SYNDROMIC AND NON-SYNDROMIC DEAFNESS, MOLECULAR ASPECTS OF PENDRED SYNDROME AND ITS REPORTED MUTATIONS

Shahzad Shaukat, Zareen Fatima*, Uruj Zehra, Ahmed Bilal Waqar*****

National Centre of Excellence in Molecular Biology, University of the Punjab, Lahore, *KRL Hospital, Islamabad,
**Serena Hotel, Islamabad, ***Molecular Biology Division, Department of Pathology, Foundation University Medical College, Rawalpindi

Deafness means partial or complete hearing impairment and is one of the most prevalent sensory defects in humans. It can be due to genetic or environmental causes or a combination of both and may be Syndromic (associated with additional clinical features) or nonsyndromic (no other recognizable abnormal associated phenotype). The overall impact of hearing impairment is greatly influenced by the severity of hearing defect and by the age of onset. If defect is severe and presents in early childhood, it has dramatic effect on speech acquisition and thereby cognitive and psychosocial development. The mutations shown in the paper results in the conformational changes of protein and influence the phenotype of the affected individuals. For recessive cases of deafness it is possible to reduce the incidence of deafness by carrier screening in the families with multiple affected individuals and genetic counselling. Pendred Syndrome can be characterized by the triad composed of familial goitre, abnormal perchlorate discharge and congenital deafness.

DEAFNESS:

Deafness means hearing impairment. Hearing impairment is classified according to several criterions.

The first criterion is type of ear defect; on the basis of which it may be conductive, sensorineural or mixed depending upon the outer and middle ear, inner ear or both.

The second criterion is degree of severity of the hearing loss, i.e., mild 27–40 dB loss; moderate 41–55 dB loss; moderate severe 56–70 dB loss; severe 71–90 dB loss and profound > 90 dB loss.

The third criterion is the age of onset and progressiveness of the impairment.

The last criterion for classification of hearing impairment is weather it is associated with other symptoms (syndromic) or weather it is the sole defect (nonsyndromic or isolated)[1].

Non-syndromic Deafness:

This is the type of deafness in which there is no other recognizable abnormal phenotype with deafness. It is more common cause of hearing loss than syndromic deafness. It may accounts for 70% of all the genetically determined cases of deafness[2]. The non-syndromic forms of hearing loss are collectively referred to as DFN for the X-linked forms, DFNA for the autosomal dominant forms and DFNB for autosomal recessive forms.

Non-syndromic Autosomal Recessive Deafness:

Various mapped loci for non-syndromic autosomal recessive hearing loss are symbolized as DFNB1, DFNB2 and so on in the order in which they are first reported or reserved. To date 30 nonsyndromic recessive deafness loci have been mapped and nine defective genes have been identified encoding connexin-26 at DFNB1 locus[3], myosin VIIa at DFNB2 locus[4], myosin XV at DFNB3 locus[5], Pendrin at DFNB4 locus[6], otoferlin at DFNB9 locus[7], transmembrane serine protease-3 at DFNB10 locus[8], cadherin-23 at DFNB12 locus[9], a Tectorin at DFNB21 locus[10] and Claudin-14 at DFNB29 locus[11].

All these loci result in hearing loss and so far no other clinical features are associated with them with the exception of DFNB4, which is associated with enlarged vestibular aqueduct[6]. DFNB2, DFNB4 and DFNB21 gene identification was aided as they had positional candidates because other syndromic or dominant deafness loci had previously mapped to the same chromosomal locations and disease causing genes identified.

Syndromic Deafness:

In syndromic cases of deafness the affected individuals have a specific pattern of additional clinical features, which are not related to audition. It may accounts for 30% of all genetically determined cases. Syndromic deafness can be either dominant (Wardenburg syndrome, Branchial-oto-renal syndrome, Stickler syndrome, recessive (Ushers syndrome, Pendred Syndrome), X-linked (Alport syndrome, Nance syndrome, Hunter syndrome) or mitochondrial. Pendred syndrome is a recessive syndrome in which hearing loss is associated with goitre (Table-1)[12].

Environmental Deafness:

Hearing loss can also result from environmental causes. The main contributing environmental factors are meningitis, mumps, perinatal complications, maternofoetal infections (Toxoplasma, Rubella and Cytomegalovirus infections), typhoid, acoustic trauma, ototoxic drugs (aminoglycoside antibiotics) and advancing age (Presbyacusis)[13]. In a pedigree in which there are individuals with deafness due to genetic causes there may be some individuals who are deaf due to environmental causes.

Prelingual deafness affects approximately 1 in 2000 infants[14]. Greater than 70% of genetically determined cases are nonsyndromic[2]. The main pattern of inheritance in severe childhood deafness is autosomal recessive (over 75%) while autosomal dominant (12–24%), X-linked (1–3%) and mitochondrial is also involved[15]. It has been estimated that 30% of prelingual deafness cases are syndromic[14]. Syndromic deafness can be either Dominant (Wardenburg syndrome, Branchial-oto-renal syndrome, Stickler syndrome), Recessive (Ushers syndrome, Pendred Syndrome), X-linked (Alport syndrome, Nance syndrome, Hunter syndrome) or Mitochondrial.

Table-1: Autosomal Recessive Syndromic Deafness Loci

Pendred Syndrome		
Locus	**Location**	**Gene**
PDS	7q21-34	SLC26A4
Usher syndrome		
Locus	**Location**	**Gene**
USH1A	14q32	Unknown
USH1B	11q13.5	MYO7A
USH1C	11p15.1	USH1C
USH1D	10q	CDH23
USH1E	21q	Unknown
USH1F	10q21-22	PCDH15
USH2A	1q41	USH2A
USH2B	3p23-24.2.	Unknown
USH2C	5q14.3-q21.3	Unknown
USH3	3q21-q25	USH3

To date 39 nonsyndromic dominant deafness loci have been mapped to different chromosomes while 13 genes are identified. Also 30 nonsyndromic recessive deafness loci have been mapped to different chromosomal locations while only 9 genes have been identified and protein structure is predicted[16].

Overall, recessive deafness tends to be more severe than dominant deafness because it is generally profound, prelingual and fully penetrant whereas dominant deafness is frequently progressive, postlingual and is often observed clinically as the presence of unilateral or mild bilateral deafness[17]. In case of recessive syndromic deafness Ushers syndrome and Pendred syndrome are most important. Allelic variants at these loci are responsible for both syndromic and nonsyndromic deafness. Some associated symptoms are also variable in onset and penetrance leading to misdiagnosis of syndromic cases as non-syndromic.

Pendred syndrome is one of the most frequent causes of congenital deafness, accounting for about 10% of hereditary hearing loss[18-20]. It is an autosomal recessive disorder, first described by Vaughan Pendred in 1896 and characterized by congenital sensorineural hearing loss combined with goiter[12]. Additional abnormalities are an iodide organification defect that can be shown by perchlorate discharge test, an abnormally developed cochlea, i.e., mondini malformation and a widened vestibular aqueduct[21]. To date 42 different PDS mutations have been identified in people with classic pendred syndrome[22-24].

For recessive cases, gene identification studies are hampered due to extreme genetic heterogeneity and limited clinical differentiation[25]. Mutations in different genes can cause the same clinical phenotype in hearing impaired individuals, even within the same family. On the other hand extreme phenotypic variation between different families (or even in the individuals in the same family) can be due to mutations in the same gene[26].

Although genes responsible for deafness have been isolated and many others localized, the molecular genetics of deafness is still in its infancy. The difficulty in localizing deafness genes arises principally from extreme genetic heterogeneity. Heterogeneity seriously hinders linkage analysis because linkage data from different families cannot be reliably pooled. Consequently, the successful chromosomal localization of genes requires large consanguineous families showing clear segregation of deafness locus. In such studies Pakistan can play an important role because of traditional consanguineous marriages[27]. These marriages provide excellent resource materials for conventional linkage analysis, identifying additional deafness loci and genes that modify deafness phenotypes.

In consanguineous marriages, the proportion of shared genes decreases with the degree of consanguinity but the risk of offspring having autosomal recessive deafness increases because both parents are carrier of the same deleterious gene. For recessive cases of deafness it is possible to reduce the incidence by increasing awareness about the effects of cousin marriages. The carrier screening within the families having multiple affected

individuals seems to be important as it can identify persons who are at a high risk. For obtaining this objective, the need is to molecularly characterize deafness and identify genes and mutations contributing to the hearing loss in the concerned country.

LINKAGE ANALYSIS:

Genetic Linkage analysis is a statistical technique used to map genes to find the approximate location of disease gene. Linkage analysis is a relationship between the loci and two loci on the same chromosome are said to be linked if the phenomenon of crossing over does not separate them.

The term linkage refers to the loci, not to specific alleles at these loci. The most common application of linkage analysis is to try and find the location, in the genome, of a gene responsible for a certain mendelianly-inherited disease[28].

Alleles at loci on same chromosome should co-segregate at a rate that is somehow related to the distance between them on the chromosome. This rate is the probability or recombination fraction (θ), of a recombination event occurring between two loci. Two loci are said to be genetically linked when recombination fraction is less than 0.5. One of these loci is the disease locus while the other is a polymorphic marker like micro satellite repeats[29]. The objective of linkage analysis is to estimate recombination fraction and to test if θ is less than 0.5 between two loci i.e. weather an observed deviation from 50% recombination is statistically significant. The recombination fraction ranges from θ= 0 for loci right next to each other through θ= 0.5 for loci apart (or on different chromosomes), so that it can be taken as a measure of the genetic distance or map distance between gene loci. This measure works well for small distances. The unit of measurement is 1 map unit= 1 centimorgan (cM), correspondingly approximately to a recombination fraction of 1%. However, because of the occurrence of multiple crossovers, the recombination fraction is not an additive distance measure and must therefore be transformed by a map function in to map distance[28].

Recombinants in the pedigrees have to be analyzed to observe the presence or absence of linkage between two loci. It is not usually possible to count these for human pedigrees. For this reason likelihood methods are used which calculate the likelihood of a given pedigree under different assumptions about the recombination fraction between two loci[29]. In these calculations, recombination and non-recombination for each possible genotype are calculated. Computers are utilized for this, as the involved calculations are quite complex. A logarithmic ratio is calculated (LOD-likelihood of Odds) denoted by Z. LOD score is logarithmic of odds that the loci are linked with recombination fraction θ rather than unlinked (θ=0.5). A score of +3 or a positive score is an indication of linkage while a score of –2 or a negative score denotes absence of linkage.

For linkage analysis it is necessary to have polymorphic markers which can be checked for inheritance with the disease locus in question. Micro satellite repeats, particularly dinucleotide and tetranucleotide repeats are very important in this aspect, as they are highly polymorphic and abundant in the genome. CA/TG repeats are most common accounting for 0.5% of the genome[29].

Pendred Syndrome:

About a century back in 1896 Vaughean Pendred described the association of congenital deafness with goitre[12]. Pendred syndrome has usually been described as a triad composed of familial goitre, abnormal perchlorate discharge and a congenital deafness[30]. Deficiency of thyroxin synthesis occurs, Thyroid stimulating hormone increases, and the thyroid gland enlargement is seen[31]. In a normal thyroid, iodide ions are actively transported in to the cells and covalently linked to thyroglobulin after oxidation in the presence of thyroid peroxidase enzyme[32]. The thyroid dysfunction is biochemically characterized by inability to organify iodine[21]. The abnormality in thyroid handling of iodide forms the basis of the negative perchlorate test. A deficiency of thyroxin synthesis leads to an increase in the thyroid stimulating hormone and eventually enlargement of thyroid gland known as goiter[33]. Another clinical feature is the structural abnormality of the hearing organ in the patients of Pendred syndrome. Mondini dysplasia of the inner ear has been determined in 50% of patients with Pendred syndrome that involves defects in the bony and membranous labyrinth, organ of corti and stria vascularis[33]. The original description of the mondini deformity was based on an autopsy examination of an eight-year-old deaf child[34]. Since then, numerous histological studies have been carried out on temporal bones demonstrating mondini type changes often in association with various other malformations[35-37].

In 1980, Schnuknecht *et al*[37] carried out histological studies in patients of Pendred syndrome and found bony cochlear changes consistent with many mondini malformation. Classical mondini inner ear deformity includes a reduce number of turns of cochlea, enlarged vestibule, abnormal semicircular canal and enlarged vestibular aqueduct[37]. Phelps *et al* (1998) have shown by computed tomography (CT) and magnetic resonance imaging (MRI) that the deficiency of intersaccular septum in the distal coil of cochlea is not a constant feature of Pendred syndrome, whereas the enlargement of endolymphatic sac and duct in association with large vestibular aqueduct is very consistent among all the patients examined by MRI[32].

Sheffield *et al* (1996) mapped Pendred syndrome to chromosome 7 to 9cM interval flanked by the markers GATA23f5 and D7S687[21]. Everett *et al* (1997) identified the Pendred gene as organized in twenty one exons and encodes a predicted 780 amino acids transmembrane protein known as pendrin[22]. Based on the homology of PDS to sulphate transporter genes it was thought that Pendrin is involved in sulphate transport[22]. However Scott *et al* (1999) reported that Pendrin is not capable of transporting sulphate but acts as a transporter of chloride iodide[38]. Using *Xenopus laevis* oocytes and XF9 insects cells, as two separate expression systems, they demonstrated that Pendrin can transport iodide and chloride but not sulphate. Further Pendrin is expressed in thyroid, Kidney and foetal cochlea. Recent studies have shown that pendrin is functionally similar to renal chloride/formate exchanger, which serves as an important mechanism of chloride transport in the proximal tubule[39]. Thus a defect in the chloride transport properties of Pendrin in the inner ear could contribute to hearing loss associated with Pendred Syndrome. Royaux *et al* (2000) have shown that Pendrin is protected in a limited subset of cells within the thyroid follicles exclusively at the apical membrane of the follicular epithelium and therefore suggested that Pendrin (Figure-1) is an apical porter of iodide in the thyroid and the function of both apical and basal iodide portes are co-ordinately regulated by follicular TG (Ftrl-5 cells) [40].

Figure-1: Structure of pendrin with 11 transmembrane domains, 6 intracellular and 6 extracellular loops.

Mutations of PDS:

Pendred syndrome is one of the most frequent causes of congenital deafness, accounting for about 10% of hereditary hearing loss. To date more than 42 different PDS mutations have been identified in people with classic Pendred syndrome (Table-2)[19,21-24]. Two reports of non-syndromic hearing loss (DFNB4) derived PDS mutations in individuals with sensorineural hearing loss have been described[6,41].

Table-2: Different Mutations in *SLC26A4* gene

Nucleotide substitutions		
S. No.	**Codon**	**Nucleotide**
1	138	aGTT-TTT
2	139	GGA-GCA
3	193	ACT-ATT
4	209	GGA-GTA
5	236	CTA-CCA
6	271	tGAT-CAT
7	369	aAAA-GAA
8	372	GCC-GTC
9	384	GAA-GGA
10	409	CGC-CAC
11	410	ACG-ATG
12	416	cACT-CCT
13	445	TTG-TGG
14	480	GTT-GAT
15	490	cATC-CTC
16	497	cGGT-AGT
17	508	ACT-AAT
18	530	cTAC-CAC
19	556	TAT-TGT
20	565	TGT-TAT
21	653	GTG-GCG
22	667	TTC-TGC
23	672	GGA-GAA
24	721	ACG-ATG
25	723	CAT-CGT

Small insertions			
S. No.	**Nucleotide**	**Codon**	**Insertion**

1	336	112	T
2	1334	445	AGTC
3		704	GCTGG
4	2182	728	G

Small deletions

S. No.	Codon	Deletion
1	250	ATGGA^GTTCTctctATTATCTAT_E6I6_G
2	305	GAAGTA^ATTGtG_E7I7_GTAAGTAGA
3	382	CGATGGG^AACcAG_E9I9_GTATGGGT
4	398	GATTC^TTCTCtTGTTTTGTGG
5	427	TCATC^TCTGCtgcGATTGTGATG
6	447	CTTGCAG^AAG_E11I11_gTATAACCCTG
7	511	TGGTC^CTGAGagTTCAGTT_E13I13_GTG
8	632	CAACC^AAGGAaATAGAGATTC
9	708	TGCGGG^TTCTtTGACGACAAC

Nucleotide Substitutions/splicing

S. No.	Relative Location	Substitution
1	+7	A-G
2	-2	A-G
3	+1	G-A
4	+1	G-A

Summary of the mutations listed

Mutation type	Total number of mutations
Nucleotide substitutions	25
Nucleotide substitutions (splicing)	4
Small deletions	9
Small insertions	4
Total	**42**

DFNB4:

DFNB4 locus was localized in a south west Indian family on chromosome 7q31 within 14cM interval flanked by the markers D7S501 and D7S530. The linkage region was already the PDS gene known to cause Pendred syndrome. When the PDS gene was examined for sequence analysis, two single base changes in the exon 13 of the coding region were found.

There was G®A transition at nucleotide position 1713, resulting in a predicted Glycine to Serine substitution at 497 (G497S). The second mutation was an A®C transversion at nucleotide position 1692, which results in a predicted Isolucine to Lucine substitution at position 490 (I490L). This family did not contain the characteristic features of the Pendred syndrome, i.e., there was no goitre in the affected individuals. The results suggested that the same gene PDS can be responsible both for syndromic and non syndromic deafness[6].

Functional difference of the PDS gene in Syndromic and Nonsyndromic Hearing loss:

Recent studies by Scott *et al* (2000) have shown that PDS mutations in individuals with Pendred syndrome differ functionally from PDS mutations in individuals with non syndromic hearing loss[39]. They compared the three common Pendred syndrome allele variants (L236P, T416P and E384G) with three PDS mutations reported only in individuals with nonsyndromic hearing loss (V480D, V653A and I490L/G497S). They found that mutations associated with Pendred syndrome have a complete loss of pendrin induced chloride and iodide transport, while alleles unique to people with DFNB4 are able to transport both iodide and chloride, although at much lower level than a wild type pendrin. It is proposed that the residual level of anion transport is sufficient to eliminate the onset of goitre in individuals with DFNB4[39].

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Address for Correspondence:

Dr. Ahmed Bilal Waqar, Molecular Biology Division, Department of Pathology, Foundation University Medical College, Rawalpindi. Tele: +92 51 4443191, +92 303 7766509

E-mail: ahmedbilal73@yahoo.com, abilal73@isd.wol.net.pk