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REVIEW ARTICLE

X-Linked Sensorineural Hearing Loss: A Literature Review

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Abstract: Sensorineural hearing loss is a very diffuse pathology (about 1/1000 born) with several types of transmission. X-linked hearing loss accounts for approximately 1% - 2% of cases of non-syndromic forms, as well as for many syndromic forms. To date, six loci (DFNX1-6) and five genes (*PRPS1* for DFNX1, *POU3F4* for DFNX2, *SMPX* for DFNX4, *AIFM1* for DFNX5 and *COL4A6* for DFNX6) have been identified for X-linked non-syndromic hearing loss. For the syndromic forms, at least 15 genes have been identified, some of which are also implicated in non-syndromic forms. Moreover, some syndromic forms, presenting large chromosomal deletions, are associated with mental retardation too.

This review presents an overview of the currently known genes related to X-linked hearing loss with the support of the most recent literature. It summarizes the genetics and clinical features of X-linked hearing loss to give information useful to realize a clear genetic counseling and an early diagnosis.

It is important to get an early diagnosis of these diseases to decide the investigations to predict the evolution of the disease and the onset of any other future symptoms. This information will be clearly useful for choosing the best therapeutic strategy. In particular, regarding audiological aspects, this review highlights risks and benefits currently known in some cases for specific therapeutic intervention.

Keywords: Cochlear implants, Hearing aids, Non-syndromic sensorineural hearing loss, Syndromic sensorineural hearing loss, X-linked sensorineural hearing loss, X-chromosome.

1. INTRODUCTION

One of the most common losses in the population is hearing loss; congenital hearing loss affects nearly 1 in every 1,000 live births [1, 2]. Hereditary hearing loss accounts for almost 50% of all congenital sensorineural hearing loss cases [3]; hereditary hearing loss can be the result of a mutation in a single gene or a combination of mutations of different genes [4]. The ear is very sensitive to mutations in genetic loci and currently many genes are known to be involved in inner-ear function. The physiology and structure of the inner ear are unique and unlike other anatomical locations. Mutations in genes that control the adhesion of hair cells, intracellular transport, neurotransmitter release, ionic homeostasis, and cytoskeletons of hair cells can lead to malfunctions of the cochlea and inner ear [5].

To date, for non-syndromic forms, at least 125 deafness loci have been reported in the literature: 58 DFNA loci, 63 DFNB loci, and 6 X-linked loci [6]. Approximately 20% of Non-Syndromic Sensorineural Hearing Loss [NSSHL] is inherited as autosomal dominant (DFNA), 80% is autosomal recessive (DFNB) and X-linked hearing loss account for approximately 1% -2% of cases of hereditary hearing loss and can be classified as rare diseases [5]. Several syndromic forms have also been associated to X-chromosome alteration.

At present, in the literature several data are known concerning X-linked types of hearing loss, but a review on this topic, summarizing known information is absent; therefore, this review presents an overview of the currently known genes related to hereditary X-linked hearing loss (syndromic and non-syndromic) and their principal phenotypic features. The purpose is to provide information useful in achieving an early and clear diagnosis so as to be able to choose the best therapeutic strategy.

2. SYNDROMIC X-LINKED SENSORINEURAL HEARING LOSS

This first paragraph reports a summary of the known syndromic forms of X-linked hearing loss with the causative genes and the loci associated (Table **1** and Fig. **1**). Below, the principal clinical, phenotypic and epidemiological aspects and the genes identified for each syndrome are briefly reported.

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Table 1. Summary statement of the X-linked hearing loss syndromic forms.

Syndrome	Gene	Locus	OMIM Number	Type and Degree of Hearing Loss in Affected Subjects
STAR syndrome	*FAM58A*	Xq28	300707	Sensorineural, monolateral, profound
JS-X syndrome	-	A deletion and a duplication on Xq28	-	Conductive or sensorineural hearing loss focused in the higher frequencies
X-linked adrenoleukodystrophy (X-ALD) syndrome	*ABCD1*	Xq28	300100	Sensorineural Hearing loss is present only in the childhood cerebral form that represents the most severe type
Charcot-Marie-Tooth (CMTX4)/ Cowchock syndrome	*AIFM1*	Xq26.1	310490	Sensorineural hearing loss of varying severity
Charcot-Marie-Tooth (CMTX5)/ Rosenberg-Chutorian syndrome	*PRPS1*	Xq22.3	311070	Variable grade of sensorineural hearing loss moderate to profound, pre-lingual or post-lingual, progressive or not progressive
PRS super activity syndrome			300661	
Arts syndrome			301835	
Alport syndrome	*COL4A5*	Xq22.3	301050	Progressive sensorineural hearing loss of varying severity
DL-ATS syndrome	*COL4A5/COL4 A6*	Xq 22.3	308940	Progressive sensorineural hearing loss of varying severity
Undefined syndrome (3)	*RS1*	Xq22.13	-	Sensorineural
X-linked hypophosphatemia (XLH)	*PHEX*	Xq22.11	307800	Sensorineural
Fabry syndrome	*GLA*	Xq22 .1	301500	Variable grade of sensorineural or mixed hearing loss. Sudden deafness cases are reported as well
X-linked deafness-dystonia-opticneuronopathy (DDON)/ Mohr-Tranebjaerg syndrome (MTS)	*TIMM8A*	Xq22.1	304700	Sensorineural hearing loss but in some cases it has been reported deafness with an auditory neuropathy-like aspect
Undefined syndrome (2)	*GPRASP*	Xq22.1	-	Congenital conductive or mixed hearing loss of varying severity
Undefined syndromes (1)	-	Deletions/ rearrangements on Xq21	-	Conductive or sensorineural hearing loss of varying severity
Charcot-Marie-Tooth (CMTX1)/ Cowchock syndrome	*GJB1*	Xq13.1	30 800	Sensorineural hearing loss moderate to severe
Cornelia de Lange syndrome	*HDAC8, SMC1A*	Xq13.1 Xp11.2	30088 300590	Conductive or sensorineural hearing loss.
Norrie syndrome	*NDP*	Xp11.3	310600	Progressive sensorineural hearing loss
OFD1 syndrome	*CXorf5*	Xp22.2	300170	Variable grade of sensorineural hearing loss
PIGA deficiency syndrome	*PIGA*	Xp22.2	311770	Mixed hearing loss
Brachytelephalangic chondrodysplasia punctata 1 (CDPX1) syndrome	*ARSE*	Xp22.3	30 950	Conductive, mixed or sensorineural hearing loss of varying severity

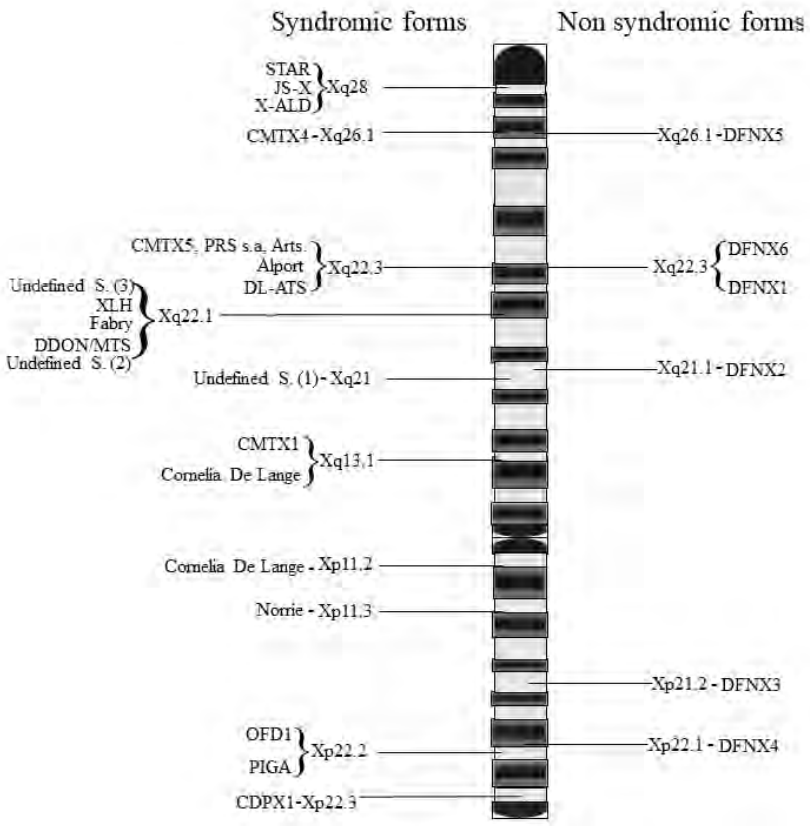

Fig. (1). Graphical representation of diseases and loci associated to syndromic (left side) and non-syndromic (right side) forms of X-linked sensorineural hearing loss.

2.1. STAR Syndrome

This rare dominant disorder is characterized by the association of telecanthus, syndactyly, renal and anogenital malformations. It is caused by mutations in the *FAM58A* gene, located on chromosome Xq28 [7] encoding a protein of unknown function. Recently, tethered cord and sensorineural hearing loss too have been associated to this syndrome [8].

2.2. X-linked Adrenoleukodystrophy (X-ALD) Syndrome

X-ALD is the most diffused perixosomal syndrome and disturbs the white matter in the nervous system and the adrenal cortex; it develops in 1/17.000 births and in 1/20.000 males [9]. About 20% of carrier females develop neurologic symptoms but with a milder phenotypes and a late onset [10]. This recessive X-linked syndrome is associated with mutation in the *ABCD1* gene that provides instructions for producing adrenoleukodystrophy protein (ALDP), which is involved in transporting fat molecules called Very Long-Chain Fatty Acids (VLCFAs) into peroxisomes [11]. Mutations in this gene can cause different phenotypes [12]. In the literature three different forms of X-linked adrenoleukodystrophy are described: a childhood cerebral form, an adrenomyeloneuropathy type, and an adrenal gland failure form called Addison disease.

Hearing loss (sensorineural) is present only in the childhood cerebral form, which represents the most severe type. Affected subjects generally present normal growth until they reach 4-10 years of age. By this time several signs can arise: changes in muscle tone, especially muscle spasms and uncontrolled movements, worsening nervous system damage, including coma, decreased fine motor control and paralysis, handwriting that gets worse, difficulty understanding what people are saying, hyperactivity, seizures, swallowing difficulties, crossed eyes and visual loss or blindness [13].

2.3. Charcot-Marie-Tooth [CMT]

This syndrome is a clinical and genetically heterogeneous hereditary neuropathy that refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy. It has been associated to thirty-six loci and more than two dozen genes, implicating pathways in myelination, radial and axonal transport, Schwann cell differentiation, signal transduction, mitochondrial function, endosome, protein translation and single-stranded DNA break repair [14].

CMT prevalence in the population is about 1/2.500 people. It can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. Regarding X-linked, six forms of hereditary neuropathy (CMTX1 - CMTX6) with a prevalence of about 3.6/1.000.000 are currently known [15]. The neuropathic process in patients with CMT disease frequently involves the vestibular nerve [16].

Hearing loss can be present in three X-linked forms: CMTX5, CMTX4 and more rarely in CMTX1 [17].

The CMTX5 form has been associated to pathogenic variants in the *PRPS1* gene. The phenotype of X-linked Charcot-Marie-Tooth disease-5, CMTX5 is also known as Rosenberg-Chutorian syndrome. CMTX5 typically presents early onset sensorineural hearing loss in addition to optic

atrophy and polyneuropathy [18]. However, patients without optic atrophy have been reported [19].

CMTX4 is referred to as Cowchock syndrome transmitted in a recessive manner. Principal symptoms associated to this form of CMT are: hearing and sensorial loss, mental retardation, muscle weakness and axonal neuropathy [20, 21].

CMTX4 has been associated to *AIFM1* gene mutation, which maps to chromosome Xq26.1, coding for Apoptosis-Inducing Factor (AIF) mitochondrion-associated 1 protein involved in development and functions of neurons [22, 23].

AIFM1 gene mutations have been also associated to spondyloepimetaphyseal dysplasia with neurodegeneration [24], cerebellar ataxia and auditory neuropathy [25] and to non-syndromic form of X-linked hearing loss (see: "non-syndromic forms" paragraph).

The CMTX1 form is associated to mutations in the gene *GJB1* (gap junction B1) which maps to chromosome Xq13.1. This gene is involved in homeostasis of myelinated axons [17] and codifies for the protein Connexin 32, which is expressed principally in oligodendrocytes and Schwann cells. For some patients with CMTX1, in addition to the classical CMT clinical phenotype, the presence of sensorineural hearing loss, late motor development, tremor, pathologic fractures or temporary central disorders have been reported [26]. Generally, a moderate to severe phenotype has been reported in affected males and a milder or absent phenotype in carrier females.

2.4. PRS Super Activity Syndrome

PRS disease is a very rare disorder characterized by an overproduction and accumulation of uric acid in the urine and blood. Until now, about thirty families have been described in literature. There are two forms of PRS superactivity (PRS s.a.): a serious form and a milder one. The first starts in infancy, while the second generally in late adolescence. In both forms, the clinical phenotype begins with a kidney or bladder stone. Without medical control and dietary restrictions, subjects can develop gout and loss of kidney function. People with the severe form may also have neurological problems, weak muscle tone (hypotonia), impaired muscle coordination (ataxia), and developmental delay [27]. The affected subjects present sensorineural hearing loss.

This syndrome is associated with some mutation of the gene *PRPS1* [28]. The *PRPS1* gene provides instructions for making an enzyme called phosphoribosyl pyrophosphate synthetase 1, or PRPP synthetase 1, a key enzyme in nucleotide biosynthesis. Different missense mutations in *PRPS1* cause a variety of disorders that include PRS-I superactivity, Charcot-Marie-Tooth disease, Arts syndrome in addition to non-syndromic sensorineural hearing loss. Generally, mutations in PRS Super Activity syndrome affect males, but affected females have been described too [29].

2.5. Arts Syndrome

The third syndrome associated to mutations in the *PRPS1* gene is the Arts syndrome which causes severe neurological problems in males [30]. Children with Arts syndrome present: prelingual progressive sensorineural hearing loss, ataxia, intellectual disability, childhood hypotonia, progressive optic nerve atrophy, peripheral neuropathy and frequent infections [31]. Females can also be affected by this condition, but with minor symptoms: sometimes, hearing loss (late onset) may be the only sign. Until now, only four families have been reported in the literature [32].

2.6. Alport Syndrome

Alport syndrome is an inherited heterogeneous disorder characterized by a nonimmune glomerulopathy, often accompanied by a progressive sensorineural hearing loss and sometimes lens abnormalities. In the literature are described autosomal dominant, autosomal recessive and X-linked forms of Alport syndrome. Its incidence is less than 1 per 5.000 individuals [33]. X-linked inheritance accounts for approximately 85% of cases. The X-linked form is associated with the COL4A5 gene (recessive mode of inheritance) that provides instructions for making one component of type IV collagen, which is a flexible protein [34]. This form presents progressive sensorineural hearing loss and glomerulonephritis, and variable ophthalmologic findings [35]. Prevalently are affected the males, but also affected females have been identified with a phenotype highly variable, probably due to inactivation of one of the X chromosomes [36]. In some of these syndromic X-linked cases other chromosomes are involved as well (chromosome 2q36-37, genes: *COL4A3* and *COL4A4*). Moreover, in the literature are also reported some cases presenting vestibular damage [37, 38].

2.7. Diffuse Leiomyomatosis, with Alport Syndrome (DL-ATS)

In some cases, mutations in *COL4A5* and contiguous X-chromosomal deletions encompassing from intron 2 of *COL4A5* to intron 1 of *COL4A6* have also been described. These variations are associated with X-linked Alport syndrome and leiomyomatosis, an over production of smooth muscle in the esophagus, trachea and female genitalia. Several cases present hearing loss too [39-41]. *COL4A6* encodes the alpha-6 chain of type IV collagen of basal membranes, which forms a heterotrimer with two alpha-5 chains encoded by the gene *COL4A5* associated with X-linked Alport syndrome. COL4A6 gene is also causative of the DFNX6 non-syndromic form of hearing loss (see below: "nonsyndromic forms" paragraph).

2.8. XLH

X-linked hypophosphatemia (XLH), is an X-linked dominant form disorder. It can cause rickets with bone deformities, dental anomalies, hypophosphatemia, hypocalciuria and increased activity of serum alkaline phosphatases [42]. Sensorineural hearing loss has been reported in some cases [43]. The prevalence of the disease is around 1:20.000. It is associated with a mutation in the phosphate-regulating endopeptidase gene (*PHEX*) gene located on chromosome Xp22.11. *PHEX* gene provides instructions for making an enzyme that is active primarily in bones and teeth. The *PHEX* protein regulates another protein called fibroblast growth factor 23.

2.9. Fabry Syndrome

Fabry disease is an X-linked lysosomal disorder with systemic clinical expression. The incidence of Fabry disease

was assessed at 1:50.000 to 1:117.000 males [44, 45], but this may be underestimated because milder forms of the disease may be more diffuse and may be underdiagnosed. The incidence of Fabry disease among nearly 35.000 neonates screened in Austria is 1:3.859 [46]. This disorder also occurs in females, although the prevalence is unknown. Subjects affected frequently present: episodes of pain, particularly in the hands and feet (acroparesthesias); clusters of small, dark red spots on the skin called angiokeratomas; a decreased ability to sweat (hypohidrosis); cloudiness of the front part of the eye (cornealopacity); problems with the gastrointestinal system.

Fabry disease also involves potentially life-threatening complications such as progressive kidney damage, heart attack, and stroke. Some affected individuals have milder forms of the disorder that appear later in life and affect only the heart or kidneys [47]. Principal audiological features are: tinnitus, sensorineural or mixed hearing loss. Hearing loss is reported in about 18-55% of affected subjects while tinnitus is reported in 17-53% of cases. In 6-36% of cases sudden deafness is also reported [48]. Vestibular dysfunction has been also described in Fabry disease [49-51].

This syndrome is associated with the gene *GLA*, which provides instructions for making an enzyme called alpha-galactosidase A [52]. This pathology is transmitted generally in a recessive mode with a high variability in phenotypic characteristics, especially in women, probably due to X chromosome inactivation. This enzyme is active in lysosomes. Alpha-galactosidase A normally breaks down a fat substance called globotriaosylceramide. Mutations in the *GLA* gene modify the structure and function of the enzyme, preventing it from breaking down this substance effectively. As a result, globotriaosylceramide builds up in cells throughout the body, particularly cells lining blood vessels in the skin and cells in the kidneys, heart, and nervous system. The disproportionate accumulation of this substance damages cells, leading to varied signs and symptoms of Fabry disease.

2.10. X-linked Deafness-dystonia-opticneuronopathy (DDON)

This recessive X-linked syndrome, also known as Mohr-Tranebjaerg Syndrome (MTS), occurs almost exclusively in males. It is associated with the gene *TIMM8A*, also known as *DDP*, which gives instructions for making a protein present inside mitochondrial intermembrane space, where it forms a complex with the protein TIMM13 and it is involved in transporting proteins to the mitochondrial inner membrane [53]. The syndrome generally begins early in life; affected subjects present problems with movement (dystonia) with a variable age of onset, optic atrophy, and psychosis, dementia and mental retardation in the more severe cases. From an audiological point of view, the presence of sensorineural hearing is reported but, in some reports the deafness presents an auditory neuropathy-like aspect with spiral ganglion deficit [54-57]. The prevalence of DDON syndrome is unknown.

2.11. Cornelia de Lange Syndrome

This multisystemic disorder has been associated to several genes: *NIPBL*, *SMC1A*, *HDAC8*, *RAD21* and *SMC3*. These genes cause Cornelia de Lange syndrome by impairing the function of the cohesin complex, which disrupts gene regulation during critical stages of early development. Mutations in the *NIPBL* gene have been identified in more than half of all people with this condition; mutations in the other genes are much less common. Two of these genes are located on chromosome X: *SMC1A* which codify for a protein of the SMC family [58], and *HDAC8* which provides instructions for the enzyme deacetylase 8 [59]. Both genes are involved in regulating the arrangement of chromosomes. In this syndrome sensorineural hearing loss is present associated with low birth weight, delayed growth, small stature, limb differences, microcephaly, thick eyebrows, which typically meet at midline (synophrys). Patients also could show other symptoms such as: long eyelashes, short upturned nose and thin downturned lips, long philtrum, excessive body hair, small hands and feet, small widely spaced teeth, low-set ears, vision abnormalities (*e.g.*, ptosis, nystagmus, high myopia, hypertropia), partial joining of the second and third toes, incurved 5th fingers (clinodactyly), episodes of pain, particularly in hands and feet (acroparesthesias); clusters of small, dark red spots on the skin called angiokeratomas; a decreased ability to sweat (hypohidrosis); cloudiness of the front part of the eye (cornealopacity); problems with the gastrointestinal system, gastroesophageal reflux, seizures, heart defects (*e.g.*, pulmonary stenosis, VSD, ASD, coarctation of the aorta), cleft palate, feeding problems and hypoplastic genitalia [60, 61]. Although the exact prevalence is unknown, Cornelia de Lange syndrome prevalence can be approximated as 1.6-2.2/100.000 [62]. The condition is probably under detected because individuals with mild or unusual characteristics may never be recognized as affected.

2.12. Norrie Syndrome

Norrie syndrome is an eye disorder that leads to blindness in male infants at birth or soon after birth. Exact incidence of the Norrie disease is unknown but more than 400 cases have been described; affected patients are frequently male, while females are generally carriers but some cases of affected females, with a milder phenotype, have been described [63]. Norrie syndrome is associated with the gene *NDP* which provides instructions for making a protein called norrin, and which seems to play a critical role in the specialization of retinal cells for their unique sensory capabilities [64]. It is also involved in determining a blood supply to tissues of the retina and the inner ear, and the development of other body systems. In this syndrome, in almost one third of individuals, progressive hearing loss, due to vascular abnormalities in the cochlea (inner ear), is present. Hearing loss usually starts in early childhood and may be mild initially and gradually become progressive. The principal non-audiological features are: abnormal development of the retina, leukocoria, and cataracts; more than half of the subjects experience developmental delays in motor skills such as sitting up and walking. Other problems may include mild to moderate intellectual disability, often with psychosis. Moreover subjects could show abnormalities that can affect circulation, breathing, digestion, excretion, or reproduction [65].

2.13. OFD1 Syndrome

Oral-Facial-Digital syndrome type 1 (OFD1) is a rare neurodevelopmental disorder in the ciliopathy group. It is transmitted with a dominant mode of inheritance and is almost always lethal in males. Annual incidence of 1/250.000 to 1/50.000 live births has been reported. This syndrome is associated with the gene *OFD1*, that provides instructions for making a protein whose function is not fully understood [66]. Researchers suspect that the OFD1 protein is essential for the normal formation of cilia [67]. In this syndromic form, characterized by varying anomalies, are principally present: cleft palate, bifid uvula, lingual cleft, numerous hypertrophic frenula, numerous milia on face, scalp, and ears, frontal bossing, hypertelorism, hypoplasia of the nasal alar cartilages, micrognathia, and bilateral brachydactyly of hands, diffuse, nonscarring alopecia with wiry, dry hair and sometimes sensorineural hearing loss in about 6% of cases [68]. In females alterations in kidney, pancreas and ovaries are also possible.

2.14. PIGA Deficiency Syndrome

This recessive X-linked syndrome is associated with the *PIGA* gene located on chromosome Xp22.2 [69]. *PIGA* encodes a protein called phosphatidylinositol glycan class A, one of the seven proteins involved in the transfer of N-acetylglucosamine (GlcNAc) from UDP-N-acetylglucosamide (UDP-GlcNAc) to phosphatidylinositol (PI) to form GlcNac-PI: the first step of GPI anchor biosynthesis and takes place on cytoplasmic side of the endoplasmic reticulum. Affected subjects present developmental block, infantile spasms, a pattern of cerebral lesions that resemble (on brain MRI) as the typical maple urine disease, contractures, dysmorphism, high alkaline phosphatase, liver dysfunction, mitochondrial complex I and V deficiency and therapy-responsive dyslipidemia with confirmed lipoprotein lipase deficiency [70]. From an audiological point of view, affected subjects present a mixed hearing loss.

2.15. Brachytelephalangic Chondrodysplasia Punctata 1 Syndrome (CDPX1)

This recessive X-linked syndrome is associated with mutation in the *arylsulfatase E gene* (*ARSE*) [71]. The enzyme codified by this gene is a type of sulfatase, which plays important roles in cartilage and bone development. The exact function of this enzyme is currently unknown: it is expected to participate in a pathway involving vitamin K. This syndrome is characterized by congenital disorder of bone and cartilage development. In detail, it is characterized by chondrodysplasia punctata [stippled epiphyses], brachytelephalangy (shortening of the distal phalanges), and nasomaxillary hypoplasia. Although most affected males have minimal morbidity and skeletal findings that improve by adulthood, some have significant medical problems including respiratory compromise, cervical spine stenosis, instability and intellectual disability. The audiological features are: mixed conductive or sensorineural hearing loss [72]. The precise incidence of this disease is unknown.

2.16. Undefined Syndromes

In addition to the syndromic forms described above, there are several other syndromic forms as yet not well defined from a molecular point of view (Table **1**). First of all, the JS-X syndrome, a recessive X-linked syndrome associated with a deletion and a duplication on Xq28 [73]. This syndrome presents outer and middle ear malformation with conductive or sensorineural hearing loss focused in the higher frequencies and some non-audiological features: laryngeal obstruction caused by bilateral vocal cord paralysis, facial dysmorphism and underdeveloped shoulder musculature.

Several other undefined syndromic forms have been associated to deletions and rearrangements in the chromosomal region Xq21 (undefined syndromes 1, Table **1** and Fig. **1**). These complex syndromes result from contiguous gene deletions and present several different phenotypes including Intellectual Disability (ID), hearing loss, choroideremia (CHM), seizures and multiple congenital anomalies [74-77]. A recent study of rearrangements in the Xq21, revealed a complex phenotype that expect inner ear malformations, vestibular problems, choroideremia and hypotonia [78]. Genomic analysis revealed in this case, for the first time, the presence of two close interstitial deletions in the Xq21.1-21.3, harboring 11 protein coding, 9 non-coding genes and 19 pseudogenes. Among these, 3 protein coding genes have already been associated with X-linked hearing loss (*POU3F4*), intellectual disability (*ZNF711*) and choroideremia (*CHM*).

Moreover, in a recent study, a Chinese family with a syndromic form has been identified with a never previously described mixture of clinical features, including ear anomalies, congenital conductive or mixed hearing loss and facial dysmorphism with bilateral ptosis [79]. In this family a missense mutation in the G protein-coupled receptor associated sorting protein 2 gene (*GPRASP2*) located on Xq22.1 chromosome has been identified (undefined syndromes 2, Table **1** and Fig. **1**). Very recently, in the literature has been described a case of a patient presenting X-linked retinoschisis with developmental delay and sensorineural hearing loss. This syndromic form has been associated to mutation in the gene *RS1* (Xp22.13) which provides instructions for making a protein found in the retina (retinoschisin) (undefined syndromes 3, Table **1** and Fig. **1**) [80].

3. NON-SYNDROMIC SENSORINEURAL HEARING LOSS

X-linked non-syndromic type of hearing loss is related to six loci (DFNX1-6) [6] (Fig. **1**). At present, however, only five genes (*PRPS1*, *POU3F4*, *SMPX*, *AIFM1* and *COL4A6*) have been identified. As described above, genes *PRPS1* (28) *and AIFM1* (22-23), and deletions involving genes *POU3F4* (see above: "undefined syndromes" paragraph) [74-78] or *COL4A6* [19, 22, 23], have also been associated to syndromic forms of hearing loss. In Table **2** are shown the clinical manifestations of non-syndromic forms and the loci and genes associated. Below are reported, in detail, the main characteristics and genes identified for each form.

3.1. PRPS1

The *PRPS1* gene, as described above, (Table **1** and "syndromic forms" paragraph) has been associated to several types of hearing loss including non-syndromic sensorineural hearing loss [81]. As regards the non-syndromic form

Table 2. Summary statement of non-syndromic X-linked hearing impairment with clinical manifestations.

Gene	Locus	OMIM Number	Onset	Type and Degree of Hearing Loss in Affected Males	Ear Anatomical Alteration
PRPS1	DFNX1 (Xq22.3)	304500	Postlingual	Progressive sensorineural; severe to profound	No alteration
POU3F4	DFNX2 (Xq21.1)	304400	Prelingual	Progressive, mixed; variable, but develops to profound	Dilatation of the internal acoustic canal, abnormally communication between the internal acoustic canal and inner ear compartment, hypoplasia of the cochlea, absence of modiolus
-	DFNX3 (Xp21.2)	300030	Congenital	Bilateral, profound	No alteration
SMPX	DFNX4 (Xp22.12)	300066	Postlingual	Progressive sensorineural; mild to profound	No alteration
AIFM1	DFNX5 (Xq26.1)	300614	Childhood onset	Auditory neuropathy and delayed peripheral sensory neuropathy	Cochlear nerve hypoplasia
COL4A6	DFNX6 (Xq22.3)	300914	Prelingual	Progressive sensorineural hearing loss of varying severity	Malformed cochlea, with incomplete partition of the cochlea and incomplete separation from the internal auditory canal

(DFNX1), recent studies report three novel missense mutations in *PRPS1*, p.Ile275Thr and p.Gly306Glu and p.A82P in subjects with non-syndromic hearing loss. For this gene is present a progressive sensorineural hearing loss form from severe to profound. Additional investigation revealed a high intrafamilial phenotypic variability, with syndromic features in hemizygous carriers complicating genetic counseling of mutation carriers [82, 83].

3.2. POU3F4

The first gene identified for a non-syndromic X-linked form of hearing loss was the gene *POU3F4* located in the DFNX2 locus [84]. Nance *et al.* in 1971 [85], described DFNX2 as a recessive X-linked condition characterized in males by profound mixed hearing loss, vestibular abnormalities and congenital fixation at the stapes with perilymphatic gusher. Computerized tomography studies in patients with DFNX2 showed some malformations as abnormal dilatation of the internal acoustic canal and abnormal communication between the internal acoustic canal and inner ear compartments. Subsequently molecular analysis revealed mutations in *POU3F4* (POU domain, class III, transcription factor 4) [86]. Human *POU3F4* is a transcription factor and it is located on chromosome Xq21.1. POU superfamily genes are involved in organ formation and cell differentiation. Inner ear development is closely associated with *POU3F4*. Patients with *POU3F4* mutations can show conductive, mixed or sensorineural hearing loss.

X-linked hearing loss type 2 (DFNX2) is found in ~50% of all families carrying X-linked non-syndromic hearing loss [87, 88]. The most frequent clinical features of DFNX2 in affected males are: hypoplasia of cochlea, enlarged internal acoustic canal and a characteristic stapes gusher upon surgery and stapes fixation [89, 90]. Anatomical anomalies of the temporal bone, revealed by Computer-assisted Tomography (CT), include dilatation of the lateral end of the internal acoustic canal, abnormally wide communication between the internal acoustic canal and inner ear compartment and, in some cases, partial hypoplasia of the cochlea [91]. Cochlear malformation was shown to consist of a relatively normal outer coat shape, absence of a cochlear modiolus, and a direct inter communication between the IAC and cochlear inner cavity. The lateral portion of the IAC was dilated. The labyrinthine facial nerve canal and superior vestibular nerve canal were enlarged. The Bill's bar was hypertrophic and partially pneumatized. A thickened stapes footplate was present and a fissura ante fenestram was absent in seven ears examined. A column shaped stapes was observed in one ear. The absence of a cochlear modiolus with a dilated lateral IAC and thickened stapes footplate were the noticeable features observed with imaging in X-linked non-syndromic hearing loss patients with a *POU3F4* mutation [92]. As a result of the widening of the internal acoustic canal, cerebrospinal fluid can enter the vestibule, which leads to the reported "gusher" phenomenon, described as fluid gushing out upon removal of the stapes footplate during corrective surgery [93]. Female carriers of a mutation in the DFNX2 usually show no hearing loss, but hearing loss in sisters or mothers of male patients has been observed in some families with *POU3F4* mutations [87, 91, 94-97]. Currently, no systematic study of hearing status and temporal bone CT scan of females carrying *POU3F4* mutations or deletions has been performed.

3.3. SMPX

SMPX encodes the small muscle protein, X-linked (*SMPX*), a cyskeleton associated protein that probably plays a main role in the maintenance of inner ear cells subjected to mechanical stress. *SMPX* is expressed in many different organs other than the ear but no evident symptoms other than hearing loss were detected in patients [98]. Mutations in this gene have been associated to DFNX4 [99], a non-syndromic recessive type of sensorineural, progressive hearing loss with postlingual onset. Initially, in males, it presents a high-frequency hearing loss that later evolves in severe to profound and involves all frequencies. Carrier females present only moderate hearing loss on the high frequencies.

Further studies confirmed the involvement of mutations of *SMPX* in sensorineural hearing loss and showed specific mutations with phenotypic characteristic (early onset with rapid progression from mild and flat to severe and sloping sensorineural hearing loss, with highly variable onset and hearing loss severity in females [100-104].

3.4. AIFM1

AIFM1 gene mutations have been associated, as described above, to a syndromic form presenting hearing loss: the Charcot-Marie-Tooth disease (CMTX4) and to a non-syndromic form: an X-linked recessive form of auditory neuropathy (AUNX1) that was described initially by Wang *et al.* [105] in the Xq23-27.3 region. This form of neuropathy has been named as DFNX5 [6]. Recently, mutations in the gene *AIFM1* have been associated to this non-syndromic form of pathology in both familial and sporadic cases presenting auditory neuropathy and late peripheral sensory neuropathy [106].

3.5. COL4A6

COL4A6, previously quoted as involved in some case of syndromic hearing loss (see above: "syndromic forms" paragraph) is the fourth gene identified for X-linked sensorineural non-syndromic hearing loss (DFNX6). Mutations in this gene have been identified as causative of non-syndromic congenital hearing loss. The alpha-6 chain of collagen type IV is part of the basement membrane of the inner ear and may have an important role in cochlea development. In some case a malformation of the cochlea has been observed in the affected subjects with incomplete partition of the cochlea and incomplete separation from the internal auditory canal and it is present progressive hearing loss of varying severity [107].

3.6. *HCFC*1

Another disease that could be associated to X chromosome is the Meniere's Disease (MD) (OMIM 156000). MD is a chronic disorder presenting cochlear and vestibular malfunction with fluctuating sensorineural hearing loss, intermittent episodes of vertigo, aural pressure and tinnitus. Some studies suggested the possibility of a familiarity for this disease [108, 109] and a case control association study reported a possible association of several single-nucleotide polymorphisms in the gene Host Cell Factor C1 (*HCFC1*) located on Xq28, encoding a chromatin-associated transcriptional regulator [110, 111].

CONCLUSION

This review offers the opportunity to obtain information that can serve to realize an early identification of the X-linked sensorineural hearing loss forms. An early identification is essential because besides being important for appropriate genetic counseling, it is also is a key element for further investigations to be carried out and to predict the evolution of the disease and the appearance of other symptoms to be monitored. Affected subjects frequently show a high phenotypic variability and a mutational analysis can help in identifying the correct pathology and can contribute to effective disease management. Complete and correct information can help in avoiding the choice of useless and even harmful treatments. For some genes, as described above, it has been observed that for different mutations there are several phenotypes, suggesting that different mutations can have various pathogenic mechanisms. As regards hearing loss treatment, for many types of hearing loss, frequently it is sufficient to utilize hearing aids, but in some cases, in particular in presence of profound hearing loss, it is frequently necessary to perform a more invasive intervention such as a cochlear implant. However, it is fundamental to know the exact etiology of the disease, because for phenotypes associated to specific mutations this treatment can be inappropriate. It is, in fact, reported in several studies that the effects of specific mutations in some genes influence negatively cochlear implant performances. So, it would be very useful to identify previously the mutated gene, to obtain important help in the choice of better rehabilitative intervention. An example is represented by hearing loss associated to medium/inner ear alterations derived by POU3F4 mutations [91-95, 97]. Sequencing of the entire *POU3F4* gene is recommended, in particular, in patients with characteristic temporal bone malformations, to realize an adequate surgical procedure [112]. In the literature, it is reported that cochlear implantation is a safe procedure for children with severe-profound hearing loss presenting inner ear malformation caused by a *POU3F4* mutation [113, 114] but, preoperative recognition of image features in these patients is important because it could show possible risks in the surgery of cochlear implantation including CSF gusher and electrode insertion into inner auditory channel. In other cases, inner ear alterations can have a late onset as in the case of cochlear nerve hypoplasia associated to *AIFM1* mutations [106] which cannot be considered a congenital alteration. So, it could be possible that subjects presenting neuropathy related to *AIFM1* mutations may have partial benefit from cochlear implantation. A similar problem (uncertain results with cochlear implants) can be associated to subjects presenting mutation in the *TIMM8A* gene showing hearing loss with typical aspects of neuropathy [56].

Additional studies are consequently required to obtain more information regarding all X-linked forms of hearing loss. These studies will be useful in helping to choose the best rehabilitative intervention determining in greater detail the short and long term benefits that subjects may gain from the selected treatment.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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