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A Common Genetic Disorder "Deafness"

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Abstract: **Deafness is a complete or partial loss of hearing, caused due to both environmental and genetic factors. It may be either none-syndromic or syndromic. In genetic deafness, Autosomal dominant, Autosomal recessive, X-Linked and Mitochondrial hearing loss are the main pattern of inheritance. In global prevalence this disease accounts for 1 per 1000 population. While the Asian countries including Pakistan have high prevalence (1.6 per 1000) than the rest of the world. Consanguineous marriages are thought to be playing a key role in the inheritance of genetic deafness. Many sources and technologies are available for the testing of hearing efficiency. But mostly Biochemical, physical and genetic diagnoses are done to diagnose the degree of hearing loss severity. In all of these the genetic test is found to be more accurate and precise for a better diagnosis. In remote areas particularly in Asian countries the ratio of genetic hearing loss is comparatively found to be high due to a common tradition of consanguineous marriages where families prefer to get married within blood relatives. These families are suitable for research purpose, because of the inheritance of gene pool in the same family affecting individuals in various generations. Throughout the world scientific communities are working on the genetics of deafness. Each year new loci and genes are identified and mapped. 50% cases in hearing impairment are due to environmental factors while 50% are due to genetic mutations. In genetic type 30% cases are found to be syndromic and 70% are none-syndromic. In none syndromic Autosomal recessive are observed to be the most common (80%). 300 genes have been predicted to be involved in hearing phenomena. To date moreover 33 genes in non syndromic Autosomal recessive and approximately 27 genes in dominant inheritance have been found.**

Keywords: **Deafness, Hearing loss, Syndrom, Inner ear, Genetic Disorder.**

I. INTRODUCTION

Deafness is found to be the most common sensory disorder which effects 1 per 1000 neonates. (Kalay et al., 2005 and Ramshankar et al., 2003). Both environmental (e.g. microbial infection acoustic trauma, toxicity) and genetic factors are involve in causing hearing loss (Morton.1991).Genetic factor is mostly observed major factor for hearing impairment (Marazita et al., 1993 and Rehm, 2003). Congenital hearing loss is highly heterogeneous defect which has been classified into syndromic (30%) and non-syndromic (70%) disorders, non-syndromic is either Autosomal dominant, Autosomal recessive, X-linked and mitochondrial mutations (Petersena and Willemsb 2006; Mukherjee et al., 2003). In syndromic deafness 400 other related inherited abnormalities are found (Gorlin R.J, 1995). It is founded that above hundred genes are involved in hearing loss. More than 130 loci have been studied in previous published data. Loci of hearing impairment are abbreviated by DFN (deafness), Furthermore Autosomal recessive, Autosomal dominant, X-linked are denoted as DFNB,DFNA and DFN respectively (Mukherjee et al., 2003).

Hearing loss is either sensorneural (inner ear malfunction) or conductive (middle ear abnormalities) (Gorlin R. J, 1995). In Case of sensorneural hearing impairment a high genetic heterogeneity has been observed. To date 139 non-syndromic hearing loss loci have been mapped, out of these 139 loci are found to be inherited in Autosomal recessive pattern. Moreover 33 genes of nuclear genome responsible for deafness have been cloned, (www.uia.ac.be/dnal). In human genome, 1% of the total 30000 genes show expression, which are involved in hearing (Friedman and Griffith, 2003). The inner ear cells are highly sensitive, having a very small size and cellular diversity, which have complicated the physiological and proteomics studies of inner ear (Thalmann, 2006).

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II. MATERIALS AND METHODS

Current review is concluded by searching and studying various literature and research papers available from various studies of scientific communities. Many search engines like journal of human genetics ,pakMediNet, pubmed, google scholar and other many open access journals were used for data available by using keywords deafness, hearing loss loci, none syndromic autosomal recessive deafness, ,diagnostic methods, treatment etc. One hundred and thirty four different articles and reports were taken from the online available sources, out of which mostly studies were found to be published in 2000 and onward were included in the present review. We also previously conducted a study on molecular characterization of congenital deafness from district maradn Pakistan.. We used linkage analysis for three deaf families and then direct sequencing was done for the linked family

2.1 Deafness and Its Classification

The complete or partial loss of hearing is termed as deafness. It is classified by several ways.

The first criteria used in classification of deafness is according to the nature of disease that either it is environmental, genetic or a combination of these both.

The second criterion is that which part of the ear is defected due to which it has used its function e.g. middle or inner ear, conductive or sensorneural.

The third one is to classify the diseases on the basis of its severity, normal, middle or high as given the table 1.

Table 1: Degrees of severity in hearing loss

DEGREE OF SEVERITY	HEARING LOSS
Normal	0-25 dB
Mild	26-40dB
Moderate	41-55dB
Moderate severe	56-70dB
Sever	71-90dB
Profound	>90dB

The fourth criteria is to categorize the deafness on the basis of the age of onset congenital, pre lingual or post lingual and progress of the impairment.

And the last criterion to classify deafness is either it is syndromic or non syndromic. (Kalatzis and petit 1998, Riazuddin et al., 2000; Khovskaya et al., 2000; Schultz et al., 2005)

2.2 Molecular Genetics of Hearing Loss:

Molecular hearing impairment is a highly heterogeneous trait. Classical approaches for the diagnosis of hearing mechanism are not sufficient to study congenital deafness due to low accuracy of biochemical methods. The main reason is that a very small number of each cell is present in the hearing organized body (ear). However Genetic approaches have high accuracy and are most beneficial and promising techniques to study hereditary deafness (Friedman and Griffith 2003, Petit 1996).

The identification and localization of genes involved in syndromic deafness started in 1990s. But up to 1994 only three responsible genes for syndromic deafness had been mapped from human genome. In syndromic deafness classification symptoms were used to categorize its different forms. For this purpose positional cloning and linkage analysis were most feasible. Especially Linkage analysis for non syndromic deafness is more difficult because it needs a single family for linkage analysis. However for these studies many deaf families have been analyzed through linkage analysis. By using molecular genetics technologies a lot of involved genes have been localized, identified an mapped. From a variety of

researches it has been concluded that 1% genes of the total genes (30,000). in human for the hearing. Approximately 300 genes are predicted to be involved in hearing mechanism in human (Friedman and Giffith, 2003).

The development and advancement in molecular tool and techniques has made it possible to understand Genetic of deafness. As 1 per 1000 persons are affected with deafness, so a huge amount of families are available for these sorts of studies. Several available databases are serving as strong tools to provide data about the hereditary deafness e.g. polymorphic genetic markers, physical maps, genetic maps, transcription database, human and mice DNA sequences databases, mouse and zebra fish models for human hearing. So from the above discussion it can be concluded that many defected genes involved in disorders of hearing will be identified and mapped in future.

2.3 Syndromic Deafness:

More than 400 different symptoms are associated with deafness, Therefore it is estimated that approximately 30% other associated disease are found along with deafness, which may be in the form of sensorineural, conductive, or mixed (Grolin et al., 1995).

2.4 Non Syndromic Deafness Nsd:

NSD is that form of hereditary hearing loss in which no other associated symptoms are observed. NSD is found to be more than syndromic deafness. It is more prevalent and account for 70% of all hereditary deafness and is almost exclusively sensorineural (Mortan, 1991; Reardon, 1992; Marazita et al., 1993).

The identification of causative genes for deafness is more challenging and required further steps in deafness research. Deafness is highly complicated because of its heterogeneity and limited clinical differentiations (Petit et al., 2001). Other feature also make it complicated e.g. very similar clinical phenotypes are generated by different mutated genes, even within a family (Masmoudi et al., 2000).

Mostly consanguineous marriages are playing a key role in hereditary deafness, because two carriers give birth to affected individuals and in this way the mutated genes are properly inherited from generation to generation making the structure of mutated genes more complicated and cause severe hearing loss (Balciuniene et al., 1998). These studies are becoming more complex due to genetic and environmental factors interplay. The consistent families are best tools to study their segregation and pattern of inheritance (Guilford et al., 1994).

Linkage analysis is helpful in refining intervals in deafness causing loci and mapping new genes. This analysis is feasible especially for identification studies of many recessive Loci. The non Syndromic deafness is further divided in different classes e.g. X-Linked (DFN), Autosomal dominant (DFNA)., Autosomal recessive (DFNB) and mitochondrial hearing loss with prevalence of DFNB is 80%, DFNA is 20%, DFN is 1% and mitochondrial is less than 1%. (Mortan, 1991; Mortanand and Nancy, 2006).

2.5. Prevalent of Autosomal Recessive Loci/Genes in Pakistan Population:

According to data available, twenty four non syndromic Loci and fifteen genes have been reported to date.

DFNB1:

For the first time a locus of non syndromic Autosomal recessive was reported in Tunisian families affected with prelingual deafness. This was mapped to 13q12 of the chromosome (Guilford *et al.*, 1994). In 1997 from a study in three Pakistani families two distinct non sense mutations were identified and was demonstrated that Cx26 is the causative gene (Kelsell *et al.*, 1997). Mutation at DFNB1 became more apparent from many studies conducted on families and general population of different region of the world (Carrasqollio *et al.*, 1997 and Scott *et al.*, 1998). In Cx26 gene seventy different mutations have been identified (Rabionet *et al.*, 2000).The prevalence of DFNB1 in India is 13.3% (Masheswari *at al.*, 2003), in Iran it accounts for 16.7% (Najmabadi *et al.*, 2005)., in Japan these are 20% (Kudo, *et al.*, 2000), while Pakistan has lower prevalence as compared to India (Santos *et al.*, 2005). Furthermore it was concluded that a complex DFNB1 locus mutation which have GJB2 and GJB6 genes can result in digenic or monogenic pattern of inheritance of prelingual deafness (Del Castillo *et al.*, 2002). The pathophysiology of DFNB1 reveals that it play a key role in potassium

(K+). Recycling, which fasten the transport of K+ ions in staria vascularis, from where these ions are rapidly pumped to endolymph thus keeping K+/Na+ balance in endolymph (Tekin *et al.*, 2001).

DFNB2:

This was the second locus for Autosomal recessive hearing loss located at 11q13.5, in a Tunisian family (Guilfor *et al.*, 1994b). In later MYO 7A gene was identified on this locus which encodes myosin VII A. (Gibson *et al.*, 1995). Forty nine exons were mapped in two Chinese families linked to DFNB2 (Liu *et al.*, 1997). Approximately hundred alleles have been described showing mutations of different types at different region (Ouyang *et al.*, 2005). The encoded protein Myosin VIIA is involved in activating filaments using activating ATPase. Myosin VII A is expressed in many tissues but most commonly at sensory cilia and is present in the entire length of stereocilia of inner hair cells (Hasson *et al.*, 1995). Myosin VIIA is also found active at opsin transport (Liu *et al.*, 1999). These proteins also roles in transduction channel adaptation of inner hair cells of the ear and these are also involved in resting tension in the gate spring of transduction channel.

DFNB3:

In a population study at Benkala, DFNB3 was identified on chromosome 17 q 11.2 (Friedman *et al.*, 1995). While familial linkages were observed and missense and non sense mutations were mapped (Wang *et al.*, 1998). MYO15A is the largest among several splice site isoform. This has sixty five exons and encodes Myosin XVa. These proteins play a role in the formation of sterocilia, especially elongation of stereocilia-bundle stair case (Belyanfeseva *et al.*, 2003). In the latest reports it is shown that Belyantsev and co-workers have transported whirlin to the tips of stereocilia by Myosin XVa in the hair cells (Belyantseva *et al.*, 2005).

DFNB4:

SLC26A4 Gene was mapped on this Locus having 21 exons, mutation in this gene leads to Autosomal recessive deafness with goiter termed as pendred syndrome and non syndromic hearing loss DFNB4. SLC26A4 is located on chromosome 7q22-31.1 (Everett *et al.*, 1997). It is estimated that 10% of the deaf patients are due to mutation at this gene in south and East Asian. Each ethnic population has a different and a diverse mutant allele series, with one or more founder mutations (Everett *et al.*, 1997, Li *et al.*, 1998). SLC26A4 codes for pendrin which is an 86-KDa polypeptide chain, expressed in thyroid and kidney as well as in cochlea (Everett *et al.*, 1997). Pendrin have nine membrane spanning domains and are multipass trans-Membrane protein. But its topology is not been determined experimentally. Pendred syndrome and non syndromic DFNB4 deafness are caused due to two different mutations at SLC26A4 gene (Scott *et al.*, 2000). They also demonstrated that complete loss of pendirn leads to pendred syndrome, in which chloride and iodide transport is entirely blocked while alleles unique to people with DFNB4 are able to transport iodide and chloride but at a very low level as compare to normal function (Scott *et al.*, 2000).

DFNB6:

For the first time this locus was identified in a consanguineous family of India at chromosome 3 q 21 (Fukushima *et al.*, 1995). Because of chromosomal homology with the linked region, the mouse mutant spinner is a candidate for DFNB6 (Naz *et al.*, 2002). They also cloned the human TMIE ortholog and found five different types of mutations in DFNB6 locus. The data about TMIE as RNA and protein is not yet available from which it is not clear to demonstrate it function in deafness.

DFNB7/11:

DFNB7/11 was mapped to chromosome 9q 13 in two consanguineous families of India (Scott *et al.*, 1996). Trans-membrane channel like gene I (TMC1) were identified in eleven families segregating DFNB 7/11 deafness from Pakistan and India (Jain *et al.*, 1995). The actual function of TMC1 is still not clear but is predicted to encode a multipass Trans-membrane protein most precisely involved in ion exchange. But in mouse TMC1 mutation were found to be involved recessive deafness segregating hearing loss and postnatal hair cells degeneration so concluded that TMC1 are involved in maintain hair cells or hair cells development (Kurima *et al.*, 2002). In a recent study TMC1 was sequenced in a Sudanese family which showed mutation at 1165c>7 in exon 13 leading to stop codon, Arg 389 X and splice site mutation 19+5G>A.

DFNB8/B10:

These loci were identified in a Palestinian family (DFNB10). Also DFNB8 in a Pakistani consanguineous family on the chromosome 21 q 22.3 (Veske *et al.*, 1996). Bonne – Tamir *et al.*, 1996). These genes encode serine protease showed by a study conducted on sequencing of this locus. Serin protease, TMPRSS3 is a only protease found to be involved in hearing loss with no syndrome this gene is present on chromosome 21 having 24 kb size. Thirteen exons are reported on TMPRSS3 gene. (Scott *et al.*, 2003). Four transcripts of this gene re reported in human, (TMPRSS3 a, b, c and d) encoding polypeptides of 454,327, 327 and 344 amino acids respectively (Scott *et al.*, 2001). But recently a fifth transcript which encodes a 538 amino acid polypeptide is reported by Ahmed *et al.*, 2004. In vivo no active function of TMPRSS3 is observed but in vitro it regulate the activity of epithetical Amiloride sensitive channel (ENaC)., which regulate and control signal pathways in the inner ear and may also control sodium level of endolymph (Guipponi *et al.*, 2002).

DFNB12:

This locus was mapped on chromosome 10 q21-q22 in a consanguineous family of Syria which causes non syndromic recessive deafness (Chaib *et al.*, 1996). CDH23 gene is localized on this locus encoding cadherin 23 proteins (Bork *et al.*, 2001). Substitution of some amino acids due to mutation in CDH23 leads to leaking or hypomorphs cadherin 23 causing loss function and non syndromic deafness is established. While null alleles of CDH23 cause vestibular dysfunction as well deafness (Astuto *et al.*, 2002). Cadherin 23 is membrane of cadherin superfamily of integral membrane protein (Jamura and Fuchs 2002). Stereacilia is interconnected into bundles through homophile Interaction of this protein, so it is thought that steraocilia bundles are normally kept organized through CDH23.

DFNB18:

This Locus was mapped in a consanguineous family of india at chromosome 11P 15.1 (Jain *et al.*, 1998). In this family mutation analysis showed defect in harmonin, exon 12 in the result which affects a stop codon region in exon 13 which show it effects both in ear and retina. The splice site mutation is also reported (216 G>A) at exon 3.

DFNB21:

This locus was reported in a Lebanese family on chromosome 11q23-25 TECTA gene is located mutation at TECTA leads to encode D-Tectorin leading to Autosomal non syndromic deafness D-tectorin are non collageneous glycoprotein components of the tectorial membrane, which is an extracellular matrix that overlies the stereocillia of the outer hair cells in the organ of corti a null allele of TECTA at DFNB 21 leads to prelingual non syndromic recessive hearing loss (Naz *et al.*, 2003), While missense mutation in TECTA leads to dominant hearing loss with various other syndromes depending upon type of amino acid mutated (Alloisio *et al.*, 1999).

DFNB23:

DFNB 23 locus is mapped in chromosome 10q 21-22 (Camp and smith 2002). St this locus PCDH15 gene was reported so mutation at PCDH15 showed recessive hearing loss in three families of Pakistan (Ahmed *et al.*, 2003). While serve mutation leads to USHIF (Ahmed *et al.*, 2003). PCDH 15 is a member of cadherin molecules (Alagramam *et al.*, 2001). Alteration in this genes/ proteins shows effects in entire stereocilia enlargement (Ahmed *et al.*, 2003).

DFNB26:

DFNB 26 was reported in a consanguineous Pakistan family with non syndromic deafness at chromosome 4q31. The family defining DFNB26 is unique as a dominant modifier.(Riazuddin *et al.*, 2000)

DFNB29:

DFNB 29 was mapped on chromosome 21 q 22 mutation its gene encodes tight junction Claudine 14 which causes Autosomal recessive hearing loss (Wilcox *et al.*, 2001). Mutation in this gene has same phenotype in mouse and human. These gene with null mutation cause profound hearing loss without effecting the normal vestibular function (Ben-Yousef *et al.*, 2003). mutation in CLDN14 are a relatively infrequent cause of non syndromic recessive deafness in the Pakistani population while the contribution of CLDN14 mutation to recessive deafness in other population is unknown and may significantly differ from Pakistani population.

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DFNB36:

This locus for the first was identified in two consanguineous families on chromosome 1p36.3 (Naz *et al.*, 2004). ESPN gene is present at this locus been reported to be involved in recessive hearing loss. Two mutation at ESPN 2469 del GTCA and 1988 del AGAG have been mapped these encodes protein called ESPN (Naz *et al.*, 2004). Donauding *et al.*, 2005 has demonstrated that dominant mutation at ESPN also leads to dominant haring loss.

DFNB37:

This locus was identified in a large consanguineous family of Pakistan at chromosome 6q13 (Ahmed *et al.*, 2003). Avraham *et al.*, 1995 reported two null mutations of MY06 in mouse. These mutations cause dominant, progressive, non syndromic hearing loss in a family (Melchionda *et al.*, 2001). Mutation analysisof My06 gene have shown three types of mutations, a single base pair insertion (36-37 ins T), a transversion mutation (647A>T) and a transition mutation (647A>T) (Ahmed *et al.*, 2003).

DFNB39:

Wajid *et al.*, reported this locus in 2003, on chromosome 7q.11.22-q21 in a consanguineous family of Pakistan.

DFNB48:

In 2005 Ahmad *et al.*, Published their novel locus which was identified in five Pakistani families, on chromosome 15q 23-q25.

DFNB49:

Ramzan *et al.*, 2004 reported DFNB 49 as a novel locus on chromosome 5q 12.3-14.1 in two consanguineous Pakistani families.

DFNB51:

A novel Autosomal non syndromic deafness locus DFNB51 was identified on chromosome 11p 13-p12 in two families from Pakistan (Sheikh *et al.*, 2005).

DFNB67:

This locus was identified and mapped on chromosome 6p21.1-p22.3. TMHS gene was found which causes DFNB67 deafness (Shabbir *et al.*, 2006)

DFNB68:

Santos *et al*, demonstrated DFNB68 as novel mutation on chromosome 19P13.2 in two unrelated consanguineous families of Pakistan in 2006.

DFNB72:

Three Pakistani consanguineous families were studied and DFNB72 was mapped on chromosome 19P 13.3 by (Ain *et al.*, 2007).

III. DISCUSSION

Deafness is found to the most prevalent disease affecting both developed and developing countries. It arises either due to environmental (e.g. bacterial, viral, toxicity or acoustic trauma) and genetic factors. The onset period varies (e.g. from birth to adult hood). 1 per 1000 population in developed countries is suffered with hearing loss, while this ratio is much higher in developing countries, which is 1.6 per 1000. 50% cases arise due to genetic involvement. The incidence of hearing loss in male is higher than female. As discussed earlier that out of genetic incidence 75% are found to e Autosomal recessive, 15% are having Autosomal dominant pattern of inheritance while 10% are estimated as X-Linked and mitochondrial or due to chromosomal aberration (Robertson *et al.*,1999, Mortan, 1991, and Reardon W, 1992). The genetic hearing impairments that are either congenital or prelingual are mostly found to be inherited through Autosomal recessive pattern. While Autosomal dominant mode of inheritance is estimated to be mostly involved in post lingual

hearing defects. Clinical categories of deafness are based on sensor neural versus conductive versus mixed hearing loss, as well as severity, age of onset, environmental influences, audio logical profile and associated symptoms in other regions of the body. For the genetic hearing impairment a variety of tools are used to identify and map the involved mutated genes. A variety of markers associated with deafness Loci are used to narrow down region for the search of a mutated gene. Through Linkage analysis of markers and Loci it is brought in front that which part of the chromosome is involved mutation. In genetic deafness, 70% are non syndromic and 30% are syndromic hundreds of associated symptoms with hearing impairment have been observed (Teas, 1989). In non syndromic hearing loss only the hearing system is disturbed (e.g. conductive, sensor neural or mixed hearing loss). On the other hand in syndromic deafness other abnormalities are seems to be present along with hearing loss. In non syndromic deafness ~15% are Autosomal dominant (DFNA1-DFNA39, ~80% are Autosomal recessive (DFNB1-DFNB30) and ~ 2% are mitochondrial all the data regarding to hearing loss e.g. locus for each disorder, markers, and appropriate references can be found on the hereditary hearing loss Home Page. Within the past few years several genes involved in non syndromic hearing loss are identified (Earnest et al 2000). Examples are, the human homoloy of drosophila diaphanous gene (DIAPH) in DFNA1, the gap junction protein conexin 26 (GJB2) in DFNB1 and DFNA3. The tectorin membrane protein tectorin (TECTA) in DFNA 8/12, the POU4F3 transcription factor in DFNA15, the putative sulfate transporter. PDS in both Pendred syndrome and DFNB4, the novel cochlea gene (COCH) in DFNA9, the unconventional myosin (MYO15) in human DFNB3 and mouse shaker 2, a gene (USH2A) with homologies to laminin epidermal growth factor and fibronectin in USHE Syndrome Type 11 and a gene with very little homology to any known protein, all of these gene have shown to be expressed in cochlea, demonstrating how knowledge of gene expression in the membranous labyrinth is critical for further understanding of hearing and deafness, majority of the reported deaf individuals belonging to those families where consanguineous marriages are common because in the same family a mutant genes flow from generation to generation. The custom of consanguineous marriages with high rate is found mostly in Asian countries. However congenital deafness is relatively common in geographical remote areas with high consanguinity. This simplifies genetic linkage analysis using homozygosis mapping in consanguineous families. Homozygosis mapping is based on the assumption that a rare mutation is inherited from a common ancestor through both parents, so that affected siblings are homozygous by descent, for polymorphic marker close to the disease homozygosis mapping is used to elucidate the gene defect in a family (Garrad 1908).

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