivity** - the proportion of target individuals (e.g. truly hearing impaired) in the screened population who are correctly identified by the screening test = true positive rate. [Screen sensitivity has to be distinguished from programme sensitivity, which is screen sensitivity multiplied by the coverage of the programme].

**Specificity** - the proportion of truly non-target (e.g. normally hearing) people who are correctly identified by the screening test = true negative rate.

**Yield** - the number or proportion of cases of a specified condition accurately identified
APPENDIX 4

HOW TO COLLABORATE WITH A MOLECULAR GENETICS LABORATORY

Pedigree suitable for genetic research

Researchers always want to hear of good families. If you think you have suitable families, contact either the laboratory working on that condition, or your national contact (see lists being prepared). What is required depends on the stage research has reached with the family condition. Initial studies use linkage analysis, whilst later stages move towards mutation analysis. In all cases, good clinical descriptions are essential, and at least some family members must be willing to donate samples, usually of blood.

1. Linkage studies.
Linkage analysis requires samples from as many family members as possible. It is important to be sure who is affected and who is unaffected.

a) *Autosomal dominant conditions:* A minimum for successful analysis would be ten individuals (affected or unaffected) each of whom has an affected parent. In order of priority samples should be collected from:
   i) affected people
   ii) their parents
   iii) unaffected people, who have an affected parent
   iv) family members who link together people in the pedigree from whom samples have been taken
   v) other individuals.

b) *Autosomal recessive conditions.* For particular studies, laboratories may set their own criteria for pedigree to be collected. In general, only families with several affected individuals are useful. The value of a family is greatest when there are many affected cases, when parents of affected people are related (consanguineous marriages), and when affected people are present in more than one branch of the family. Minimum useful families would be:
   i) three affected children born to unrelated parents
   ii) two affected children born to consanguineous parents.
Families more than twice this minimum size are particularly valuable for research. Unaffected individuals (apart from parents of affected individuals) are of less value for analysis in recessive than in dominant conditions.

c) *X-linked inheritance:* Any family at least two affected males has some potential for linkage analysis, especially if they have different mothers. Samples should be taken from:
   i) affected males
   ii) women with an affected brother and an affected son or grandson
   iii) mothers and unaffected brothers of affected males
   iv) both parents of carriers
Offspring of unaffected males, and women with no affected descendants do not usually give useful information for linkage.
d) *Mitochondrial inheritance:* Linkage analysis is not useful for mitochondrially inherited conditions.

2. **Mutation analysis**

Once the condition has been mapped, smaller families can be useful and the emphasis of genetic research moves towards mutation detection. The priority samples become:

- i) a sample from a single well-described affected individual, from each separate family.
- ii) with an autosomal dominant condition, if an affected person appears to be the first in the family and unexpectedly has unaffected parents, the samples from that person and those parents are valuable.
- iii) with X-linked conditions, samples from affected males are more valuable than samples from females, even obligate carriers.
- iv) if mitochondrial inheritance is suspected, samples from a single clearly affected individual, and preferably also the person’s mother, should be taken. Analysis of mitochondrial mutations is a specialised area, and it is important to discuss plans in advance with the laboratory.

**How to collect and send the samples:**

- **a) Blood samples for linkage analysis:** a venous blood sample, preferably 10ml, is taken into EDTA, stored at room temperature or 4°C but not frozen and despatched to the laboratory to arrive within 48 hours if at all possible.

- **b) Blood samples for mutation analysis:** For many investigations a sample taken as above is suitable; but a laboratory may request blood for a chromosome analysis of for setting up a cell line. In this case, blood, preferably 10ml, is taken into litium heparin, kept at room temperature and sent at room temperature to arrive at the laboratory within 48 hours.

- **c) Tissues in addition to blood** are particularly valuable for mitochondrial mutations, and the opportunities afforded by biopsies performed during the clinical work-up, e.g. muscle biopsies, should be borne in mind. Tissue samples should be frozen (-70°C) without fixation.
2. STUDY GROUP ON EPIDEMIOLOGY OF GENETIC HEARING IMPAIRMENT

Group Co-ordinator - Agnete Parving (Copenhagen, Denmark).


Continuing from the conclusions of the Work Group Meeting February 1996 in Copenhagen (see report on epidemiology) preliminary surveys of data, including birth cohorts 1975-1979 and 1985-1989, had been circulated (Table 1 and 2).

The following criteria for inheritance were agreed upon:

1. Exclusion of any other known factor causing hearing impairment.

2. Criteria for inheritance should be based on family history and a hearing impairment should be categorized as familial ("inheritance"), if:
   I. One or both parents/grandparents affected; two or more generations affected.
   II. Pedigree suggesting inheritance.
   III. Two or more children with unaffected parents.
   IV. Consanguinity to any degree.
   V. Only child with unaffected parents but with affected cousin(s).
   VI. Pedigree indicating X-linked inheritance.
   VII. Pedigree indicating mitochondrial inheritance.
   VIII. Recognised syndrome.

It was emphasized that the clinical audiological diagnosis of "hereditary" hearing impairment is a diagnosis of probability upon which the clinician and the geneticist establish their collaboration.

The preliminary survey data show a great variation in the proportion of inherited hearing impairment in the birth cohort 1975-1979 from the various countries (i.e. local areas in the country). For the 1985-1989 cohorts the proportion varies between 28 to 45% (Table 1 and 2).

It was recognized that this variation may reflect true differences between countries, however, the samples are small, and uniform criteria for the category of inheritance had not been met. Thus it was decided that each representative revise his/her data, according to the above clinical criteria for inherited hearing impairment. The data should preferably be revised in both cohorts, but the 1985-1989 cohort is most appropriate,
as this 5 year birth cohort is still available as part of a surveillance program in each country/area. The results of the first revision are indicated in Table 3.

The working group focused on the **unknown category**, comprising a proportion of 16-54% in the 1975-1979 cohort and 21-40% in the revised 1985-1989 cohort. It was decided to systematically subject the **birth cohort 1985-1989** to a protocol for aetiological evaluation. Minimal requirements for the protocol were set-up.

**Minimal requirements for aetiological evaluation:**

**Definition of aetiological evaluation:** this is a long-term ongoing process as part of a surveillance program!

**Minimal requirements:**

1. Thorough clinical evaluation but not necessarily referral to a paediatrician.
2. Thorough ENT examination including vestibular testing at an appropriate age (test procedures proposed by working group III).
3. Ophthalmological referral at the time of identification to an ophthalmologist, who is aware of the associations between hearing impairment and ophthalmological signs/symptoms.
4. CT-scan at an appropriate age.
5. Urinalysis at the time of identification and repeated after at least ten years of age.
6. ECG at least once at an appropriate age.
7. Thyroid function tests (whatever available and decided by the individual physician) at an appropriate age.
8. Serological testing (dependent on history) before the age of 1 year.

**It was decided that within the next two years, the unknown category in the birth cohort 1985-1989 (i.e. 21-40%) should be subjected to this minimum evaluation protocol.**

Additional data from well-defined identical birth cohorts, i.e. 1985-1989 with permanent hearing impairment ≥ 50 dB HL for the better ear hearing level, averaged across 0.5-4 kHz, would be welcome.

**Prospective studies based on the protocol** were preferable. However, it was realised that recent birth cohorts would be under-ascertained to various degrees in the different countries. However, those countries (areas), in which were established registries representing prospective data were welcomed. Their data would be valuable in the long
term perspective, however, it was recognized that utilization of the data would be exceeding the time period for the EU Concerted Action.

Epidemiology of genetic hearing impairment in ADULTS:
The immediate impression was that only a few people (if any) had appropriate epidemiological data containing information on factors causing hearing impairment in adults with specific emphasis on heredity.

It was left to the steering committee to proceed with the resolution of this problem.
The data in the surveys have been given by:
   K. Welzl-Müller, Austria
   S.D.G. Stephens, Wales, UK
   A. Parving, Denmark
   Georgio Grisanti, Sicily, Italy
   Martti Sorri, Finland
   Oscar Dias, Portugal
   K. Konrådeson, Sweden
   C. O'Donovan, Ireland
   H. Fortnum/A. Davis, England
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3. STUDY GROUP ON VESTIBULAR INVOLVEMENT

Group Co-ordinator - Linda Luxon (London, UK), Claes Moller (Goteborg, Sweden)

VESTIBULAR TEST PROTOCOL

(GROUP 3: P. Huygen, L. Luxon, C. Moller, D. Monzoni, L. Odkvist, E. Raglan, F. Wuyts)

0. IDENTIFICATION: Patient ID ___________________Examination Center_________

1. ANAMNESIS

1.1 Date of test ________d/mos/yr
1.2 Date of Birth ________ d/mos/yr
1.3 Sex m/f
1.4 Childhood motor milestone 0-12 years
   1.4.1 When was the child able to support his/her head ________ months
   1.4.2 When was the child able to sit without support ________ months
   1.4.3 When was the child able to crawl ________ months
   1.4.4 When was the child able to stand up with support ________ months
   1.4.5 When was the child able to walk without help ________ months

1.5 Problems with:
   1.5.1 Running ________ yes/no/don’t know
   1.5.2 Bicycling ________ yes/no/don’t know
   1.5.3 Skating (roller, ice) ________ yes/no/don’t know
   1.5.4 Walking in darkness ________ yes/no/don’t know
   1.5.5 Walking on uneven surface ________ yes/no/don’t know
   1.5.6 Motion sickness ________ yes/no/don’t know
   1.5.7 Gymnastics and sport activities ________ yes/no/don’t know
   1.5.8 Turning head left or right during bicycling ________ yes/no/don’t know
   1.5.9 Walking in sand ________ yes/no/don’t know
   1.5.10 Balance in shower ________ yes/no/don’t know

1.6 Vestibular symptoms

1.6.1 Acute attacks of vertigo
   1.6.1.1 Character: rotational, linear, other _________________________________
   1.6.1.2 Duration of symptoms (e.g. 3 months) ________d/mos/yr
   1.6.1.3 Length of an attack (e.g. 20 min) ________ sec/min/hr/d
   1.6.1.4 Frequency of attack (number/month over last 6 mos) ________________
   1.6.1.5 Associated symptoms: Tinnitus, Increased hearing loss ________________

1.6.2 Prolonged Imbalance
   1.6.2.1 Lateropulsion ________________ yes/no
   1.6.2.2 Lightheadedness/faintness ________________ yes/no
   1.6.2.3 Drunken feeling/unsteadiness ________________ yes/no
1.6.3 Oscillopsia
1.6.3.1 **Spontaneous** yes/no
1.6.3.2 **Movement induced** yes/no

**1.7 Family History:** Family members with balance dysfunction
Specify who, and what

**1.8 History**
1.8.1 Trauma including Whiplash ______yes/no/don’t know
1.8.2 Infection (e.g. Meningitis) ______yes/no/don’t know
1.8.3 Ototoxic drugs ______yes/no/don’t know
1.8.4 Perinatal problems (>72 hrs in SCBU-Couveuse) ______yes/no/don’t know

**2. CLINICAL EXAMINATION**

2.1 **Ear-nose and throat** examination Normal/Pathological
Specify if pathological

2.2 **Cranial nerve** examination Normal/Pathological
Specify if pathological

2.3 **Nystagmus** detection
2.3.1 **Spontaneous** nystagmus yes/no
2.3.2 **Gaze-evoked** nystagmus yes/no
2.3.3 **Head-shaking** nystagmus yes/no
2.3.4 **Positional** nystagmus yes/no

**3. TESTING**

3.1 **Caloric testing** (Bithermal-Binaural (250cc)) by preference and for age>4 years
3.1.1 In darkness yes/no
3.1.2 Right 30°C (slow phase velocity) ______ deg/s
3.1.3 Left 30°C ______ deg/s
3.1.4 Right 44°C ______ deg/s
3.1.5 Left 44°C ______ deg/s

3.2 Jongkees formulas for
3.2.1 **Labyrinthine asymmetry:**
\[
\frac{(LW+LC)-(RW+RC)}{[LW+RW+LC+RC]} \times 100 = \text{______}\%
\]
3.2.2 **Nystagmus preponderance:**
\[
\frac{(LW+RC)-(LC+RW)}{[LW+RW+LC+RC]} \times 100 = \text{______}\%
\]
3.2.3 **Hypoactive**(*) yes/no
(*) If total sum of 4 irrigations < 40 deg/sec in the dark, or if response is below own normative limits)

If no response:
3.3 Tap water calorics (18-22°C), 1 minute irrigation: Nystagmus present? yes/no

3.4 **Recording mode** of eye movements
3.4.1 Frenzel yes/no
3.4.2 EOG yes/no
3.4.3 Video yes/no
3.4.4 Infra Red yes/no
3.4.5 Scleral Coil yes/no

3.5 **For children < 4 years** or those not cooperative with the above assessments, the presence or absence of vestibular function should be assessed by a rotational test in the dark, evaluating the presence of a nystagmic response.

Nystagmus present yes/no

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<td>ABSENT (bilateral)</td>
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<td>CENTRAL VESTIBULAR INVOLVEMENT</td>
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MEETINGS AND WORKSHOPS
Organised within the HEAR project

organiser: Elisa Calzolari (Ferrara)
London, 11th April 1996

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SECOND WORKSHOP “EUROPEAN WORKING GROUP ON GENETICS OF HEARING IMPAIRMENT”
organiser: Alessandro Martini (Ferrara)
Milano, 11-13 October 1996 at CRS-Amplifon Auditorium

Program:

FRIDAY OCTOBER 11th, 1996
• Pre-session meeting of Study Groups
• Concerted Action Budget Discussion

SATURDAY OCTOBER 12th, 1996
• Joint session of Study Groups
  - joint discussion
• L. Saggin, M. Mazzoli (Padova-Ferrara): An internet database on genetic non-syndromic hearing impairments

Plenary Session
• The Study Groups present the current state of their work on: Alessandro Martini: Welcome and Introduction

Invited lecturer
• Karen Steel (Nottingham): Genetics of deafness
• Peter Phelps (London): Radiology of inner ear defects
• Ségolène Aymer (Villejuif): Genetics of cranio-facial malformations

Free papers


L.M. Luxon (London): Neuro-otological findings in Pendred’s syndrome

F. Wuyts, P.H. Van de Heyning, H. Kingma, D. Van Dyck, P. Scheunders (Antwerp): Three dimensional video-oculography for the detection of genetic vestibular disfunction at the level of the three semicircular canals and the otoliths


J. Ylikoski, U. Pirvola, M. Saarma (Kuopio) Therapy of deafness by growth factors

SUNDAY OCTOBER 13th, 1996

Invited lecturers
- Guy van Camp (Antwerp): Locating genes for hearing loss
- William Kimberling (Omaha): Molecular approaches to mutation identification
- Richard Smith (Iowa City): Homozygosity mapping applied to hereditary hearing impairment - localizing recessive deafness genes
- Christine Petit (Paris): Physiopathology of Usher syndrome type IB

Free papers


A. Meyer zum Gottesberge, K. Nolting, A. Reuter, H. Weiner (Dusseldorf): Mpv 17 - glomerulosclerosis gene is essential for the inner ear function

L. Tranebjærg, T. Fagerheim, A. Holdo, B.E. Holdo, P. Raeymaekers (Tromso): Gene mapping of Usher syndrome type II to a 5.2 cM region of chromosome 1q41

K.A. Brown, G. Karbani, G. Parry, L.L. Moynihan, A.H. Janjua, Li Al Gazali, V.E. Newton, A.F. Markham, R.F. Mueller (Leeds): Assessment of the contribution of the loci DFNA1 - 10 and DFNB1 - 9 in inherited hearing loss in two populations; the United Arab Emirates and the British Pakistani population

S. Uimonen, I. Hassinen, M. Sorri, K. Majamaa (Oulu): Prevalence of the base pair 3243 mutation of the tRNA gene in the mitochondrial DNA in a population-based cohort of patients with sensorineural hearing impairment

POSTERS
- A. Mclnerney, R. Winter, M. Bittner-Glindzicz (London): Dominant hemifacial microsomia in a four generation pedigree
- A. Bojano, L. Califano, P. Capparuccia (Benevento): Hereditary dominant non-syndromic progressive hearing loss in a large family in Southern Italy
- G. Grisanti, A.M. Amodeo, S. Crinò, E. Martines (Palermo): Recessive hearing impairment in two birth-cohorts in Western Sicily
• G. Lina-Granade, M. Kreiss, L. Collet, A. Morgon (Lyon): Cochlear irregularities in obligate carriers of recessive genetic hearing loss and in controls
• E. Orzan, M. Turrini, L. Bartolomei, A. Scaringi (Padova-Vicenza): Inherited progressive sensorineural hearing loss and mitochondrial point mutation
• A. Parving, D. Stephens (Copenhagen-Cardiff): Factors causing permanent hearing impairment in identical birth-cohorts in two different European Countries
• A. Quaranta, F. Bellomo, A. Scaringi (Bari): Genetic deafness in Apulia: a fifteen years survey
• D. Stephens, F. Zhao, V. Newton (Cardiff-Manchester): The effect of frequency sweep rate on audioscan notches
• F. Zhao, D. Stephens, R. Meredith (Cardiff): Parameter analyses of audioscan notches in carriers of genetic hearing loss
• K. Kirschhofer, J.B. Kenyon, D.M. Hoover, P. Franz, K. Weipoltsammer, F. Wachtler, W.J. Kimberling (Wien): Autosomal dominant congenital severe sensorineural hearing loss - localisation of a disease gene to chromosome 11q by linkage in an Australian family
• M. Pfister, F. Apaydin, U. Brandle, C. Engel, H.P. Zenner, S.M. Leal (Tubingen): Genetic mapping of non-syndromic hearing loss genes: a study with Turkish families
• J. Sumegi, J.D. Eudy, Ji Yi Wang, C.B. Talmadge, Bi-Fang Li, M.D. Weston, Su-Fang Yao, M. Ma-Edmonds, L. Overbeck, E. Uzvolgyi, G. Klein, E.J. Stanbridge, W.J. Kimberling (Omaha): The construction of a Yeast Artificial Chromosome (YAC) Contig in the Vicinity of the Usher Syndrome Type Iia (USH2a)Gene in 1q41 and the Isolation of Candidate Genes
• J. Tyson, S. Bellman, V. Newton, P. Simpson, M.E. Pembrey, M. Bitner-Glindzicz (London): Mapping of DFN2 to Xq22
• T. Van Agtmael, P. Van Hauwe, P. Coucke, O. Demiryan, Y. Kabakkaya, W. Balemans, R.J.H. Smith, A. Parving, C.W.R.J. Cremers, G. Van Camp, P. J. Willems (Antwerp): A large consanguineous Turkish family with Pendred syndrome is linked to chromosome 7q31
• G. Van Camp, W. Balemans, C. Coucke, H. Capon, P.J. Willems (Antwerp): Linkage to known deafness loci can be efficiently tested by fluorescent multiplex analysis
• G. Van Camp, G. Raes, R. Smith, P.J. Willems (Antwerp-Iowa City): The hereditary hearing loss homepage: keeping up with an increasing number of deafness genes over the internet
• G. Van Camp, W. Balemans, P.J. Willems (Antwerp): Automated gene localization studies on a fluorescent DNA sequencer using the Linkage Designer software
• K. Verhoeven, R.J.H. Ensink, G. Van Camp, I. Schatteman, L. Van Laer, C.W.R.J. Cremers, P.J. Willems (Antwerp-Nijmegen): Hearing loss is the predominant symptom in a family with a point mutation in the mitochondrial tRNA<sup>Ser(UCN)</sup> gene
• P. Van Hauwe, P. Coucke, G. Van Camp, J. Meyers, I. Schatteman, C.W.R.J: Cremers, H. Kunst, P. Van de Heyning, P.J. Willems (Antwerp-Nijmegen): Analysis of key-recombinants in 5 linked families maps the DFNA2 gene to a 2 cM region on chromosome 1p

• L. Van Laer, G. Van Camp, E.D. Green, P.J. Willems (Antwerp-Bethesda): A YAC contig from the DFNA5 deafness region on chromosome 7p14-15 contains the HOXA cluster and the hnRPA2B1 gene

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Otoacoustic Emissions and the european projects on hearing impairment: AHEAD - HEAR - PAN
organisers : F. Grandori, M. Tsakanikos, N. Apostolopoulos, D. Douniadakis
Athens, November 16, 1996
FUTURE MEETINGS AND WORKSHOPS
Organised within the HEAR project

Workshop on:

SUSCEPTIBILITY FACTORS IN HEARING IMPAIRMENT. THE EUROPEAN COLLABORATION OF CONCERTED ACTIONS ON HEARING: AHEAD/HEAR/PAN

Prague, June 18, 1997

Pre-Conference Workshop, Satellite activity of the 3rd EFAS Conference on Audiology, Prague, June 18-21, 1997 (Organiser: F. Grandori)

Survey of the European Projects on Hearing from the Biomedical and Health Research Programme of the European Commission (Biomed 2)

15.00 Advancement of Hearing Assessment Methods and Devices - AHEAD (F. Grandori, Italy)
15.15 European Working Group on Genetics of Hearing Impairment - HEAR (A. Martini, Italy)
15.30 Protection Against Noise - PAN (D. Prasher, UK)
15.45 Discussion

Lectures

16.00 Susceptibility factors (J.M. Aran, France)
16.30 Otoacoustic emissions as a tool for quantifying noise induced changes (D.T. Kemp, UK)
17.00 Susceptibility to noise: protective mechanisms (B. Ceranic, UK)
17.30 End of meeting

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Study Group 5 on Identification of Genes; Satellite Meeting at the 29th Annual Meeting of the European Society of Human Genetics, Genova, Italy 17-19th May 1997.

organiser: Andrew Read

Genova, 19th May 1997
Study group 3 on Vestibular Involvement, Satellite Meeting at the 9th International Symposium on Audiological Medicine, Aalborg, Denmark 25-28 May 1997.

organizers: Linda Luxon and Claes Moller
Aalborg, at 3 pm Wednesday, May 28 1997