ROLE OF GENETICS IN HEARING LOSS
A REVIEW

Register No. M9905

An Independent Project Submitted as part fulfillment
for the First year M.Sc. (Speech & Hearing) to University of Mysore.

ALL INDIA INSTITUTE OF SPEECH AND HEARING, MYSORE-570006
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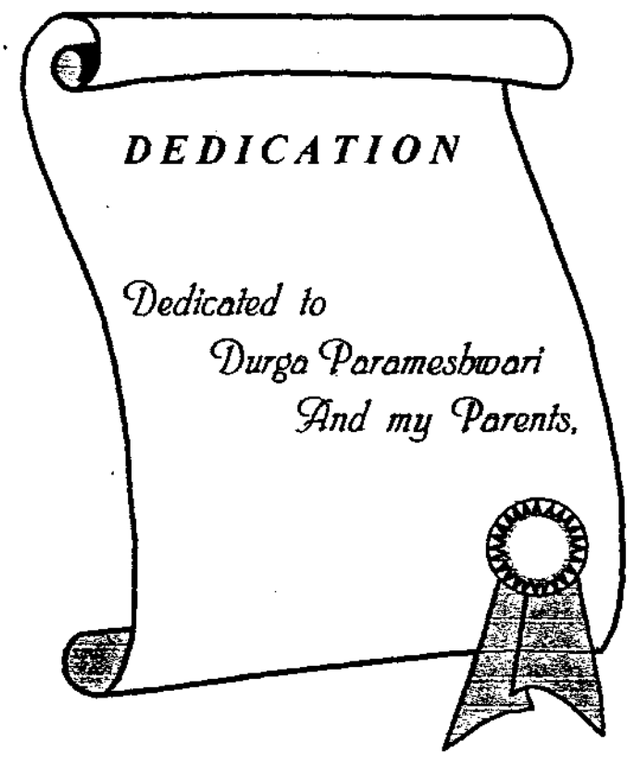
DEDICATION
Dedicated to
Durga Parameshwari
And my Parents.

Certificate

This to certify that the Independent Project entitled "Role of genetics in Hearing Loss - A Review" is tbe bonafide work done in partfulfillment for tbe degree of Master of Science (peech and Hearing) of tbe student with Register No. M9905.

Mysore
May 2000

director
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5peech &. Hearing,
Mysore - 570006

Certificate

This is to certify that the 9ndependeni Project entitled "Role of geenetics in Hearing loss - A Review" has been prepared under my supervision and guidance.

Mysore
May 2000

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Declaration

I *hereby declare that this independent ^Project entitled "Role of genetic in Hearing loss - A Review" is the result of my own study under the guidance of Dr.K. Rajalakshmi, Lecturer, department of Audiology, All India institute of (Speech and Hearing, Mysore, and has not been submitted earlier at any other University for any other diplomo or Degree.*

Mysore *RegisterNo.M9905*

May 2000

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"The word impossible is never in your dictionary and we follow your foot prints ,we will be proud to say we are 'AIISH,ians' through out the journey of our career. "

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Anna , 'Oh, its years since I have seen you, but you kept track off the changes in my personality, career ,attitude. This care and love of yours makes me take pride in having a brother like you. "Anna, I miss you".

Raji , A sister, whom I am thankful to as your support and advises have always made me think. "Raji I respect you".

Nandha , Though not said many at times, its understood that our love is strong and we stand for each other at all times. Brother your stupid jokes (You call it, "Sense of Humor ?") mischevious talks have brought laughter and fun in my life. "Nanda I Adore You".

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Tom, Jerry, Sailesh, Sathish ,"Comments, Comments and Comments!!"

My best critics. But the one who tells your faults lets you know they care!!. Thank you Guys !!

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Prakash, Daddy, Vasanthi, Prats, Bhanu (Ma'am). SBB (Ambedkar), Abhi, Libran, Bhaloo, 12th man, Arul, Chaya, Sindhuja,

'Some people make life beautiful by just being in it,'

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"Gods speaks to us in many ways"

Oh God. I thank you for all these people and it is your blessing that has made me come through this adventure and I pray that you would lead me further ahead.

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CHAPTER- 1

INTRODUCTION

An introduction to genetics

Certainly one of the most exciting fields of biological science, is genetics. This is the study of the mechanisms of heredity by which traits or characteristics are passed from generation to generation. Not only has modern genetics had a compact history being essentially a product of the twentieth century, but also it has made almost explosive progress from the discovery in 1900 of Mendel's basic observation of the 1860s' to a fairly full comprehension of underlying principles at molecular level. As our knowledge of these operating mechanisms developed, it became apparent that they are remarkably similar in their fundamental behavior for all kinds of organisms, whether man or mouse, bacterium or corn. But genetics quest for truth and understanding is far from completed, as in other sciences the answer to one question rises new ones and opens whole new avenues of inquiry.

AIM OF THIS PROJECT

Scientists who work in the genetic sciences probably know as little about speech, language and hearing as communication scientists known about genetics. Clinicians assessing patients tend to focus on physical anomalies because their medical backgrounds make this familiar territory. Molecular geneticists who spend their time in the laboratory and who often observe the effects of mutated genomes on animals ranging from fruit flies to mice do not have the opportunity to interact with disorders of communication or people who study them. Thus, while cancer

researcher are finding genes that cause breast and colon cancer, neuro-scientists are studying the effects of the genes that cause Huhtngton and Alzheimers diseases. With the exception of a relatively few genes which have been found to cause deafness, few scientists in the area of communication disorders have been deeply involved in the most active and growing field in the health sciences today human genetics.

The purpose of this project is to introduce a few basics of both clinical and molecular genetics. This collection of details is meant to be introductory and perhaps will provide an impetus for speech language pathologists and audiologists to learn more and establish relationships with genetic counselors, clinical geneticians, dysmorphologists, cytogeneticists and molecular geneticists in their region. Started simply, almost all-human disorders, with the possible exception or trauma and infection, have some type of genetic component. This includes speech language and hearing disorders. Hopefully this project will provide a starting point for additional interaction between the communicative sciences and the genetic sciences. A few concepts such as, basics of heredity, how genes work and are expressed in people, how to gather information that might reveal a genetic basics for the communicative impairment, namely hearing loss, and genetic counseling are discussed.

CHAPTER-2

REVIEW OF LITERATURE

It is well established that as much as six thousand years ago man kept records of pedigrees of such domestic animals as the horse or of the crop plant like rice. Because certain animals and plants were necessary for his survival and culture, man has since the beginning of recorded history at least, attempted to develop improved varieties. But the story of mans concern with heredity during bis lifetime on this planet has been, until recently one of interest largely in results rather than in fundamental understanding of the mechanisms involved.

Course of genetics

As one examines the development of ideas relating to the mechanisms of transmission of traits, he finds the way replete with misconceptions, many of them naive in the light of modern knowledge. These theories may be divided roughly into three categories.

1) Vapours and fluids
2) Preformation
3) Particulate.

Such early Greek philosophers and Pythogoras (500B.C.) proposed that 'vapours' derived from various organs unite to form a new individual. Then Aristotle assigned a 'vitalizing' effect to semen, which he suggested, was highly purified blood, a notion that was to influence thinking for almost two thousand years.

By the seventeenth century sperm and egg had been discovered and Dutch scientists Swammerdam theorized that sex cells contained miniatures of the adult. Literature of that time contains drawings of models or manikans within sperm heads which imaginative workers reported seeing - (fig, 1).

Such theories of preformation persisted well into the eighteenth century, by which time the German investigator Wolff offered experimental evidence that no preformed embryo existed in the egg of the chicken.

But Maupertius in France, recognizing that preformation could not easily account for transmission of traits to the offspring from both parents, had proposed in the early 1800's that minute particles one from each body part, united in sexual reproduction to form a new individual. In some instances he reasoned, particles from the male parent might dominate those from the female, and in other cases the reverse might be true. Thus the notion of particulate inheritance came into consideration. Maupertius was actually closer to the truth, in general terms, than anyone realized for more than a century.

Charles Darwin suggested, in the ninteenth century, essentially the same basic mechanism in his theory of pangenesis, the central idea of which had first been put forward by Hippocrates (400 B.C). Under this concept, each part of the body produced minute particles (gemmules) which were contained in the blood of the entire body but eventually concentrated in the reproductive organs.

Thus an individual would represent a 'blending' of both parents. Moreover, acquired characteristics would be inherited because, as parts of the body changed

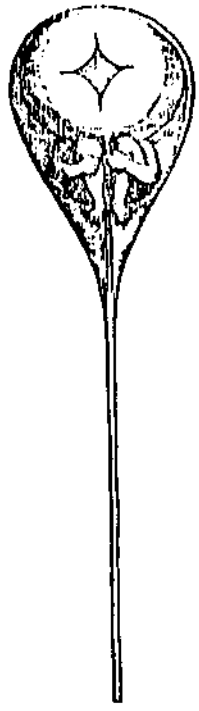


Fig. 1 Homunculus, "little man in a sperm cell."

so did the pangenes they produced. A champion weight lifter, therefore, should produce children with strong arm muscles, such transmission of acquired traits we know does not occur.

Pangenesis was disproved in the same century by the German biologist Weismann.

In a well known experiment he cut off the tails of mice for twenty two generations, yet each new lot of offspring consisted only of animals with tails. If the source of pangenes for tails was removed, how, he reasoned could the next generation have tails? . Yet inspite of these early problems with the idea of particulate inheritance, its basic concept is the central core of our modern understanding.

Most attempts to explain observed breeding results failed because investigators generally tried to encompass simultaneously all variations, whether heritable or not. Nor was the progress of scientific thought or the development of suitable equipment and techniques ready to help point the way. It was the Augustinian monk Gregor Mendel who laid the ground work for our modern concept of the particulate theory. He did so by observable contrasting traits in a controlled breeding program. Both by his method and by his suggestion of causal "factors" (which we now call *genes).* Mendel came closer to a real understanding of heredity than anyone had in the preceding five thousand years or more, yet he only opened the door for others. An understanding of the cellular mechanisms was still to be developed.

Fields of study useful in genetics

After an initial and appropriate preoccupation with descriptive genetics, scientists turned naturally to problems of the mechanics of the processes they observed. The ***"what"*** of the earliest twentieth century rapidly gave way to a concern with *"how"*. Parellels between inheritance patterns and the structure and behavior of cells were noted by a number of pioneer investigators. Thus, *'cytology'* rapidly became an important adjunct to genetics. In fact, a pair of papers by Sutton as early as 1902 and 1903 clearly pointed the way to a physical basis for the burgeoning science of heredity. Sutton concluded his 1902 paper with a bold prediction; and called attention to the probability that (the behavior of chromosomes) may constitute the physical basis of the Mendelian law of heredity. Truly the door was there by opened to an objective enumeration of the physical mechanisms of the genetic processes.

As the science of genetics developed rapidly during the first quarter of this century, a considerable body of knowledge was built up for such organisms as Drosophila, Corn, the Laboratory Mouse, and Tomato concerning what traits are inherited and how different expressions of these are related to each other. Genetic maps were constructed for these and other species showing relative distances between genes on their chromosomes. Geneticists began to turn from concern with inheritance patterns of such traits as eye color in fruit flies to problems of "how" the observable trait is produced. Especially in the period, since the beginning of World War II, a central question has been the structure of the gene and the mode of its operation. As the search for answers proceeded ever more deeply into

molecular levels, an increasingly important part in genetic study has been played by chemistry and physics. Contribution of these sciences have been such as to enable geneticists to gain a clear concept of the molecular nature of the gene and its operation.

Practical application of genetics

Genetics appeals to many of us not only because we are parts of an on going genetic stream but also because it has had such an exciting history in which theory has evolved out of observation and led, in turn, to experimental proof of fundamental operating mechanisms of course any sciences may make the same claim but the history of mans knowledge and understanding of genetics is to other sciences as a time-lapse movie of a growth process is to a normal-speed film. A fraction of a century ago the scientific community at large knew nothing of genetic mechanism. Now, however, we can, with considerable accuracy, even construct molecular model of genes, atom by atom. But besides being a fascinating intellectual discipline intimately related to our selves, genetics has many important practical applications. Some of these are fairly familiar; others may be less so.

The history of improvement of food crops and domestic animals by selective breeding is too well known . Increase in yield of crops like corn and rice, improvement in flavor and size as well as the production of seedless varieties of fruits, and advances in meat production of cattle and science have markedly benefited mankind. As the population of the world continues to increase this practical utilization of genetics is likely to assume even greater significance.

The problem of breeding disease-resistant plants is likewise a never-ending one. Applications of genetics in the general field of medicine are numerous and growing. Many diseases and abnormalities are now known to have genetic basis. Haemophilia, some types of diabetes, an anemia known as haemolyticicterus, some forms of deafness and of blindness, several haemoglobin abnormalities and Rh incompatibility are few conditions mat fall into this category. Recognition of their inherited nature is important in anticipating their possible future occurrence in a given family, so that appropriate preventive steps may be taken.

Closely related is the who field of genetic counseling some estimate of the likelihood of a particular desirable or undesirable trait appearing in the children of a given couple can be provided by one who has sound genetic training and some information on the ancestors of the prospective parents. Questions encountered might range from the probability of a couple having any red-haired children to the chance of muscular dystrophy appearing in the offspring.

Genetics has its legal applications too. Analysis of blood type, a generally determined character may be used to solve problems of disputed parentage. Questions of baby mixups in hospitals, illegitimate children, and estimate claims can often be clarified by genetics. (Burns, G. W, J %9).

Thus study of genetics by scientists provide an understanding of the mechanism of inheritance yet, our quest for the "why" and "how" of genetics will grow ever more specific until we are able to answer the deepest molecular levels penetrated by science. In this processes we should not only acquire some

fundamental genetics knowledge about ourselves, but also sharpen our powers of critical, analytical, skeptical thinking.

Material basis of genetics

We can begin by noting a fact obvious to all of us. Living systems are highly complex. For example, the most elementary studies soon reveal the wealth of biochemical activities that a cell must contain just to survive. Yet we also know from everyday observation that each organism must have not only the reproducing systems like itself as well. The best evidence available today indicates that this information is contained (coded is the popular term) in a remarkable set of substances which is passed on from one generation to the next, and which in large measure prescribes the nature of the succeeding generation. These substances we refer to as *'the material basis of heredity'*.

The cellular elements

All organisms consist of cells. Moreover whether they consist of one cell or of thousands they grow and reproduce by cell division. Man is a multicellular organism and he too, grows by increase in cell size and division of bis constituent cells. He reproduces by producing certain cells *(gametes), sperm* (male) and *eggs* (female) which fuse to give rise to a single fertilized egg cell *(zygote).The* zygote is capable of growing and dividing and of ultimately giving rise to a new multicellular individual .The information needed to reproduce a complex multicellular individual is thus transmitted through a single cell, and each dividing cell in turn must contain the information required to produce itself. The elements

of heredity belong to the cell, therefore, rather than to the organism and in considering the material basis of heredity, we are free to focus on the processes involved in the reproduction of single cells. (Gardner , E-J.1968).

"What elements within cells can be expected to carry hereditary information?"

During cell division, the nucleus divides by an elaborate mechanism *(mitosis)* that leads to the production of an exact copy of each constituent chromosome. It is the *"chromosomes"* in the nucleus that carry the material basis of heredity.

Mitosis

A mitotic cell division is simply a division that produces two cells, each with identical chromosomes. In brief,

1) The chromosomes contract and gather independantly of one another on a plane approximately in title center of the cell.

2) Each chromosome is then seen to be tightly paired with its previously synthesized copy.

3) The sister strands, or chromatids, then separate, one to each end of the of the cell and two identical sets of chromosomes are formed

4) The nuclei reorganize and the cell divides into two. (Gardner. E.T. 1983).

Meiosis

In somatic mitosis the chromosomes are always duplicated before cell division takes place.

If this kind of distribution took place in germ cells being doubled in each generation. Hence they undergo *"reduction division"*. At this time the somatic number of chromosomes is halved, so that the gametes posses first half the number found in the somatic cells. Thus the integrity of the chromosome number is maintained. This process is known as meiosis (Singleton, 1967).

What are genes?

"Genes" are the basic unit of inheritance. These are ultimate units of heredity (Altenburg.E,1970). They provide the instruction for growth and development of a fertilized ovum into a baby and may continue to provide instruction for bodily functions throughout a person's lifetime. The genes are arranged in string like structures which are called *"chromosomes ".(Levine* 1968).

Chromosome ("chromos"-color, "soma"-body Altenburg.E.1960)

There are *46* chromosomes or *23 pairs* of chromosomes. The 2 members of each pair of chromosome are known as *homologs.* One homolog in each pan- comes from the individual mother and other from the father. If the chromosomes are stained and examined under a microscope one sees that they are of varying lengths and have light and dark bands. This is what makes it possible to identify the individual chromosomes. Twenty-two pairs of chromosomes are numbered for identification. They look the same in males and females and are called *"autosomes"*. The 23rd pair is called the sex chromosomes because they determine the sex of the child. Females have two identical sex chromosomes called *'X'* chromosome. Males have an *'X'* and 'Y' chromosome. Each chromosome has a characteristic length and position of the centrosome allowing each projection to be

called an *"arm",* paired *long* and *short* arms. The short arms are designated as *"p"* and the long arms as *"q".* Reference to a specific arm of chromosome 1 would be to lp or lq, to chromosome 2 as 2p and 2q and so forth. A "+*sign* " or

" - *sign", "before"* a chromosome number indicates the *addition* or of an entire chromosome. This represents a numerical *chromosomal aberration* . An example is the karyotype 47, XY, +21, which is that of a male with an extra number 21 chromosome (i.e, trisomy 21, Downs syndrome). In contrast, a + sign or - sign *"following"* a chromosome number represents an *increase* or *decrease* in chromosome length. This represents a structural chromosomal anomaly. One example is Cri-du-chat syndrome, represented as 46, XX, 5p- meaning 46 chromosomes in a female with deletion of the short arm of the number 5 chromosome. This basic form of descriptive reference is referred to as *"karyotype"* nomenclature. (*J*acobson.J *1997).*

Different traits are determined by gene pairs. A person with similar genes in *homologous* at that locus. One with different genes is *heterozygous* for that locus. The ways in which the genes are homozygous or heterozygous determine the different types of inheritance. The three main types of inheritance are

1) Autosomal dominant

2) Autosomal recessive

3)Sex linked.

Autosomal Dominant

An autosomal gene is one of the autosome or 22 pairs of chromosomes that are not sex chromosomes. Dominant means that the gene is expressed even when there is only one copy of the gene. A person with an autosome dominant hearing loss has one gene for the loss. The other gene in that pair is probably a recessive gene that codes for normal hearing. That individual has a *50%* chance of passing on the hearing loss gene to each child, (fig ,2).

Autosomal Recessive

Autosomal recessive means that the gene is not expressed unless there are 2 copies of the gene. Usually the autosomal recessive, hearing loss genes have been on both sides of the family for many generations, but no one has had hearing loss. Those people who have one copy of the gene and no hearing loss are carriers. Their gene in that particular pair provides the dominant message for normal hearing. When 2 carriers have a child, there is a *25%* chance the child will receive both hearing loss genes and have a hearing loss. There is a *25%* chance that the child will receive neither hearing loss gene and *50 %* chance that the child will be a carrier like the parents, (fig,3).(Jung.J.H 1989).

X-linked recessive

X-linked refers to a gene mat is on the 'X' chromosome; most X-linked hearing loss genes are recessive. When a female who is a carrier for X- linked deafness and a hearing male have children, all the daughters will be hearing because each daughter will receive a dominant normal X- from the father. Each

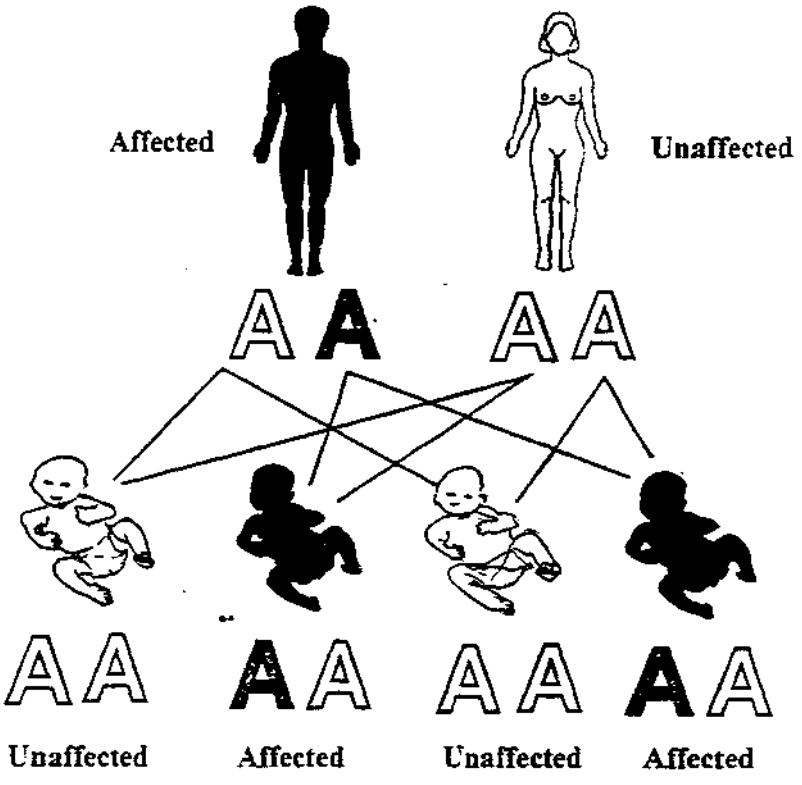


Figure 2. Schematic illustrating autosomal dominant pattern of inheritance resulting in a 50% recurrence risk. The white "A" represents the normal allele on one paternal chromosome, the gray "A" represents the mutant allele on the other paternal chromosome. The mother has two normal A alleles. The possible segregations of the A gene is represented by the row of affected and unaffected infants at the bottom. Because these alleles are located on autosomes, the sex of the parent and child does not affect the inheritance of the trait.

will have an equal chance of receiving the X chromosome with the gene for deafness or the X with the normal gene from her mother. Since males receive only one X that is from the mother, each son will have an equal chance of being hearing or deaf (fig,4).

When a man with X- linked deafness and a woman with two normal hearing genes have children all their daughters will be carriers because the father has only the one X chromosome to pass to all his daughters. All their sons will be hearing because the father can only pass the Y to his sons (fig,5). (*OxOrlit),* &t a1. 1995).

It has been noted that the most common forms of genetic hearing impairment are the autosomal recessive forms accounting for about 80% of cases, autosomal dominant forms accounting for about 15% and X-linked inheritance for (2-3%) of cases.(Fraser,1976;Rose et al,1977;Newton,1985;Morton,1991).

"DNA : The genetic material"

Evidence that nuclear DNA is the genetic material comes from both direct and indirect observations. Among the direct observations one can cite the following

1) DNA is present in all nuclei of an organism,

2) During cell division DNA is confined to the chromosomes,

3) The amount of DNA in each somatic cell is constant for a given species.

4) The amount of DNA in the gametes is half of that in the somatic cells.

5) There is no appreciable variation in the composition of DNA found in the gametes and other cells of an organism.

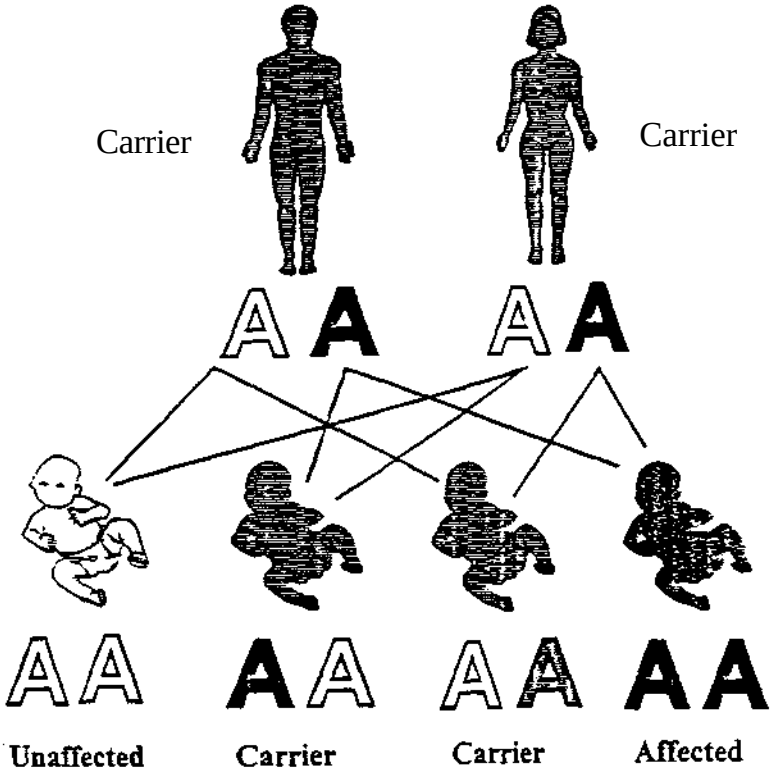


Figure 3. Schematic illustrating autosomal recessive pattern of inheritance when both parents are carriers of a mutant allele that is not expressed as long as the other allele is the normal one. Based on the possible segregation of the alleles, 25% of the possible offspring will inherit both mutant alleles and will be affected, 50% will be unaffected carriers, and 25% will be unaffected noncarriers.

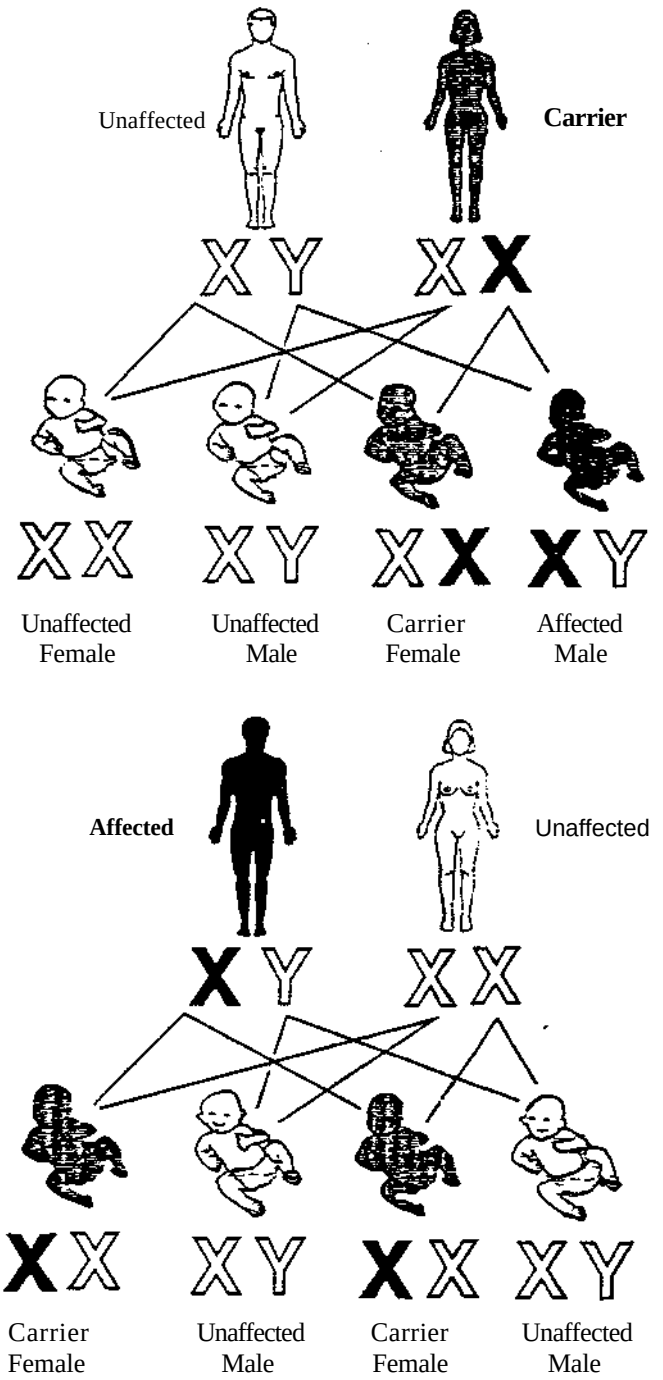


Figure 4.5 Schematic illustrating X-linked recessive pattern of inheritance resulting in a 50% recurrence risk for male offspring. In this case, the mutant allele is carried on the X chromosome. When the mother carries the X-linked recessive trait (*top*), it is not expressed in the mother because the other X chromosome has the normal allele. The trait is therefore expressed only in male offspring who have no corresponding normal allele because they do not have a matching X chromosome in their sex chromosome pair (they have a Y chromosome instead). Of the possible female offspring, there is a 50% probability they will be carriers and a 50% probability they will not. If the father is affected (*bottom*), there will be no affected males (no males inherit the X chromosome from the father), and both possible segregations resulting in females will produce carriers.

6) The efficiency of ultra violet radiation in including heritable changes in the genetic material is maximal at wavelength of maximal absorption of DNA. (Allen F.Calvert, 1968).

Functions of DNA

1) Storage of genetic material

2) Transfer of genetic information.

Storage of **genetic material**

It is now well established that the genetic information is carried by the DNA in the form of **a** code made up of four nucleotide bases. Genetic information is coded by 4 units of the DNA called bases : *Adenine (A),* ***Thyamine(T),*** ***Guanine*** *(G)* and *Cytosine (C).* The sequency of bases along one polynucieotide strand is not random. DNA stores genetic information by the choice of one of the four nucleotide bases at each individual position. Thus the sequence of nucleotide bases along **a** polynucieotide strand acts as a genetic code which determines the species of an organism and differences between individuals within that species. The code is read from one end to the other. Three nucleotides represent information specifying one amino acid in the protein to be synthesized. This triplet of nucleotieds is known as *"codon".* The codon of 3 nucleotides using only four different bases will code for 64 aminoacids. This is more than sufficient, as only 23 different amino acids are involved in the synthesis of normal protiens. The code is largely, if not entirely universal. That is certain DNA base sequence will encode for identical aminoacid in diverse organisms.

Principles of medical genetics

Most diseases have at least some genetic element in its pathogenesis and etiology; so it is useful to remember that disease tends to fall into 3 general classes as far as the role of genetic factors is concerned. For one group, one has

1) Simply inherited-that is Mendelying disorders-which are individually rare,

2) One has the more common conditions which are multifunctional in their causation Le, both environmental and genetic factors appear to be involved.

3) Third, one has the chromosomal abberations most of these are not inherited at least not in usual sense of the word; however as involved genetic material and therefore represent one category of genetic disease.(Allen.F.Calvert, 1968).

Thus depending on the pattern of inheritance the disease is expressed in the following generations.

Methods to Localize Genes

It is important to locate the gene or genes responsible for a particular disease in order to better understanding the pathophysiology of that disorder. The responsible gene may be absent, duplicated or mutated. According to Cohen (1996),there are different techniques that can be used to identify a gene and the associated disorder.

"How DNA is studied ?"

A human cell contains 6 x 10^6 base pillars (6 million ldlobases (Kb) or 6000 megabases (Mb) of DNA. Thus the central problem in studying human DNA is now to recognize the one sequence of interest against a huge background or irrelevant but chemically identical DNA. Essentially there are 2 ways of doing this,

1) Hybridizing the sequence of interest to a labelled probe or

2) Cloning it, (Read .A. 1989).

1. DNA hybridization and southern blotting

In the early 1970's scientists discovered that bacteria had enzymes could attack foreign DNA and cut the DNA up into little prices. What was interesting was that these enzymes were restricted to a specific sequence of the genetic alphabet to make the cut. This is why they are named *"restriction enzymes (RE)"*. There are over 200 restriction enzymes known and many cut the DNA in different places. (Muller, R.F. 1994).

A Genetic Probe

A genetic probe is piece of DNA that matches the message, one is trying to find. This probe also may be labeled with a radioactive chemical.

The technique for finding genes is, first cut the DNA with a restriction enzyme. All the pieces of DNA after one of these cuts are called *restriction fragments.* Next separate cell the cut DNA by the size of the resulting pieces. Put the DNA in a gel (like unflavored jell) and pass an electric current through the gel,

the DNA will migrate in the direction of the current. The smaller pieces will migrate further than the larger pieces. Next transfer the DNA to a piece of filter paper. Use the radioactive labeled probe to find the restriction fragments that match the probe. The probe will attach to the restriction fragments it matches. Finally, we can see where the probe attached to the DNA on the paper by exposing it to a sheet of unexposed X-ray film. This is *autoradiography*. We can estimate the size if DNA fragments by how far they have migrated. Small pieces move farther than bigger pieces. All the DNA fragments revealed by this technique are called RFLP, which stands for ***Restriction fragment length polymorphism.***

2 Cloning

Cloning of a fragment of DNA provides large quantities of identical sequences from even a single molecule. A clone is a large number of molecules, all identical to an ancestral molecule, (Gardner, E.J., 1983).

a) Cloning in vivo — genomic and complementary DNA libraries :

Exon A segment of a gene that becomes part of the mature messenger RNA after splicing out of introns.

Introns In split genes, a segment that is transcribed into nuclear RNA, but is subsequently removed from within the transcript and rapidly degraded.

Genetic Marker Any genetic character that is vendelian and polymorphic. In practice, almost always polymorphisms.

Genomic DNA is the DNA as it occurs in the cell nucleus, complete with all the introns and the non-coding DNA lying between genes (intergenic DNA).

c DNA It is an artificially produced DNA copy of a mature mRNA. cDNA is made using a special enzyme reversed transcriptase.

If a DNA fragment of interest can be inserted into a living cell, then when the cell proliferates the inserted DNA may proliferate with it. This can produce an unlimited supply of the pure fragment .usually E.coli bacteria are used for this purpose.

The Key to understanding cloning is to appreciate the necessity for a vector. A fragment of DNA simply injected into a cell will not be replicated. In order to be replicated and stably propagated, the DNA must be provided with various functions recognized by the host cell, Particularly Replication initiation sequences. DNA fragments are cloned as recombinant molecules covalently linked (inserted) into a vector molecule that provides this function (this is the origin of the term recombinant DNA). Additionally the vector must provide some feature enabling cells containing recombinant molecules to be recognized and selected. The initial result of a cloning experiment is usually a large collection of independent clones, representing either a collection of cDNAs' from some cell type or multiple fragments produced by breaking up genomic DNA. These clone libraries must be screened to find any desired clone, which may or may not be present. Libraries are screened by using hybridization assays or by Polymerase Chain Reaction as described below.

b) Cloning in vitro- the poiymerase chain reaction (PCR):

Polymerase chain reaction enables any short DNA sequence to be replicated specifically and to an unlimited degree even starring from a single molecule with very quick and simple manipulation. The DNA polymerase enzymes that replicate DNA assemble a new strand out of mononuclotides lined up on a template strand. But they cannot start with a bare template. They can only extend an existing primer, which forms a short, double stranded region. In a complex mixture of single stranded DNA it is possible to control which DNA sequences are replicated by supplying only certain primers. In PCR this selectivity is used to start a chain reaction in which just the chosen sequence is replicated as libitum. This requires two primers bracketing the selected regions. To carry out a PCR, the input DNA primers .monomers & DNA polymerase are mixed and put through cycles of temperature changes that control the various phases of the reaction. Each cycle takes about 1-2 min and theoretically doubles the quantity of the selected sequence whilst ignoring all others. Thus an hour or two of temperature cycling in **an** automated hearing block will create and overwhebning preponderance of the selected sequence. (Dallapiccola, 1995).

The strategy for discovering **disease genes**

Genes responsible for hearing loss (or any other disease) could in principle be identified in 3 ways :

1. Through studying affected cells, identifying an altered protein, working out the aminoacid sequence of the protein and using this sequence with reverse genetic

coding to design a probe to isolate the gene encoding that protein (The functional approach).

2. Through guessing that a previously characterized gene might be responsible and showing that mutation in that gene are found in people with hearing loss (The candidate gene approach).

3. Through mapping the chromosome location of the gene and then identifying genes at that location and testing them for mutation in affected people (The positional cloning approach). (Read,A. 1989).

Genetic Mapping

Suppose a man inherits dominant hearing loss from his mother, caused by a gene or chromosome1,that he received from his mother, while the five unaffected children should inherit his other copy of chromosome 1. All his other chromosomes should segregate randomly. Thus we could discover which chromosome carried a disease gene by following each chromosome through a sufficiently a large family where the disease is segregating and seeing which chromosome tracks with the disease. This could be an example of *"linkage analysis"* which is the principal means of genetic mapping.

Linkage Analysis

Linkage analysis is one of the most important procedures for pedigree analysis and has assumed considerable significance for prenatal diagnosis of diseases in which the defective gene is not expressed in amniotic fluid cells. When

two genes are tightly linked, it is often possible to determine the nature of linkage with in a given family. When this linkage relationship is established one can infer the presence or absence of one gene from the presence or absence of other gene or marker sequence (Botstein ,et al 1980). Therefore when a gene is not expressed in amniotic fluid cells but is linked to another expressible gene or marker sequence.linkage analysis can prove handy in describing its inheritance pattern.

Hereditary hearing loss:

Hearing impairment is the result of abnormal ear development or abnormal ear function or both. It can be acquired or congenital. Acquired hearing loss can occur as the result of an injury (from traumatic, infections, toxic, neoplastic, or systemic sources) to the ear drum, ossicles, cochlea, auditory nerve, brainstem or central auditory processing center. This can occur some time in the uterus, during birth or even later in life. Congenital hearing loss exists as birth. About half of all congenital deafness discovered during childhood is related to genetic **abnormalities. (Schukencht.H. 1980).**

What is heredity deafness ?

Heredity deafness is hearing loss that is inherited or passed down from the parents to their children. This type of hearing loss may be inherited from one or both parents who may or may not have a loss of hearing themselves. Hereditary material or genes are located on chromosomes, which are found in each cell of the body. Genes provide instruction for specific trait s or characteristics such as hair color and blood type. Defective genes can also pass along traits such as hearing loss or speech and language disorders (Shprinzen.R.J 1997).

The heredity hearing loss that result from defective genes may be syndromic or Nonsyndromic, dominant or recessive. Syndromic hearing loss is associated with specific traits additional to hearing impairment for e.g. hearing, balance and visual problems in Ushers syndrome. Nonsyndromic hearing impairment has hearing loss as its only characteristics.

Dominant transmission of deafness requires only one faulty gene, from either the mother or father to cause the hearing loss, whereas recessive transmission of deafness requires a faulty gene from both mother and father. The majority of inherited hearing loss (80-90%) is caused by autosomal recessive genetic disorders. The remaining 10-20% is autosomal dominant and X- linked (1-%) disorders. Inherited hearing loss is transmitted from parents to their children. It has been estimated that half of the faces of profound congenital sensorineural deafness have a genetic etiology (Chung and Brown, 1990); this includes at least 400 syndromes and possibly as many as 100 Nonsyndromic loci (Morton, 1991). However, hearing may not be diagnosed until later in life. The seventy of the hearing impairment can be seeable or progressive in nature. More than 50 types of heredity hearing losses are classified by the age of onset, severity genetic mode of transmission and other clinical findings. In contrast to Nonsyndromic hearing loss, syndromic types of hearing impairment occur together with an aggregate of physical abnormalities or deformities.

In most cases single cause (e.g. a gene mutation) accounts for all morbidity. Syndromic hearing impairment can occur sporadically or can be hereditary. Sporadic syndromic disorders occur spontaneously often, these are caused by multiple factors such as genetic, non genetic and chromosomal aberration.

"Mapping Hearing Loss Genes,,,,,,,,,,"

Today's most promising areas of research for hearing and balance disorders involve molecular biology and molecular genetics. Molecular biology is the study

of chemical reactions within cells and the overall functioning of cells. Molecular genetics is the study of genes, which instruct cells through the production of proteins. Proteins allow cells to do their individual job that, in turn, help the body part they are associated with do what it should. Genes are found on chromosomes. Each chromosome contains hundreds of genes. Molecular geneticists are working hard to locate the genes for hearing and balance (Robertson, Khetarpal, Gutierrex-Espeleta, Bieber & Morton, 1994). Once these genes are located, scientists can determine what proteins they produce and how those proteins contribute to the development, maintains, and function of the hearing and balance systems.

The first step towards identifying the gene underlying a clinical phenotype is normally to map the gene. Maps are of two types

1) The Physical Map

2) The Genetic Map

The physical map of gene loci gives their position and distance on individual chromosomes, expressed in base pairs (bp) related to cytogenetic features of the chromosome such as banding pattern.

The genetic map gives the relative position of gene loci as determined by the frequency of recombination of 1 %. The female genetic map is about 40 % longer than the male map, because recombination occurs almost twice as often in oocytes as in spermatocytes.

Physical Mapping

Physical mapping includes chromosome mapping, where a gene or DNA sequence is assigned to a specific chromosome or sub-chromosomal region

DNA mapping, using a finer level of analysis which provides mapping into at the DNA level, including the physical relationship between DNA sequence polymorphnism and the gene structure. Physical mapping is used to map DNA clones or sometimes-defined protein, but it cannot be used directly to map clinical phenotype.

The main chromosome mapping techniques include :

Gene dosage studies

A decreased amount of gene product in an individual with a deletion or increase in amount in a trisomic subject, suggests the assignment of a structural gene to the particular unbalance chromosome.

Use of somatic cell hybrids :

These are obtained by fusing cells taken from two species. Human rodent hybrid cells preferentially lose human chromosomes. Eventually producing more or less stable cell lines containing a full rodent genome but only one or a few human chromosomes for chromosomal mapping, a panel of such somatic cell hybrid clones is selected that retain different human chromosomes. Hybrid cell mapping panels, for sub-chromosomal localization of genes or markers, can be constructed by using human cells that have chromosomal deletion or translocation. Expressed proteins can be mapped by comparing the human chromosome content

of hybrid cells that do and do not produce the protein and cloned. DNA segments can be mapped by using DNA hybridization or PCR to establish which hybrid cells contains the sequence.

Chromosomes are recognized and tracked by using *"genetic markers"*.

Genetic marker is any character that is inherited in a simple mendilian way and that is polymorphic i.e. exists in variant forms in the population so that we can distinguish different forms as they segregate through the family.

Lod Scores

We need a statistic for deciding whether a marker really does track with a disease and the favored measure in the *"lod score"*. Lod means logarithm of the odds (of linkage versus no linkage). Positive lod scores favor linkage, negative scores are evidence against linkage. A lod score of +3.0 corresponds to the conventional p=0.05 threshold of significance, whilst a lod score of -2.0 is significant evidence against linkage. Lod scores larger than -2.0 but smaller than+3.0 are not considered significant, Lod scores are logarithmic to the base 10, so a lod score of 4.0 is ten times as convincing as a lod score of 3.0. Computer programs are available for calculating lod scores from pedigree and marker data.

Positional cloning

Once a gene has been mapped to a particular chromosomal location, it must be cloned- but this can be far from easy. The problems of searching for an unknown gene increase more than linearly with the size of the region to be

searched and become almost insuperable when the region is much over one million base pairs. The initial mapping is likely to locate the gene only to within 10-20 million base pairs (each chromosome contains 50-150 million base pairs of DNA).

As the candidate region is narrowed down, other clues are sought. Sometimes additional clues can be obtained from individuals with chromosomal abnormalities, or from linkage disequilibrium. Linkage disequilibrium or allelic association is a phenomenon in which the frequencies of certain marker alleles among affected people average from the frequencies in the general population (Green.et al995). This happens if most of the affected people in the population, although apparently unrelated, are actually part of one extended family. It is seen only for markers located very close to the disease gene, so it can provide a valuable clue to the location of the disease gene. Checks are made on known genes in this region and sometimes this reveals the disease gene without the labour of positional cloning. If there is no such lucky break, the next stage is to identify a series of contiguous clones that cover the entire candidate region This area is then searched for genes using a number of techniques such as screening cDNA libraries, cDNA selection ,exon trapping and computer analysis of DNA sequence.

In situ hybridization

Single stranded labelled DNA sequences are incubated with standard chromosome preparation so that they hybridize to the homologous DNA sequence. As mentioned earlier the probe is labelled radioactively but for gene mapping this method has been superceded by fluorescence in situ hybridization (FISH)

(Ott,1991). The probe is labelled with a dye that fluorescence in ultra violet light, so that its position on the chromosome can be seen directly under a fluorescence microscope. Several differently colored probes can be used simultaneously to order clones along a chromosome. This is one of the most powerful and direct methods for physically mapping and cloned DNA sequence.

Genetic mapping

Thus initial mapping of genes causing hearing loss, or any other clinically defined phenotype, the method of choice is usually genetic mapping.

The procedure include

1) Family linkage analysis

2) Genetic markers

3) Lod scores

4) Recombinant and non-recombinant offspring

Identifying genes with a candidate region

Identification of gene sequence with in the target chromosome region (Collins 1992)

1) Northern blotting

2) CDNA selection

3) CPG island selection

4) Cross-species sequence homology

5) EXON trapping

6) Computer analysis of genomic DNA sequences.

Molecular Biology And Genetics Of Hearing

Over the past 10 years, researchers have located genes for many different kinds of hearing impairments. This means that scientists know on which chromosomes the genes are located. Scientists have found that almost every chromosome has at least one gene that is involved in hearing or balance. This confirms how complex the development and function of the ear is. Scientist's next job is to determine the composition of the genes and, there by, the specific jobs that the genes perform and the role they play in hearing and balance development and function.

Genes are found not only on the 23 pairs of chromosomes in the nucleus of each cell but also on chromosomes in the mitochondria in the cytoplasm inside each cell. Cells contain 100's of mitochondria (involved in the metabolism, or energy, of the cell) that, in turn, contain 2-10 chromosomes. Research has demonstrated that mitochondrial chromosomes are involved some hearing disorders.

In 1992, scientists identified the first mitochondrial gene responsible for a form of hearing impairment. In that case, members of large Arab-Israeli family were found to have one nuclear gene and one mitochondrial gene that contributed to their hearing impairments (Jaber et al., 1992). Since then, the same scientists found a family in New Zealand with a type of deafness that results from **a** gene located in the mitochondria (Fischel-Ghodsian, Prezant, Fournier, Stewart and

Maw, 1995). That same gene was identified in members of a Scottish family who are all deaf.

Discovery of genes involved in development of the Ear.

Not only are scientists locating the genes that contribute to hearing impairment, they are also locating the genes involved in the normal development of the ear. Scientists have found the genes responsible for collagen, which is involved in the structure and connection of tissues, and for the development of melanocytes (cells that produce coloring or pigmentation in tissues, including parts of the inner ear that require melanocytes to function properly)(Tachibana et al., 1996; Tsukamoto, Nakamura and Niikawa, 1994).

Genetic predisposition to hearing impairment

Through research it is known that genes are fragile and can be influenced by outside agents. Physicians and scientists have known for some time that certain drugs, though they can be useful, can also threaten hearing and balance. One such group of drugs is known as aminoglycoside antibiotics. Because of adverse side effects, physicians use these drugs only when all other options are exhausted, and then only at the lowest effective dose possible. Yet even small doses can effect some peoples hearing and balance. Research has demonstrated that some people have mutations or changes in a mitochondrial gene that makes them unusually susceptible to hearing impairment when aminoglycosides are used (Fischel-Ghodsian, Prezant, Bu & Oztas, 1993). This knowledge may help identify people who are unusually susceptible and sensitive to hearing and balance damage.

Families with this pattern of susceptibility to aminoglycosides have been found in China and Japan.

Research efforts such as these confirm that genetic factors may contribute to other hearing and balance disorders that were previously attributed solely to other factors. For e.g., varying susceptibility to noise-induced hearing loss and age-related loss (Presbycusis) suggests that a genetic predisposition for these disorders may exist. Investigations into the molecular mechanisms operating in these forms of hearing impairment or fundamental to understanding and preventing them, and treating individuals with them.

Genes Related To Hearing Loss

This section review's some conditions (syndromic and Nonsyndromic) of hearing loss associated with chromosomal abnormalities. Usher syndrome is characterized by sensorineural hearing loss and retinitis pigmentosa (chronic, progressive inflammation of the retina with atrophy and pigmentary infiltration causing decrease peripheral vision).It accounts for at least 50% of the cases of deafness and blindness in the United States. There are three types of Usher; all are autosomal recessive. Type I has profound bilateral sensorineural hearing loss with vestibular dysfunction and prepubertal retinitis pigmentosa. Type II has bilateral, symmetric, moderate to severe hearing loss with normal vestibular function. Type III is characterized by progressive sensorineural hearing loss. Visual loss in type II is less severe than that in types I, but progresses is faster. Chromosome 11 mutation is associated with Usher syndrome type I. Chromosome 1 and 3 mutations are linked to types II and III, respectively.

Waardenburg syndrome consists of pigmentory abnormalities, such as premature graving of hair, vitiligo in 20% of cases, white forelock (white tuft of hair) in 30% of cases (Hageman and Delleman, 1977), heterochromis hides (different colored iris), dystopia canthoram (laterally placed medial canthy), broadened nasal root, synophrys (one confluent eyebrow),and unilateral or bilateral sensorineural hearing loss (20 %). Type I Waardenburg syndrome has dystopia canthorum and type II does not Type II is often associated with bilateral congenital hearing loss. Chromosome 2 mutation is associated with Waardenburg syndrome type I (gene is PAX3) (Foy et. al., 1990), where as chromosome 3

mutation is linked to type II (gene is MITT) (Hughes et. al ., 1994). Regardless, this is an autosomal dominant syndrome with a high degree of penetrance and variable expressivity. In other words the affected individual can inherit the mutation in only one chromosome. All affected individuals will have at least some degree of physical defects as a result of the genetic mutation. The birth prevalence of Waardenburg syndrome is 20-30 per 1000,000 (Cohen, 1996).

Treacher- Collins syndrome (Mandibulofacial dysostosis) is noted for ear anomalies (small ears, canal atresia. conductive or sensorineural hearing loss, and vestibular dysfunction), mandibular hypoplasia, downward slanted palpebral fissures (eyes slanted down), eyelid coloboma (notching of eyelid) and groove and pouch malformation. Cleft palate and congenital velopalatal insufficiency are found in 35% and 30 % of cases, respectively (Peterson- Falzone and Pruzansky, 1976).More than half of the cases occur sporadically. Chromosome 5 is linked to mis autosomal dominant disorder. The treacle gene is responsible for the hearing loss.

Branchio-oto-renal (BOR) syndrome consists of bronchial cleft anomalies, malformed ears, preauricular pits, hearing loss (conductive, sensorineural, or mixed), renal hypoplasia, or agenesis. This autosomal dominant disorder is linked to chromosome 8 and is found in 25per 1,000,000 births (Cohen; 1996). Pendred syndrome is an autosomal recessive disorder with congenital sensorineural hearing loss and thyroid goiter enlargement due to a defect in thyroid hormone formation (thyrosine iodinization). 50% of the individualized have a hypothyroid condition.

There is an association with mondini deformity (cochlear malformation). Chromosome 7 anomaly is linked to pendred syndrome.

X-linked mixed hearing loss with stapes gusher is a nonsyndromic, X-linked hearing impairment. Patients have congenital, progressive, or mixed hearing loss. Female carriers (those who have only one copy of the gene) have mild, mixed, OT pure sensorineural hearing loss. Male patients not only have hearing loss but also abnormal vestibular function. There is a high incidence of prelymphatic gusher with stapdotomy (creating a whole in the stapes food plate). CT scans can help making the diagnosis by revealing the incomplete bony separation between the cochlear and the modulus. This phenomenon occurs in males with in one family. The responsible gene is POU3F4 (Dekok etal.,1995).

There are as many as 200 genes responsible for nonsyndromic genetic hearing impairment

Autosomal-dominant, delayed -onset nonsyndromic disorders are divided into four categories: early onset, low frequency, mid frequency and high frequency. The hearing impairment is sensorineural in nature and can progress to severe or profound level. Chromosome 5 is associated with this disorder.

(Lenhanh .P.1999).

"Genetic Counseling"

Any couple who have had a child with a serious abnormality must inevitably reflect on why this has happened and whether any child / children they choose to have in future could be similarly affected. Individuals who have a family history of a serious disorders are likely to be equally concerned that they could either develop the disorder or transmit it to future generation. A many adults are often unaware that it could be due to a a genetic cause despite (in some instances) a family history of hearing impairment and the widespread availability of genetic counseling services (Nance, 1971 ; Israel, 1989 ; Lindrout et. al., 1991 ; Amos et. al., 1992). Realization of the needs of such individuals and couples and awareness of the importance of providing them to accurate and appropriate information has led to the widespread introduction of genetic counseling clinics, with the establishment of clinical genetics as a recognized medical specialty.

In 1940 Sheldon Reed at the University of Minnesota coined the term genetic counseling and set down some guidelines for its use.

Genetic Counseling provides information to referred clients:

Genetic counseling is intended to educate an individual or family about the hereditary or non-hereditary nature of a given trait The counselor does not hold back information on the long-range economic or psychological effects of having a child with a defect or the medical care available. Everything a parent wants to know about the disorder with its diagnosis, its outcome, and the risk of recurrence

its impact on the family, its cost and its potential presence in collateral relatives is given to the family. The family may then use this knowledge is deciding whether or not to plan additional pregnancies.

Genetic counseling is a communication process, which addresses an individuals concern relating to the development and or transmission of hereditary disorder.

A preferable definition for genetic counseling might be

"an educational process that seeks to assist affected and or at risk individuals to understand the nature, of the genetic disorder, its transmission and the options available to them in management and family planning".

Genetic counseling has been defined by the *American Society of* ***Human*** *Genetics* (Ad Hoc committee on genetic counseling 1975) as

a communication process which deals with the human problems associated with the accurence, risk of occurrence, of a genetic disorder in a family ".

An individual who seeks genetic counseling is known as a *consultant.* During the genetic counseling process it is widely agreed that the counselor should try to ensure that the consultant is provided with information which enables him/her to understand:

1) The medical diagnosis and its implications in terms of prognosis and possible treatment.

2) The mode of inheritance of the disorder and the risk of developing and / or transmitting it.

3) The choice or option available for dealing with the risks .

It should include a strong communicative and supportive element, so that those who seek information are able to reach their own fully informed decisions without under pressure or stress.

Steps in Genetic Counseling

- Understanding of the diagnosis based on history, examination and investigation
- Risk assessment
- Communication
- Discussion of option
- Long term contact and support (Fraser et. al., 1978)

Understanding of the diagnosis based on history, examination and investigation

Generally, families have only a partial understanding of the disease for which they request genetic counseling. Commonly, couples are referred without any prior knowledge that the disorder is genetically determined. Although the counseling process should not be a prediction of doom, it is necessary that the couples have an adequate understanding of the natural history of the disease. The

extent of this part of the discussion will depend on the couples, prior knowledge and experience with the disorder for which they are being counseled where a living proband i.e. affected individual exists, considerable concern will likely be present for his prognosis and management.

Calculating and presenting the risk

In some counseling situation calculation of the recurrence risk is relatively straight forward and requires little more than a reasonable knowledge of mendelian inheritance. However, many factors such as delayed age of onset, reduced penetrance and the use of linked DNA markers can result in the calculation becoming much more complex. The provision of a recurrence risk does not simply involve conveying a start risk figure in isolation. It is very important that information which is provided is understood and mat parents are given as much background information as possible to help them reach their own decision. As a working rule of thumb, recurrence risks should be quantified, qualified and placed in content

Qualification- the numeral value of a risk:

Most prospective parents will be familiar to some degree with the concept of risks, but experience indicates that a risk of 1 in *A* can easily be mis-interrupted or remembered as 4 in 1, 1 in 40 or even 14 %. An equally alarming but entirely understandable misconception is that this risk applies only to every fourth child, so that having had an affected child there should be no problems with the next three children. It is therefore vital to emphasize that the risk applies to each child, and

that chance does not have a memory. The most after quoted analogy is that of the tossed coin which can not be expected to remember whether it came down to heads or tails at the last throw and can not therefore be expected to know what it should do at the next throw.

It is also important that genetic counselors should not be seen exclusively as prophets of doom. Continuing the penny analogy, the good side of the coin should also be emphasized. For example a couple faced with a probability of 1 in 25 that their next baby will have a neural tube defect should be reminded that there are 24 chances out of 25 that their next baby will not be affected.

Qualification — the nature of risk

Several studies have indicated that the factor which most influence parents when deciding whether or not to have another child in the nature of the long term burden associated with a risk rather than its precise numerical value. Therefore a high risk of 1 in 2 for a trivial problem such as an extra digit (polydactyl) will detect very few parents in contrast a low risk of 1 in 25 for a disabling conduction such as a neural wise defect can have a very significant effect. Other factors such as whether a conduction can be successfully treated, whether it is associated with pair and suffering and whether prenatal diagnosis is available, will be relevant to the decision making process.

Understanding of the available options

The decision making process is simplified for the couple by preparing a list of the available options and discussing the merits of each option. It is a food practice to draw up a list with the couple of all the theoretical options and include the advantages and disadvantages of each option. These include the following.

1) Have no farther children

The advantage of this option is that the couple will avoid the possibility of an affected child, the disadvantage is that they may not be able to complete the family they desired.

2) Take a Chance

This will allow them further children of their own, but they will have to accept the risk of an affected child. It may well be that originally the couple will reject this idea only to reconsider it after a period of examining the other alternatives. When a significant risk exists, it can be helpful to ask that the couple assume that another pregnancy would result in an affected child, men examine what that would mean to the child, them and other family members.

3) Adoption

This will allow the couple to complete their family without having a child with the disorder for which they are at risk. Some couples find it difficult to accept a child that is not their own. A second disadvantage is that adoption has become a time. Consuming and expensive process with many couples unable to obtain a child after several years of waiting.

4) Prenatal diagnosis

This option requires that the disorder under question is detectable by prenatal diagnosis and that the couple is willing to undergo what may be an expensive series of tests with the result that they may be confronted with the issue of an elective abortion.

5) Divorce

This option is not raised as a potential choice that the couple may seriously consider, but it does allow several points to be made. It tends to underscore the fact that situations can change and that reproductive life is measured in years, so that decision should be well thought through.

6)Sterilization

For a young couple with no children but a high risk of producing an affected child, a sterilization procedure should not be considered lightly.

It should be pointed out that the risks might change given a different spouse. For autosomal dominant disorders, the risk will not change for one member of the couple with a new spouse but will for the other. For autosomal recessive disorders, a new spouse reduces the risk to each. This leads to the next spouse.

7) Artificial Insemination

This will allow the couple to greatly reduce the risk to a pregnancy if the disorder is autosomal recessively inherited, 2. If the husband is affected with a dominantly inherited disorder, or if he carries a balanced chromosomal rearrangement the husband may feel a closer bond to such a child than he might for an adopted child. It can be suggested that he consider this as semi-adoption.

Artificial insemination can however, is a time consuming and expensive undertaking. The child will have the mother as the source of half the genes, but the husband will not be the source of the other half. As with adoption although the risks are greatly reduced no final guarantee of a normal child can be given.

8) In vitro fertilization with donor ova

The use of donor ova for in vitro fertilization has the same impact or risk reduction for the wife that artificial insemination has for the husband.

Both of these latter two options should be raised with couples without any prejudgment as to their likelihood of actual use. It is unlikely that either of these two option will be the couples with out any prejudgment as to their likelihood of actual use. It is unlikely that either of these two options will be the couples initial choice, but they may come to seriously consider them after reviewing other options.(Carlson, 1985)

Communication and support

Communication is a two-way process. Not only does the counselor provide information but he or she also has to be receptive to the fears and aspirations, expressed or unexpressed, of the consultant. Information must be presented in a clear, sympathetic and appropriate manner.

Often an individual or couple will be extremely upset when first made aware of a genetic diagnosis. Every one involved in the genetic diagnosis needs it remembers that the delivery of potentially distressing information cannot be carried out in isolation. Genetic counselors need to take into account the complex psychological and emotional factors, which can influence the counseling dialogue. When possible, technical terms should be avoided or if used fully explained. Questions should be answered openly and honestly, and if information is lacking it is certainly not a fault or sign of weakness to admit that this is so.

Consanguinity and interest:

A consanguineous marriage is one between blood relatives who have at least one common ancestor no more remote than a great-great grandparent is. A union between first degree relatives (brother-sister or parent-child) is referred to as being incestuous. Marriage between first-degree relatives is forbidden is almost every culture.

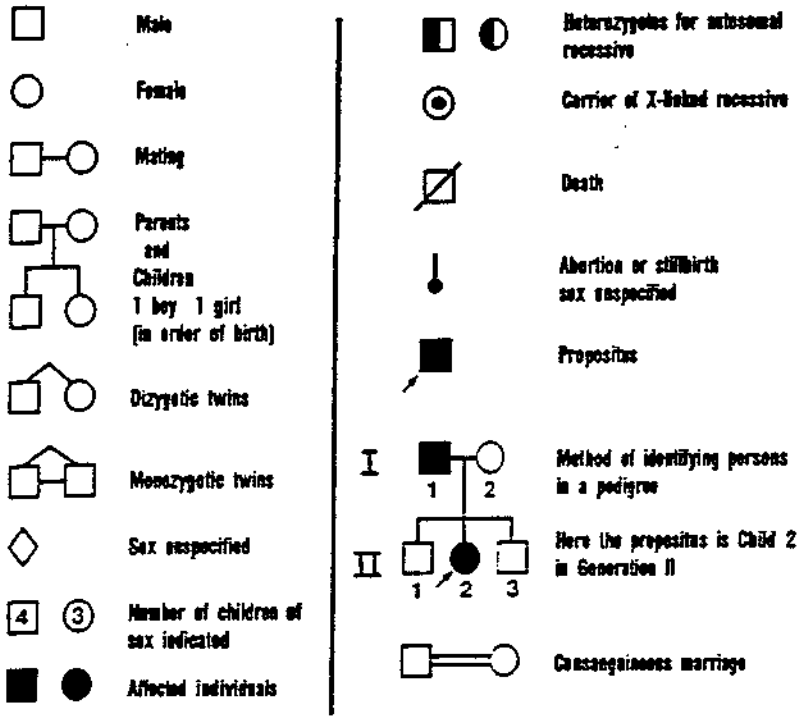
Marriage between second degree relatives is also illegal in many countries, although uncle-niece marriage is common in parts of India.

Several extensive studies have shown that among the offspring of consanguineous marriage there is an increase in both morbidity and mortality with an increased incidence of congenital structural abnormalities and conditions which present later, such as deafness and mental retardation. Fortunately the overall risks are usually relatively small risks are usually relatively small so that most consanguineous couples can be offered reassurance that they do not run a particularly high risk of having a handicapped child.

Based on the study of children born to consanguineous parents it has been estimated that most individuals carry between 2 and 6 lethal recessive mutation plus one autosomal recessive mutation for a harmful but viable disorder. As most prospective consanguineous parents are concerned primarily with the risk that they will have a handicapped child, it is customary to estimate this risk on the assumption that each common ancestor carried one deleterious recessive mutation. (Fraser etal 1976).

Therefore for first cousins, the probability that their first child will be homozygous for their common grandfather's deleterious gene will be 1 in 64 (fig, 6).

Similarly the risk that this child will be homozygous for the common grand-mother's recessive gene will also be 1 in 64.This gives a total personality that the child will be homozygous for one of the grand-parents deleterious genes of 1 in 32. This risk should be added to the general population risk of 1 in 40 that any baby will have a major congenital abnormality to give an over all risk of approximately



Symbols commonly used in pedigree construction.

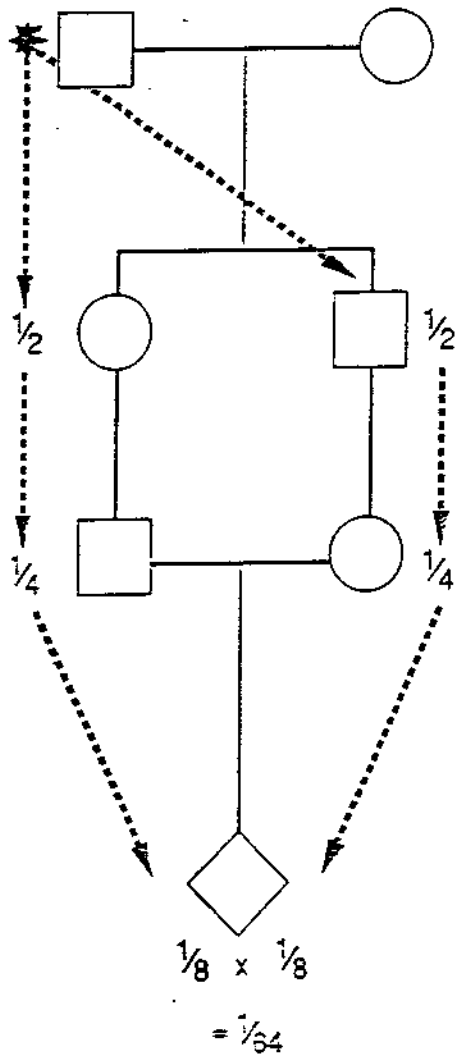


Fig. 6.
Shows the probability that the first child of first cousins will be homozygous for the deleterious allele (*) carried by the common great-grandfather. A similar risk of 1 in 64 will apply to the deleterious allele belonging to the common great-grandmother giving a total risk of 1 in 32.

1 in 2 that a child born to first cousin parents will be either malformed or handicapped in some way. Risks due to consanguinity for more distant relatives are much lower.

For consanguineous marriages there is also a slightly increased risk that the child will have a multifactorial disorder, such as one of the common congenital malformations.

In practice this risk is usually very small. In contrast a close family history of an autosomal recessive disorder can convey a relatively high risk that a consanguineous couple will have an affected child for e.g. If the sibling of someone with an autosomal recessive disorder marries a first cousin, the risk that their first baby will be affected equals 1 in 24(Connor,et al1994)..

Incestuous relationships are associated with a high risk of abnormality in offspring with only half the children of such union being entirely healthy.

The genetic counselor:

Genetic counseling is most effectively conducted when there is a multidisciplinary team including clinical geneticists, cytogeneticists, biochemical geneticists, genetic associates, social workers, and other specialists needed to determine the specific in formation that is to be conveyed to a family. The person who actually conveys this information to the family logically would seem to be a person skilled in counseling.

Families expect the counselor to be knowledgeable about the disease in question not only are they interested in the genetics but they are also concerned about the specifies of the disease, its nature, prognosis treatment and available sources of assistance. Because of these concerns, some maintain that only a physician is capable of meeting all of these counseling needs. However, only in the minority of genetic disorders will the physician-geneticist be the physician primarily responsible for the long-term management of the patient. For the great majority of disorders' requiring genetic counseling the use of a team approach will not require a physician-geneticist as the counselor.

The counselor must be available and acceptable to the family and in a position to provide the necessary help. Within any given genetics program, a number of people may participate in genetic counseling and certain individuals may be more appropriate in certain situation. M.D's, Ph.D's, nurses, social workers and genetic associates, counselor with the support that each of them requires a team approach to genetic counseling.

RECENT RESEARCH ON HEREDITY DEAFNESS

"TheMDCD"

The National institute of deafness and other communication disorders (NIDCD) have established the heredity hearing impairment research registry (HHIRR) to collect and distribute information on heredity hearing disorders. The HHIRR is located at the Boys town national research hospital in Omaha. Nebraska. The registry collects and maintains data on individuals and families to have heredity hearing loss, including the genetic, medical, audiologic, epidimologic and "* denographic information. These data are available to researchers, clinicians and patients by request. The address in NIDCD, HHIRR, 555N. 30th street Omaha, NE-68131.

*"**Human genome** research"*

All of the genes for a species are referred to as the genome of that species. Human genome research is an effort to identify and sequence or read the code of all the human genes. In the United States Congress has appropriated funds to the department of energy and the National institute of health for support of the human genome project to study the human genome.

It has been estimated that an average of approximately $200 million annually from the United States budget will be required to complete the project in about 15 years. The US is not alone in this endeavor; scientists in many other countries are pressing the same goal. The human genome organization (HUGO) is

an international organization which co-ordinates human genome research efforts around the world.

"The Indo-Us Project"

Principles of the Indo-Us project

Objectives:

The proposal envisages he application of contemporary genetic techniques and molecular biology to hearing and deafness research. It would make possible the chromosomal localization of previously unknown genes of hearing impairment. This will allow the investigation of candidate genes on the linked regions for their role in hearing. This will eventually lead to cloning and sequencing of genes involved in hearing; and will allow a more complete understanding of the biology of hearing, enable more accurate genetic counseling, and contribute in future to better approaches for management of deafness. Obtaining such information would be crucial step for the development of gene therapy to treat disorders of hearing impairment Identify chromosomal regions that contain genes causing Nonsyndromic hereditary hearing impairment (NSHHI) in India.

The project represents a continuum of a series of collaborative activities undertaken since 1990, by the All India Institute Of Medical Sciences, New Delhi, India and the National Institute Of Deafness and Other Communication Disorders (NTDCD), National Institutes of Health, Berhesda, USA.,(Kabra,M 1999).

CHAPTER- 3

SUMMARY AND CONCLUSION

Using advanced technologies such as EOAE and ABR, we are able to identify individuals with hearing impairment at an early age. All interventions including hearing aids, preferential seating (sitting at the front of the classroom, with better hearing ear closer to speaker), classes for the hearing impaired, and surgeries can be offered to patients right away. Genetic hearing impairment is caused by genetic aberrations. Until we can reintroduce normal genes, we can only treat their symptoms. The more we know about the pathophysiology of a particular disease, the more quickly and effectively we can identify the gene responsible for the hearing loss. Gene mapping for specific types of hearing loss can be extremely challenging in the face of other environmental factors, preferential mating (consanguinity or people who are deaf marrying each other), and infections, which complicate the picture. Once a gene is linked to a specific type of hearing impairment it is conceivable to replace the genetic deficiency with normal genes. Another alternative is to introduce the gene into the patient with subsequent conversion of the target cells back to normal.

However, gene therapy in hearing impairment is still at the research stage. With more ambitious, large- scale collaboration among the many research centers, such as the national center for human genome research of the national institute of health and the environmental research section of the department of energy, its hoped that gene therapy will soon be available.

Thereby an extensive, though not, all inclusive, review on the basics of genetics and Hearing Impairment is studied. It is hoped that it may provide a guideline for the audiologist and Speech pathologist to gain knowledge regarding the role of **"Genetics In Hearing Impairment".**

REFERENCES

Altenburg, E.(1970). Genetics. Calcutta: Oxford & IBH publishing Co.

Arons, K., Israel , J., Marazita, M.(1992).Cited in Muller, R. F. (1995). Genetic counseling for hearing impairment, In A. Martini, A. Read & D. Stephens. (Eds.), Genetics & hearing impairment (pp. 225 - 264). Tyne : Whurr publishers.

Arnos, K. S., Cunningham, M., Israel. J., & Marazita, M.(1992). Cited in Arnos, K.S. (1999). Genetic counseling for hearing loss. The Volta Review, 99, 85 - 96.

Bolstein, D., White, R. L., Skolnick, M., Davis, R.W. (1980). Cited in Dallapicobla, B., Menganelli, R., & Read, A. P.(1996). Methods of identifying hearing loss, hi A. Martini, A. Read & D. Stephans.(Eds.), Genetics & hearing impairment (pp. 33-47). Tyne: Whurr publishers.

Burns, G. W. (1969). The science of genetics: an introduction to heredity. New York: The Macmillan company.

Clavert, *A* F. (1968). Chemical basis of inheritance, hi Bartalos, M (Ed.). Genetics in medical practise (pp. 29-41). Philadelphia: J. B. Lippincott company.

Carlson, E.A. (1985). Human genetics. East-west press private limited: New Delhi.

Chung, C.S., & Brown, K. S. (1970). Cited in Smith, S. D., Kimberling, W. J., Schaefer, G. B., Horton, M. B., & Tinley, S. t. (1998). Medical genetic evaluation for the etiology of hearing loss in children. Journal of Communication Disorders, 31,371-389.

Cohen, M. M. (1996). Genetics, Syndromology, & Craniofacial anomalies. In C. D. Bluestone & E. S. Stool (Eds.), Paediatric Otolaryngology (pp. 33 - 51). Philadelphia: W.B. Saunders.

Cohen, M. M. (1996). Cited in Lenhanh, P. T. & Kenneth, M. G., (1999). Hereditary hearing loss. The Volta Review, 99, 63 - 99.

Collins, F. S.(1992). Cited in Dallapiccola, B., Menganelli, R., & Read, A. P. (1996). Methods of identifying hearing loss. In A. Martini, A. Read & D. Stephans. (Eds.), Genetics & hearing impairment (pp. 33 - 47). Tyne: Whurr publishers.

Connor, J. M. & Ferguson, S. (1994). Essential Medical genetics, Oxford: Black well scientific publishers.

Dallapiccola, B., Mengarelli , R., & Read, A. P. (1995). Methods of identifying hearing loss, In A. M. Martini, A. Read & D. Stephans .(Eds.), Genetics & hearing impairment (pp. 33 - 47). Tyne: Whurr publishers.

De Kok, Y. J., Van der Maarel, S. M., Bitner - Gundyicy, M., Huber, I., Monaco, A. P., Malcom, S., Pembrey, M. E., Ropers, H. H., & Cremers, F. P.(1995). Cited in Hennanh, P. T. & Kenneeth, M. G., (1999). Hereditary hearing loss. The Volta Review. 99, 63 -- 99.

Fischee-Ghodsian, N., Preyant, T. R., Bu, X., & Oytas, S. (1993). Cited in James, B. S. (1999). Research on hearing & balance-current & future developments. The Volta Review, 99, 29 - 42.

Fischee-Ghodsian, N., Preyant, T. R., Fournier, P., Stewart, I. A., & Maw, M. (1995). Cited in James, B. S. Jr. (1999). Research on hearing & balance-current & future developments. The Volta Review, 99, 29 - 42.

Foy, C, Newton, V., Wellesley, D., Harris, R, & Head, A .P. (1990). Cited in Lenhanh, P. T. & Kenneth, M. G. (1999). Hereditary hearing loss. The Volta Review, 99, 63 -- 99.

Fraser, G. R.(1976). Cited in Agnette Parving (1996). Epidemology of genetic hearing impairment. In A. Martini, A. Read & D. Stephens (Eds.), Genetics & hearing impairment (pp. 73-81). Tyne: Whurr publishers.

Fraser, G.R_ (1976). The Causes of profound deafness in childhood. Baltimore: Johns Hopkins University Press.

Fraser, J. A. & Pembrey, M. E. (1978). An Introduction to medical genetics Baltimore : Johns Hopkins University Press.

Gardner, E. J. (1968). Principles of genetics. New Delhi: Wiley Eastern Private limited.

Gardner, E. J. (1983). Human hereditary, New York: John Wiley & Sons.

Gorlin, R. J. Toriello, M.V., & Cohen. M. M. Jr. (1995). Hereditary hearing loss & its syndromes. New York: Oxford University.

Green, E. D., Cox, D. R., Myers, R M., (1995). Cited in Dallapiccola, B., Menganelli, R., & Read, A. P. (1996). Methods of identifying hearing loss. In A. Martini, A. Read & D. Stephans (Eds.), Genetics & hearing impairment (pp. 33-47). Tyne: Whurr publishers.

Hageman, M. J., & Delleman, J. W. (1977). Cited in Lenhanh, P. T., & Kenneth M. G., (1999). Hereditary hearing loss. The Volta Review, 99, 63-99.

Hughes, A. E., Newton, V. E., Hill, X. Z., & Read, A. P. (1994). Cited in Lenhanh, P. T., & Kenneth M. G., (1999). Hereditary hearing loss. The Volta Review, 99, 63 - 99.

Israel, J., (1989). Cited in Muller, R F. (1995). Genetic counseling for hearing impairment. In A. Martini, A. Read & D. Stephens (Eds.), Genetics & hearing impairment (pp. 225-264). Tyne : Whurr publishers.

Jaber, L., Shohat M, Bu, *X.*, Fischee-Ghodsian, N., Yang, H. Y., Wang, S. J., & Rotten, J. I. (1992). Cited in James, B. S. (1999). Research on hearing & balance-current & future developments. The Volta Review, 99, 29-42.

Jacobson, J. T. (1997). A review of genetic hearing loss. The Hearing Journal, 50, 10-21.

Jung, J. H. (1989). Genetic syndromes in Communication disorders, Texas: Pro-ed incorporation.

Kabra, M. Objectives of Indo-Vs Project (an unpublished data from the perspectives of the Indo-US project).

Lenhanh, P. T., & Kenneth M. G., Fast, (1999). Hereditary hearing loss. The Volta Review, 99, 63 - 69.

Levine, R. P. (1968). Genetics .(Edn. 2). London: Holt, Renehart & Winston, incorpotion.

Lindhout D., Frets. P, & Niermeyer, M, (1991). Cited in Muller, R. F. (1995). Genetic counseling for hearing impairment. In A. Martini, A. Read & D. Stephens (Eds.), Genetics & hearing impairment (pp. 225 - 264). Tyne : Whurr publishers.

Morton, N. E. (1991). Cited in Agnette Parving (1996). Epidemology of genetic hearing impairment. In A. Martini, A. Read & D. Stephens (Eds.), Genetics & hearing impairment (pp. 73 - 81). Tyne : Whurr publishers.

Morton, N. E.(1991). Cited in Smith, S.D, Kimberling, W. J., Schafer, G. B., Horton, M. B., & Tinley, S. T., (1998). Medical genetic evaluation for the ecology of hearing loss in children. Journal of Communication Disorders, 31, 371 - 389.

Muller, R. F., Young I. D. (1995). Emerys elements of medical genetics. (Edn. 9), Edinburgh: Churchill Livingstone.

Nance, W.E.(1971). Cited in Muller, R. F. (1995). Genetic counseling for hearing impairment. In A. Martini, A. Read & D. Stephens (Eds.). Genetics & hearing impairment (pp. 225-264). Tyne : Whurr publishers.

Newton, V. E.(1985). Cited in Agnette Parving (1996). Epidemology of genetic hearing impairment. In A. Martini, A. Read & D. Stephens (Eds.), Genetics & hearing impairment (pp. 73-81). Tyne: Whurr publishers.

Ott, J. (1991). Analysis of human genetic linkage. Baltimore: Johns Hopkins University press.

Peterson - Falyone, S. & Pruzansky, S. (1976). Cited in Lenhanh, P .T., & Kenneth M.G., (1999). Hereditary hearing loss. The Volta Review, 99, 63 - 99.

Read, A. P. (1989). Basic Genetics mechanisms. In A. Martini, A. Read & D. Stephens (Eds.), Genetics & hearing impairment (pp. 18-31). Tyne : Whurr publishers.

Robertson, N. G., Khetarpae, U.. Gutierren-Espeleta, G. A., Bieber, F. R., & Morton, C. C. (1994). Cited in James, B. S. Jr. (1999). Research on hearing & balance- current & future developments. The Volta Review, 99, 29 - 42.

Rose, S. P., Conneally, P. M., & Nance, W.E. (1977). Cited in Agnette Parving (1996). Epidemology of genetic hearing impairment. In A. Martini, A. Read & D. Stephens (Eds.), Genetics & hearing impairment (pp. 73 - 81). Tyne: Whurr publishers.

Schukencht, H. F. (1980). Cited in Smith, S. D.; & Harker, L. A. (1998). Single gene influences on radiologically - detectable malformation of the inner ear. Journal Of Communication Disorder,31, 391- 410.

Shprintzen, R. J. (1997). Genetics, syndromes & communication disorders. London: Singular publishing group inc.

Singleton, W. R.(1969). Elementary genetics (Edn. 2). New Delhi: East- West press private limited.

Tachibana, M., Takeda, K., Nobukuni, Y., Urabe, K., Long, J. E., Meyers, K. A., Aaronson, S. A., & Miki, T. (1996). Cited in James, B. S. Jr. (1999). Research on hearing & balance- current & future developments. The Volta Review, 99, 29 - 42.

Tsukamoto K. Nakamura, Y.,& Nirkawa, N. (1994). Cited in James, B.S. (1999). Research on hearing & balance- current & future developments. The Volta Review, 99, 29 - 42.

GLOSSARY

ALLELE (Allelomorph) - One of several possible forms of a particular gene.

ALLELIC ASSOCIATION -- Allele A1 at locus A and allele B1 at locus B are associated if the frequency of B1 is significantly different in people carrying A1 than in the general population. This may indicate that the A and B loci are close together on the same chromosome.

AMINOGLYCOSIDE - One of a group of antibiotics, derived from various species of Streptomyces. Which interfere with the function of bacterial ribsosomes and which are generally ototoxic.

AUTOSOME - A chromosome other than a sex chromosome.

AUTOZYGOSITY MAPPING - A method of mapping recessive characters in inbred families by looking in affected people for chromosomal segments that are identical on the maternal and paternal chromosomes. Much used for recessive non-syndromal hearing loss.

BASE PAIR (bp) - The basic unit of the DNA double helix, used as a measure of the length of a piece of DNA.

CARRIER - A phenotypically normal person who is heterozygous for a recessive condition.

cDNA - A synthetic DNA complementary to a messenger RNA molecule.

CENTIMORGAN (cM) - In genetic mapping, loci lcM apart show 1 % recombination.

CENTROMERE - A region of chromosome to which spindle traction fibres attach during mitosis and meiosis.

CHROMATIDS - The daughter strands of duplicated chromosome joined by a single centromere.

CHROMOSOMES - Structural elements of various signs found in the nucleus of a cell and containing the major part of the hereditary material (the genes). The main chemical components of a chromosome are proteins and DNA. They are capable of self - duplication, thus ensuring that identical genetic material is handed to each of the daughter cells resulting from a cell division.

CLONES - Identical copies of an organism, cell or DNA sequence.

CONGENITAL - Present at birth. No necessary connotation as to genetic or nongenetic (e.g., Rubella syndrome is congenital but nongenetic).

CONSANGUINEOUS - Of spouses, having a genetic relationship closer than usual in the population.

CpG ISLAND - A specialized DNA sequence often found close to genes and so providing a means of recognizing genes in genomic DNA.

DELETION - The loss of a segment of the genetic material from a chromosome.

DIPLOID - Possessing a double set of chromosomes, one set from the mother and one set from the father (synonym 2n).

DNA- Deoxyribonucleic acid. The main chemical component of the genetic material in a chromosome.

DOMINANT - A phenotype which is manifest when present in the heterozygous state.

DUPLICATION - The occurrence of a chromosomal segment in duplicate resulting from chromosome breakage and reunion of non corresponding ends, (unique crossing over).

EUKARYOTIC - Organisms whose cells have nuclei enclosed by membranes; these include all animals and plants, but not bacteria, which are prokaryotic.

EPIDEMIOLOGY - The study of the relationship of various factors determining the frequency and distribution of disease.

EXON - A segment of gene that becomes part of the mature messenger RNA after splicing out of introns.

EXPRESSED SEQUENCE TAG (EST) - A short partial cDNA sequence, supposed to be sufficient to define a gene uniquely. Techniques exist to identify EST's on a very large scale.

EXPRESSIVITY - The range of phenotypes expressed by a given genotype under any given set of environmental conditions.

FISH (fluorescence *in situ* hybridization) - A gene mapping technique in which fluorescently labelled DNA clone is used to pick out its cognate sequence in spread of chromosomes under the microscope.

FUNCTIONAL APPROACH - In gene cloning, cloning a gene through knowing its function or knowing the aminoacid sequence of the protein it encodes.

GAMETE - A mature male or female reproductive cell; spermatozoon or ovum; normally, with a haploid set of chromosomes.

GENETIC MAPPING - Working out the order and spacing of genes along a chromosome by observing the frequency of genetic recombination between loci in

breeding experiments or human pedigrees. Genetic map distances are measured in centimorgans (q.v.).

GENETIC MARKER - Any genetic character that is Mendelian and polymorphic. In practice, almost always DNA polymorphisms.

GENOME — All the genes carried by a single gamete.

GENOMIC DNA - DNA as it occurs in the genome of an organism, complete with all the non-coding sequences.

GENOTYPE — The genetic constitution of an organism.

GESTALT - The overall appearance of a patient an important part of syndrome recognition.

HAPLOID - Possessing a single set of chromosomes as in the reproductive cells (synonym: In).

HETEROZYGOUS - Having two dissimilar alleles at a locus.

HOMOPLASMY - Having all mitochondria genetically identical (normal or abnormal).

HUMAN GENOME PROJECT - The international research effort to map and characterized all human genes and ultimately define the complete DNA sequence of the human genome.

HYBRIDISATION - In DNA technology, allowing two complementary DNA or RNA strands to form a double helix.

IMPAIRMENT - An abnormality of function as a result of a disease or malformation, e.g. elevated auditory threshold.

I**NSERTION** - The addition of one or more base pairs into a DNA molecule.

INTRON - In split genes, a segment that is transcribed into nuclear RNA, but is subsequently removed from within the transcript and rapidly degraded.

KARYOTYPE - The chromosomes of an individual systematically arranged from photomicrographs of a single cell nucleus.

KILOBASE (kb) - 1000 base pairs, a measure of the size of a piece of DNA.

LIBRARIES - In molecular genetics, collections of random genomic DNA or c DNA fragments cloned into a vector.

LINKAGE - Two loci are linked if alleles at the loci tend more often than by chance to co-segregate into gametes.

LINKAGE ANALYSIS — Typing individuals in a pedigree or breeding experiment for alleles at two or more loci to check whether they are co-segregating.

LINKAGE DISEQUILIBRIUM - A common cause of allelic association (q.v.). Linkage disequilibrium is seen between alleles at two loci when the chromosomal segment carrying mem in apparently unrelated people is in fact often derived intact from a common ancestor.

LOCUS - The position that a gene occupies on a chromosome.

LOD SCORE - A statistical measure (logarithm of the odds for or against linkage) which is the outcome of linkage analysis.

m **RNA** - Messenger RNA.

MEGABASE (Mb) — lmillion bases (a measure of size of DNA fragments).

MULTTFACTORIAL - Governed by many factors, which may include genetic and environmental factors.

MUTATION - The process by which a gene undergoes a structural alteration.

NON-PENETRANCE - The situation when a person does not manifest a character despite having a genotype that normally produces that character. Typically seen when a dominant disease skips a generation.

NON-SYNDROMAL - (In relation to hearing loss) a loss unaccompanied by any other abnormalities.

NORTHERN BLOT - A technique for examining mRNA present in a given tissue sample.

PCR (POLYMERASE CHAIN REACTION) - A technique for producing unlimited numbers of copies of short segment of DNA. PCR is the key technique in much of molecular genetics.

PEDIGREE - A family ; the family tree.

PENETRANCE - The proportion of individuals of specified genotype that show the expected phenotype under a given set of environmental conditions.

PHENOTYPE - The sum total of all observable features of developing or developed individual.

PHYSICAL MAP — A map showing the physical locations of genes or sequences on chromosomes or cloned DNA fragments. Physical map distances are measured in base pairs, kilobases, megabases etc., or in terms of the chromosomal bands recognized by cytogeneticists.

POLYGENIC — A character dependant on the interaction of a number of genes (strictly, a very large number of genes, each with a very small effect).

POLYMORPHISM - The existence of two or more genetically different classes in the same interbreeding population at frequencies such that the rarest could not be maintained simply by recurrent mutation, A common working definition is that at least two alleles should have frequencies above 1 % in the population.

POSITIONAL CANDIDATE APPROACH - in cloning disease genes, a strategy in which a candidate chromosomal region is defined by linkage analysis, and then genes already known to map to this region are tested to see if they cause disease.

POSITIONAL CLONING APPROACH - Cloning a gene using only knowledge of its approximate chromosomal location. A difficult task.

POSTNATAL - occurring after birth.

PRENATAL - occurring before earth.

PRENATAL DLAGNOSIS - determination of the karyotype or phenotype (or sex) of a fetus, usually prior to 20 weeks of gestation. A variety of techniques, especially amniocentesis and cell culture is employed.

PROBE — in a molecular genetics, a piece of DNA or RNA labelled with a radioactive isotope or tagged in other ways, used to pick out sequences to which it can hybridized.

PROKARYOTIC - Organisms whose cell lack membrane bound nucleus containing chromosomes. The group comprises all bacteria, not animals or plants.

Recessive — A character that is manifest only in the homozygous state, not in hetero2ygotes.

RECOMBINANT - of **an** individual or a gamete, having a combination alleles different from the combination inherited by the parent. Of DNA, a sequence made by joining two previously separate sequences.

RFLP - Restriction fragment length polymorphism, a type of DNA polymorphism used as a genetic marker (but now largely superseded by micro-satellites, q.v.).

RNA - Ribonucleic acid.

SEX LINKED - A gene, or character determined by a gene, located on the X (or sometimes the Y) chromosome; the pedigree pattern resulting therefrom.

SOMATIC CELL HYBRIDS - Hybrid human-rodent cells grown in the laboratory and used to help map genes to specific chromosomal locations.

SPECIFICITY - The ability of a test to categorize the normal individuals as being normal.

SPORADIC - Of a character, not obviously running in the family.

STRINGENCY OF HYBRIDIZATION - The degree to which imperfectly matching DNA sequences are able to hybridize in an experiment, which the experimenter controls by choosing temperature and salt concentration.

SYNDROMAL - (In relation to hearing loss) A loss accompanied by other abnormalities. Some would describe pure hearing loss, but with a strikingly characteristic audiogram or age of onset, as syndromal.

TRANSCRIPTION FACTORS - Cellular proteins that regulate transcription of specific genes.

VECTOR - A DNA molecule able to survive and replicate in cells, into which DNA sequences to be cloned can be incorporated.

VNTR (VARIABLE NUMBER OF TANDEM REPEATS) - A class of DNA polymorphism, including micro-satellites, widely used as genetic markers.

X CHROMOSOME - A sex chromosome that normally occurs singly in the male, but in duplicate in the female. The X comprises of a non-homologous segment and probably a homologous segment corresponding with a part of the Y.

X **LINKAGE** - linkage due to the presence of a gene on the X chromosome; the term is applied especially to genes on the non homologous segment of the X chromosome or to traits dependant on such genes for their expression.

YEAST ARTIFICIAL CHROMOSOME (YAC) - A cloning vector that can be propagated in yeast cells. Larger DNA fragments can be cloned in YAC's than in any other current vector.

Y CHROMOSOME - A sex chromosome that normally occurs singly in the male, but is totally lacking in the karyotype of the female. The Y comprises of non homologous segment probably a homologous segment corresponding with a part of the X.

ZYGOTE - A cell formed by the fusion of male and female gametes; a 'fertilized egg'-