Original articles

A new X linked recessive deafness syndrome with blindness, dystonia, fractures, and mental deficiency is linked to Xq22

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Abstract

X linked recessive deafness accounts for only 1.7% of all childhood deafness. Only a few of the at least 28 different X linked syndromes associated with hearing impairment have been characterised at the molecular level. In 1960, a large Norwegian family was reported with early onset progressive sensorineural deafness, which was indexed in McKusick as DFN-1, McKusick 304700. No associated symptoms were described at that time.

This family has been restudied clinically. Extensive neurological, neurophysiological, neuroradiological, and biochemical, as well as molecular techniques, have been applied to characterise the X linked recessive syndrome. The family history and extensive characterisation of 16 affected males in five generations confirmed the X linked recessive inheritance and the postlingual progressive nature of the sensorineural deafness. Some obligate carrier females showed signs of minor neuropathy and mild hearing impairment.

Restudy of the original DFN-1 family showed that the deafness is part of a progressive X linked recessive syndrome, which includes visual disability leading to cortical blindness, dystonia, fractures, and mental deficiency. Linkage analysis indicated that the gene was linked to locus DXS101 in Xq22 with a lod score of 5.37 (zero recombination). Based on lod-1 support interval of the multipoint analysis, the gene is located in a region spanning from 5 cM proximal to 3 cM distal to this locus. As the proteolipid protein gene (PLP) is within this region and mutations have been shown to be associated with non-classical PMD (Pelizaeus-Merzbacher disease), such as complex X linked hereditary spastic paraplegia, PLP may represent a candidate gene for this disorder.

This family represents a new syndrome (Mohr-Tranebjærg syndrome, MTS) and provides significant new information about a new X linked recessive syndromic

type of deafness which was previously thought to be isolated deafness.

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X linked recessive deafness is rare, accounting for 1.7% of all childhood deafness.^{1,2} A number of clinically recognisable X linked syndromes are also accompanied by deafness.³ According to Bach *et al*,⁴ at least 28 different X linked disorders cause hearing impairment. However, only a few have been characterised at the molecular level.³

The classification of non-syndromic X linked deafness recognises four types of deafness: X linked, early onset, progressive sensorineural (McKusick 304700, DFN-1), congenital sensorineural (McKusick 304500, DFN-2), progressive mixed deafness with perilymphatic gusher (McKusick 304400, DFN-3), and high tone sensorineural deafness (McKusick 304600, DFN-4).⁵ The category of DFN-1 is based on the description of one Norwegian family reported in 1960.⁶

This report presents a restudy of this Norwegian family with DFN-1.⁶ The early onset, progressive sensorineural deafness was found to be associated with progressive dystonic movements, spasticity, mental deterioration, aggressive behaviour, and significant visual disability leading to blindness. The condition thus represents a previously unrecognised X linked recessive syndromal deafness. Furthermore, the gene for this syndrome was found to be linked to genetic markers in Xq22. This report emphasises the value of clinical restudy of previously published families. Moreover, a new classification system for deafness which includes the molecular genetic information is needed.

Methods

Information on all affected males was compiled from medical records, including successive audiological assessments. Sixteen affected males were known, of whom 10 were alive and all had clinical examinations. They ranged in age from 14 to 60 years.

Figure 1 Partial pedigree of family 8160 showing 16 affected males in five generations.

MOLECULAR AND LINKAGE ANALYSIS
Genomic DNA was isolated from blood lymphocytes as previously described⁷ using the “salting out” method. Southern analysis using various X chromosome markers was carried out as previously described.⁷⁻⁹ Probes were labelled by primer extension.¹⁰ Once linkage was established to probes in Xq21-q22, (CA)_n repeat polymorphisms DXS990,¹¹ DXS456,¹² and COL4A5¹³ were used as specified. The amplified products were analysed on 6% polyacrylamide gels according to previously published protocols.¹⁴ One trinucleotide repeat, DXS101,¹⁵ was used incorporating ³²P dCTP and polyacrylamide gel electrophoresis.¹² Two point disease to marker linkage analysis was conducted using MLINK of linkage (V5.1)¹⁶ and multipoint analysis was carried out using LINKMAP,¹⁷ with the mutation rate and gene frequency set at 0.3 × 10⁻⁵ and 0.0001 respectively.

A mutation in the PLP gene involved in spastic paraplegia¹⁸ was assayed as follows. Exon 4 of the gene was amplified using primers previously described¹⁹ in a total volume of 50 µl. Following amplification, the PCR products were purified by ethanol precipitation and resuspended in 20 µl of H₂O. One half of the product was digested with *AccI* according to the supplier’s protocol. The digestion products

were separated on a 1% NuSieve GTG agarose gel.

Results
The pedigree is fully compatible with X linked recessive inheritance (fig 1). At the time of the restudy, 10 affected males were alive. Two (V-11 and VII-25) had died at the age of 59 and 16, both severely affected by the disorder. There was no medical information on two males (in generation III). Two other males (generation IV) died from tuberculosis at the age of 26 and 28 years. No descendants of the collateral branches of the family have been traced. The main clinical findings are summarised in table 1.

The unique association of deafness, spasticity, dystonia, ataxia, mental retardation, neuropathy, hip fractures, and progressive visual disability leading to blindness is strikingly similar in all affected, but with considerable variations in severity. The disorder was progressive in all 10 affected males aged 14 to 60 years. Several males had suffered fractures. The type of end stage neurological abnormalities also varied and included spasticity, dystonia, and mental deterioration.

Table 1 Clinical findings in affected males. The four affected males in generations III and IV were known to be deaf, but no information was available on other symptoms. The two affected males in generation IV died from tuberculosis aged 26 and 28 years.

Pedigree	Age	Age of deafness	Impaired vision	Spasticity	Dystonia	CT/MRI abnormality	Fractures	Sensory evoked potential (SEP)	Muscle biopsy	ERG	Other
VII-25	16	?	?	+++	+++	+++	-	NI	NI	NI	Died aged 16
V-11	59	?	+++	++	++	NI	-	NI	NI	NI	Died aged 59
V-12	62	4	+++	++	+	NI	+	NI	NI	NI	
V-14	54	3	+++	++	+++	++	+	NI	Neurogenic atrophy	NI	
V-3	53	7	+	+	+	NI	+	NI	NI	NI	Aggressive
VI-1	48	5	++	+	-	NI	+	NI	NI	N	
VI-7	47	4	++	+	+	++	+	N	N	N	
VI-2	44	4	++	+	-	++	-	Abnormal	NI	Abnormal	
VI-14	43	5	++	+	+	++	+	Abnormal	NI	N	Aggressive
VII-24	24	3	+	++	+	NI	-	N	NI	N	Aggressive “MBD”, aggressive
VII-8	17	4	(+)	+	-	NI	-	NI	NI	N	Scoliosis, aggressive
VII-20	14	2	(+)	(+)	-	-	-	NI	NI	N	

N=normal, NI=not investigated, - =not present.
+ =mildly affected, ++ =moderately affected, +++ =severely affected.

Figure 2 (A) Audiogram from affected male VII-8, aged 2½ years. (B) Audiogram from VII-8 aged 6 years 7 months. The audiograms show progression of the hearing loss. Audiograms up to the age of 2½ years were normal.

CASE REPORT

V-14

This male was 54 years old when restudied. The main findings are listed in table 1. Cerebral CT scan at the age of 50 showed diffuse central and cortical atrophy which was a typical finding in all affected males older than 40 years.

He had an unremarkable early infancy and developed some speech and hearing which declined rapidly from the age of 3. At the age of 13 the hearing loss was >80 dB and spanned all frequencies tested (500–4000 Hz). He had to give up his living as a fisherman at 41 years because of severe visual disability. For more than 10 years the visual disability had slowly progressed after a very insidious onset with photophobia. At the age of 49 the visual fields were restricted to 5° and visual acuity was limited to finger counting. Early in his life there was no indication of colour vision or night vision difficulties. He had a fracture of the femoral neck at 52 years after falling on the ice. There was no evidence of osteoporosis. Physical examination showed normal head circumference, no facial dysmorphic features, and normal testicular size. Histological examination of a muscle biopsy showed neurogenic atrophy. There was no evidence of amyloid deposits.

Urinary and serum metabolic screening, including phytanic acid and very long chain fatty acids, were normal.

VII-25

He died at the age of 16 and the proposed diagnosis was “dystonia musculorum deformans”. No necropsy was performed. This male was the most severely affected with a very early onset of the neurological abnormalities. He was born at term, with normal birth weight, and walked unassisted before 12 months and talked at the normal age. By history and audiological evaluation he had a 40 dB hearing loss at the age of 7, and at 11 years the hearing loss was 70 dB. His fine motor skills deteriorated and his gait became ataxic from the age of 7, and progressed rapidly. A year later he was not able to walk or sit. Thereafter he developed ulnar deviation of both hands, involuntary movements, opisthotonus, and hyperactive deep tendon reflexes. It was not known whether he was blind. His brother (VII-24) also had a more rapidly progressive course than other family members at a comparable age.

HEARING LOSS

Deafness was the first presenting symptom in all males. Based on family information and information from a deafness registry, a total of 16 males were affected. Hearing impairment was suspected between 18 months and 5 years. Typically, some language was acquired but three males (V-11, VII-8, and VII-20) never developed intelligible language. Fig 2A and B shows audiograms from one affected male, VII-8, and clearly indicates the early but post-lingual onset and progressive nature of the hearing loss. CT scan of the temporal bone in VI-7 did not show dilatation of the lateral end of the internal auditory meatus. Vestibular studies, including caloric stimulation, smooth pursuit tracking, and saccadic eye movements, in VI-7 were normal.

NEUROLOGICAL AND NEUROIMAGING FINDINGS

Several males were restless and irritable with anxiety and aggressive outbursts. One male (VII-8) born after an uncomplicated pregnancy and delivery was designated as having “minimal brain dysfunction” even before hearing impairment was evident.

Paranoid symptoms included fear of poisoned food, imaginary visual impressions (“stars seen”), imaginary pulling long hairs out of the eyes, and severe itching without skin abnormalities. The youngest living male examined by cerebral CT scan (VII-20) at the age of 14 had no atrophy or other abnormalities. In five affected males over the age of 40, CT scan showed generalised atrophy and no particular cerebellar or basal ganglia pathology. Based on previous studies cerebral atrophy was known to be present exceptionally early in the most severely affected male (VII-25) at the age of 7. Cerebral MRI scan in one male (VI-7) did not show white matter abnormalities. All

Table 2 DNA markers used for the linkage studies.

Probe	Locus	Location	Recombination frequencies θ						θ_{max}	Z _{max}
			0-00	0-01	0-05	0-10	0-20	0-30		
99.6	DXS41	Xp22.1	-4.03	-2.35	-1.05	-0.56	-0.18	-0.05	0.55	0.00
L1.28	DXS7	Xp11.4	0.06	0.06	0.04	0.03	0.02	0.00	0.00	0.06
M27 β	DXS255	Xp11.22	-1.57	0.36	1.50	1.78	1.68	1.25	0.12	1.80
p8	DXS1	Xq12	-0.11	-0.11	-0.11	-0.10	-0.09	-0.06	0.99	0.11
cX37.1	DXS153	Xq12	-6.62	-3.64	-1.62	-0.82	-0.15	0.87	0.37	0.12
RX214	DXS441	Xq13-21	-1.16	0.75	1.86	2.08	1.88	1.37	0.11	2.08
pZ11	CHM	Xq21.2	0.11	0.11	0.09	0.70	0.03	0.01	0.00	0.11
pDP34	DXYS1	Xq21.3	1.36	2.28	2.72	2.68	2.22	1.55	0.06	2.73
p19-2	DXS3	Xq21.3	-2.27	-0.28	0.97	1.28	1.34	1.08	0.16	1.37
AFM136yc7	DXS990	Xq21.3	2.56	3.48	3.82	3.66	2.94	2.06	0.05	3.82
cX52.5	DXS101	Xq22	5.37	5.31	5.00	4.56	3.52	2.33	0.00	5.37
pXG-12	DXS94	Xq22	1.16	1.12	0.99	0.85	0.59	0.38	0.00	1.16
S9	DXS17	Xq22	4.26	4.19	3.86	3.45	2.62	1.78	0.00	4.26
A13.RI	DXS87	Xq22	0.35	0.33	0.26	0.18	0.07	0.01	0.00	0.35
XG30B	DXS456	Xq22	1.47	2.39	2.79	2.69	2.16	1.44	0.05	2.79
COL4A5	COL4A5	Xq22	-0.72	0.24	0.79	0.88	0.78	0.56	0.11	0.88
p43-15	DXS42	Xq24	1.06	1.71	2.42	2.51	2.10	1.42	0.08	2.51
p22-33	DXS11	Xq24	0.85	0.83	0.72	0.61	0.39	0.23	0.00	0.85
C11	DXS144E	Xq26	-1.81	-0.87	-0.29	-0.11	-0.05	0.13	0.33	0.01

affected males over the age of 54 had dysphagia. In some males there was mild peripheral neuropathy, verified by EMG, neurography, or muscle biopsy. The neurological symptoms and findings represent involvement of basal ganglia, corticospinal tract, and brain stem and indicated a progressive, diffuse, generalised encephalopathy.

VISUAL ABNORMALITIES

The general impression was that photophobia occurred from approximately the age of 15 with

preserved colour and night vision. In their mid-thirties, the males complained of lack of effect of stronger glasses and visual acuity was reduced to 0.2 (20/100) or less. Full field electroretinograms in six affected males (VI-1, VI-7, VI-14, VII-8, VII-20, VII-24) and two obligate carriers (V-10, VI-9) showed normal retinal function. In these patients the visual abnormalities suggest involvement of the central visual pathways. Ophthalmological examination of VI-2 including electroretinograms showed retinal dysfunction including both rods and cones. Bilateral large central scotomas were also found, and changes in the central retina showed findings compatible with central choroidal areolar dystrophy.²⁰ These findings were not observed in other family members.

OTHER STUDIES

The following studies were performed in at least one affected male and were normal: head circumference, electrocardiogram, electroencephalogram, testicular size, serum and spinal pyruvate and lactate, high resolution chromosome RBA banding of cultured peripheral lymphocytes, urinary microscopy, and urinary excretion of monosaccharides. In plasma from at least one affected male we measured very long chain fatty acids, bile acids, phytanic acid, and pristanic acid. The levels of plasmalogens in erythrocytes and peroxisomal enzymes in cultured skin fibroblasts were also normal. Special staining of muscle tissue for amyloidosis was negative. There was no history of infections or other evidence for immune deficiency. None of the affected males had dysmorphic facial features.

Since the original report of this family,⁶ two affected males (VI-1 and VI-2) have reproduced, indicating fertility.

OBLIGATE CARRIERS

Four obligate female carriers (VI-9, V-4, V-9, V-10) had a neurological examination. They were in the age range 42 to 72 years. V-4, V-10, and V-13 had mild hearing loss (age range: 57 to 70 years). V-10 had a 30-45 dB non-progressive hearing loss detected at the age of 52, which was unchanged by the age of 66.

Figure 3 Logarithm of odds of linkage of MTS: multipoint analysis versus map of markers in Xq12-q23. The fixed order and genetic distance were set as follows: DXS153 - 0.03 - DXS441 - 0.06 - DXYS1X - 0.05 - DXS3 - 0.02 - DXS990 - 0.15 - DXS94 - 0.01 - DXS17 - 0.01 - DXS456 - 0.01 - COL4A5 - 0.02 - DXS11 - 0.05 - DXS42 - 0.05 - DXS144E. Multipoint lod scores correspond to location scores divided by 4.6.

V·13 had a 50–70 dB hearing loss at 57 years. V·4 had a 70 dB unilateral hearing loss. The same two obligate carriers (V·4 and V·10) had decreased achilles tendon reflexes and mild reduction of pain and temperature sensation, possibly signs of mild neuropathy. Another obligate female carrier (VI·12) had a normal audiogram at the age of 33 years. No neurological examination was done.

LINKAGE ANALYSIS AND MOLECULAR STUDIES

Linkage analysis was initiated using a collection of Southern based DNA markers, spread along the X chromosome. Tight linkage was found to the probe DXS17 in Xq22 with a lod score of 4·26 at zero recombination (table 2). Available microsatellite markers, in association with Southern based markers clustered in the Xq21–q22 region, were then used to refine the localisation of the MTS gene further. Tight linkage was established to DXS101 with a lod score of 5·37 and no recombination. Recombination was observed with DXS990 proximal in Xq21·3 and DXS456 distal in Xq22 (table 2). Multipoint analysis (fig 3), using nine markers localised in Xq21·3–q22, located the disease locus near DXS101 with a location score of 6·4 (zero recombination). Using lod-1 support interval to define the limits of localisation, the multipoint analysis places the likely location for the MTS gene within a region spanning from 5 cM proximal to DXS101 to 3 cM distal to this locus.²¹ Kobayashi *et al*¹⁸ recently showed that a family with spastic paraplegia had a point mutation (T to C) in exon 4 resulting in a Ile substitution for Thr at residue 186. This mutation was assayed for in our family by taking advantage of the fact that the T to C alteration generates an *AccI* site.¹⁸ All affected males and available carrier mothers were found to be negative for this mutation (data not shown). So far, continuing SSCP analysis of the PLP gene (exons 1, 3, 4, and 6) has not shown any alterations.

Discussion

The unique combination of deafness, behavioural abnormalities, dystonia, spasticity, ataxia, mental deterioration, visual disability, and fractures suggests a new X linked recessive syndrome (MTS). Our restudy of this family, initially reported⁶ as non-syndromic deafness, clearly indicates that the disorder is an example of another X linked deafness syndrome. In addition, we present audiological evidence of early onset of the deafness (fig 2A and 2B). The clinical pattern suggests a progressive neurodegenerative disorder affecting CNS, basal ganglia, corticospinal tract, and possibly the brain stem. The occurrence of hip fractures in many affected males (all >40 years) could be secondary to dystonia and ataxic gait since no osteoporosis was found. No biochemical or neuropathological abnormalities have been identified, but the regional mapping to Xq22 points to candidate genes possibly involved. A second DFN-1 family has been reported from South Africa with adolescent onset mild X

linked hearing impairment²² but no visual or neurological symptoms. No genetic linkage has been reported and the question of allelic disorders or different X linked mutated gene therefore remains unresolved.

Regional localisation of MTS to Xq22 makes it possible that genes in this region become candidate genes for this disorder. Pelizaeus-Merzbacher disease (PMD) maps to Xq22²³ and is known to result from mutations in the proteolipidprotein gene (PLP).²⁴ Clinically, however, deafness and dystonia are not typical in PMD and the progressive loss of vision is accompanied by optic nerve atrophy in PMD. In late stages of PMD, white matter substance shows abnormal signal attenuation on MRI, which was normal in a 47 year old severely affected male in the present family. The recent reports of mutations in the PLP gene leading to a complex X linked spastic paraplegia^{18,25} justify a search for mutations in this gene in the present family. PLP may represent a candidate gene for MTS although one of the spastic paraplegia mutations¹⁸ was not found to be present in this family.

It seems reasonable to disregard the gene for X linked agammaglobulinaemia (XLA), which also maps to Xq22,^{26,27} as a candidate gene, since there was no evidence of immune deficiency. However, there is a report of a patient with XLA, dystonia, and deafness who is deleted for the 3' end of the XLA gene and a flanking expressed sequence, DXS1274E.²⁸ These data do not exclude that a gene near XLA could be involved in the MTS phenotype. No deletions in the PLP gene or the transcribed sequence 5D8 (DXS1274E) or FC12 were detected²⁸ (M Bitner-Glindzicz, unpublished data). Other mutations, such as single base pair substitutions, have not been excluded.

The possibility of anticipation is suggested by two brothers (VII·24 and VII·25) who had an earlier onset and more severe course. In contrast to most affected males, VII·25 had significant diffuse cerebral atrophy on CT scan at the age of 7. The search for the gene will therefore include methods specifically detecting trinucleotide repeats within Xq22.

Alport syndrome (sensorineural deafness, interstitial nephritis, and retinal pathology) is caused by mutations in the COL4A5 gene. The recombination between the present disease gene and a COL4A5 probe combined with lack of kidney disease seems to exclude the COL4A5 gene and maps the syndromic deafness proximal to the COL4A5 gene.

A familial syndrome with dystonia, neural deafness, hyperactivity, and dysarthria²⁹ is somewhat similar to the syndrome in the present family. Neuropathology showed neuronal loss and gliosis in the basal ganglia. Unfortunately, the authors have not been able to trace the original family for genetic linkage studies, but the two families may present the same X linked disorder. X linked dystonia as an isolated neurological finding has only been described in the Philippines and the gene has been mapped to Xq13·1.³⁰ It is therefore unlikely that there should be any relationship to the present syndrome.

A considerable number of X linked syndromes with deafness have been mapped to regions other than Xq22.³ These include albinism-deafness syndrome mapping to Xq26.3-q27.1,³ Norrie disease mapping to Xp11.2-11.3³ (gene cloned), and otopalatodigital syndrome type I³ mapping to Xq28, as well as the syndrome described by Gustavson *et al* mapping to Xq26.^{31,32} In a family with syndromic X linked deafness³³ a recent restudy showed linkage to DXS984 in Xq26-q27.³⁴ Based on the genetic linkage information, they can be disregarded as allelic diseases to the present disease.

There are several purely clinical reports of single families with X linked deafness in association with various symptoms: high tone deafness, spastic paraparesis, and growth retardation³⁵; ataxia³⁶; muscular atrophy, polyneuropathy, and optic atrophy³⁷; optic atrophy, muscular atrophy, and neuropathological calcifications³⁸; basal ganglia symptoms and microcephaly.³⁹ None included genetic linkage studies. The clinical picture was in all cases different from the present family.

Even considering the syndromic pattern of the X linked deafness in the present family, mapped genes for non-syndromic deafness cannot be totally disregarded because of the possibility of a contiguous gene syndrome.

Previous linkage studies in several families^{2,40,41} have shown genetic heterogeneity in X linked recessive non-syndromic deafness. The gene responsible for X linked mixed deafness with perilymphatic gusher and stapelial fixation (DFN-3) is linked to genetic markers in Xq21.1.⁴²⁻⁴⁵ Further mapping of the region containing the gene has been done by molecular characterisation of deaf patients with microdeletions in that region.^{44,46,47} A gene for severe congenital sensorineural deafness (DFN-2)⁴⁸ was closely linked to genetic markers in Xq12 in one family. The present classification of non-syndromic X linked deafness does not show consistency between audiological, neurological, and genetic findings, and needs to be revised.^{49,50} The radiological abnormalities with gross dilatation of the internal auditory meatus, for example, have been shown both in DFN-3⁵¹ and in DFN-2.⁴⁸ The audiological criteria used previously are, therefore, not reliable in the classification of X linked non-syndromal deafness. Most recently, another gene for X linked non-syndromal deafness has been mapped to Xp21.2 which contains the Duchenne muscular dystrophy gene.⁵²

In conclusion, we have restudied a family with X linked deafness and shown a complex progressive syndromic disorder.⁵³ We propose that the syndrome is called Mohr-Tranebjærg syndrome (MTS). As more syndromic and non-syndromic deafness genes are mapped and ultimately cloned, it should be possible to develop a genetically and clinically useful classification. The present family, which represents a new syndrome and has been mapped to Xq22, provides significant new information for this process.

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