DFNA49, a novel locus for autosomal dominant non-syndromic hearing loss, maps proximal to DFNA7/DFNM1 region on chromosome 1q21-q23

M A Moreno-Pelayo*, S Modamio-Høybjør*, A Mencía, I del Castillo, S Chardenoux, M Fernández-Burriel, M Lathrop, C Petit, F Moreno

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Approximately 1 in 1000 children is born with a serious permanent hearing impairment (pre-lingual deafness), and it is estimated that more than half of these cases in developed countries are due to genetic factors.^{1–3} The prevalence of hearing loss increases dramatically with age; it is estimated that approximately 5% of people under 45 years of age have a significant loss of hearing, increasing to approximately 50% by 80 years of age.¹ Age related late onset hearing loss (presbycusis) is a heterogeneous trait with many suspected causes.⁴ Genetic or environmental factors such as diabetes, mitochondrial mutations, or environmental noise exposure may contribute to the trait. In addition, hearing loss beginning at late childhood, youth, or later, clearly segregates as a monogenic autosomal dominant Mendelian trait in many families. The hearing loss phenotype in these families is usually non-syndromic—that is, the hearing loss is not associated with other anomalies, and it accounts for up to 20% of the cases of non-syndromic sensorineural inherited deafness. This type of hearing loss is usually progressive, affecting a particular range of frequencies in each case.⁵ To date, 36 loci for autosomal dominant non-syndromic sensorineural hearing loss (ADNSSL) have been mapped, and 17 deafness genes from these loci have been identified.⁶ These genes encode a wide variety of proteins; some have known function but for most, the underlying mechanisms leading to hearing impairment are uncertain. Given the few described mouse models for progressive hearing loss,⁷ our current understanding of post-lingual and progressive deafness relies on the identification of genes through human mapping studies. In this work we describe the mapping of a novel DFNA locus on chromosome 1q21–q23 segregating in a Spanish family with post-lingual and progressive hearing loss.

PATIENTS AND METHODS

Family data

We ascertained a four generation family (S277) segregating ADNSSL, through the Hospital Universitario Materno Infantil. The pedigree consists of 31 members, fourteen of them affected (fig 1). Informed consent was obtained from all study participants and from parents of subjects younger than 18 years. Clinical history interview and physical examination of members of this family ruled out environmental factors as the cause of the hearing loss. Peripheral blood samples were collected from 27 family members and DNA extraction was performed following standard methods. Tympanometry indicated proper functioning of the middle ear, and acoustic reflex thresholds showed the presence of recruitment in affected subjects. Clinical and instrumental evaluation did not reveal any evidence of syndromic features. Pure tone audiometry was performed to test for air conduction (125–8000 Hz) and bone conduction (250–4000 Hz).

Key points

- Autosomal dominant inheritance accounts for about 20% of the cases of hereditary non-syndromic sensorineural hearing loss (NSSL)—that is, hearing loss not associated with other clinical features. So far, 36 loci have been mapped in familial cases that segregate autosomal dominant NSSL (DFNA), and 17 genes have been identified.
- Here we report the location of a novel autosomal dominant deafness locus on 1q21–q23, DFNA49, found by studying a large Spanish family with non-syndromic, progressive mid-frequency hearing loss of post-lingual onset. A maximum lod score of 6.02 at $\theta=0$ was obtained for markers D1S3784 and D1S3785. Analysis of recombinant haplotypes placed the deafness locus within a 4 cM region defined by markers GDB:190880 and D1S3786.
- This genetic interval is proximal to and does not overlap with the previously identified loci, DFNA7 and DFNM1, on 1q21–q23.
- Screening of candidate genes within the DFNA49 interval (*KCNJ9*, *KCNJ10*, *ATP1A2* and *CASQ1*) did not reveal the mutation causing this deafness.

Where possible, results from previous audiological tests were collected.

Genotyping and linkage analysis

A wide genome scan was performed with 394 microsatellite markers distributed with an average spacing of 10 cM (ABI Prism Linkage Mapping Set 2; Applied Biosystems, Foster City, CA, USA). Markers for the exclusion of all known DFNA loci and for fine mapping of the critical interval were taken from the Génethon human linkage map⁸ and from the Marshfield chromosome 1 map (<http://research.marshfield-clinic.org/genetics>). Additional short tandem repeats (STRs) in the DFNA49 region were identified by inspection of publicly available sequence data (NCBI: <http://www.ncbi.nlm.nih.gov>). Flanking primers were designed for polymerase chain reaction (PCR) amplification of these

Abbreviations: ADNSSL, autosomal dominant non-syndromic sensorineural hearing loss; NSSL, non-syndromic sensorineural hearing loss; PCR, polymerase chain reaction; STRs, short tandem repeats

STRs. The amplicons were confirmed to be polymorphic microsatellite markers and deposited into the GDB database (<http://www.gdb.org>), being assigned the following D numbers: D1S3780 (GDB: 11511382), D1S3783 (GDB: 11511388), D1S3784 (GDB: 11511390), D1S3785 (GDB: 11511392), and D1S3786 (GDB: 11511394). The order of markers used in this work was established by integrating genetic and physical maps (NCBI).

Fluorescently labelled alleles were analysed in an ABI Prism 310 automated DNA sequencer (Applied Biosystems). Linkage analysis was performed using the Linkage 5.1 software package.⁹ Two point lod scores between the deafness locus and each marker were calculated under a fully penetrant autosomal dominant mode of inheritance, setting the disease allele frequency to 0.00001 and considering marker allele frequencies to be equal to each other.

DNA sequencing analysis

Four candidate genes, *KCNJ9* (MIM600932), *KCNJ10* (MIM602208), *ATP1A2* (MIM182340) and *CASQ1* (MIM114250) in the DFNA49 interval were screened by heteroduplex analysis and direct sequencing of PCR products generated from genomic DNA of affected subjects. Primers were designed to amplify each exon and adjacent intron-exon boundaries. PCR was performed by standard procedures as previously described.¹⁰ Heteroduplex analysis was carried out in mutation detection enhancement gels (BioWhittaker, Rockland, ME, USA) according to the manufacturer's protocol. Sequences of PCR products were analysed in an automated DNA sequencer (ABI Prism 310; Applied Biosystems).

RESULTS AND DISCUSSION

Clinical features

Affected subjects of the family present a symmetrical, bilateral, and progressive nonsyndromic sensorineural hearing loss. The hearing loss appears in the first decade of life in affected members. The earliest clinical evidence of hearing loss in the family was obtained from individual III:12 at the age of 8 years. Initially, the hearing loss in this family is moderate for low and mid frequencies and mild for high frequencies (4000–8000 Hz), so the affected members show in this stage a gently upsloping audiometric profile. Later, it progresses to moderate in the 125–250 Hz and 4000–8000 Hz ranges and to severe in the 500–2000 Hz range (U shaped audiometric profile) in the fourth decade. Linear regression analysis, based on all available audiograms from affected subjects, showed a 0.7 dB/year age linked progression of the hearing loss at all frequencies. Affected subjects of the family did not exhibit either tinnitus or clinical features suggestive of vestibular dysfunction.

Linkage analysis

Linkage to previously published loci responsible for autosomal dominant deafness (DFNA) was investigated in a core pedigree of 26 persons (subject IV:3 is 20 months old, clearly below the age of deafness onset, and therefore he was not included in the linkage analysis) obtaining negative results. A wide genome search was then performed to map the deafness locus, using a set of 394 microsatellite markers with an average spacing of 10 cM. Interestingly, the two point lod scores obtained for markers D1S498 (3.01 at $\theta = 0$) and D1S484 (3.72 at $\theta = 0.05$) on chromosome 1q21–q23

Figure 1 Pedigree and haplotype analysis of the Spanish family S277. Black symbols represent affected subjects. Haplotypes are represented by bars, with the haplotype associated with hearing loss in black. At the time of the study affected subjects III:12, III:11, III:10, III:9 and III:8 were 8, 14, 15, 17 and 18 years old respectively.

Figure 2 Physical and genetic maps of the chromosome 1q21-q23 region showing the localisation of DFNA49 and DFNA7/DFNM1 critical intervals. cM, centimorgan; kb, kilobase. *KCNJ9* (OMIM #600932); *KCNJ10* (OMIM #602208); *ATP1A2* (OMIM #182340) and *CASQ1* (OMIM #114250). For clarity, the genetic and physical distances are not represented to scale.

were suggestive of linkage to this region (fig 2). We then tested additional markers spanning this region, and evidence of linkage to markers D1S3780, D1S3783, D1S1167, and D1S2707 was found, with maximum two point lod scores of 6.02 at $\theta = 0$ for markers D1S3784 and D1S3785 (table 1). Extensive alterations of the disease gene frequency or the allele frequencies of microsatellite markers did not change the conclusions of the analysis. The inspection of recombinant haplotypes in subjects III:9 and II:8 placed the hearing loss locus between the proximal marker GDB: 190880 and the distal one D1S3786, which define a critical interval of about 4 cM for the novel locus, DFNA49 (fig 1 and 2). All the patients in the family share the same disease haplotype, which is also carried by the 20 month old child IV:3. Periodic audiometric examination of this subject will be performed to precisely determine when the hearing impairment begins in this family.

Another dominant locus for hearing loss (DFNA7) was mapped to a 22 cM region on 1q21-q23 between D1S104 and D1S466 in a Norwegian family¹¹ (fig 2). The DFNA7 interval has been reported to include the DFNM1 locus, a dominant modifier that suppresses the DFNB26 phenotype.¹² The

DFNA7/DFNM1 region had previously been excluded for linkage in our family. As shown in fig 2, a genetic distance of 6 cM separates this interval and the one defined for DFNA49. It should also be noted that the audiometric response associated with DFNA7 and DFNA49 in the reported families is clearly different. DFNA7 patients show a sharply sloping audiogram affecting the high frequencies, instead of the U shaped audiometric pattern found in the DFNA49 affected subjects.

Candidate gene analysis

No genes for syndromic deafness have been mapped to DFNA49 critical interval. This interval spans 0.9 Mb and includes 23 known genes and several predicted or poorly characterised genes according to the annotation in the NCBI database. Of these, we selected *ATP1A2*, *CASQ1*, *KCNJ10* and *KCNJ9* for screening of mutations (fig 2).

ATP1A2 consists of 23 exons¹³ and encodes the NaK-ATPase $\alpha 2$ subunit, which is responsible for the catalytic activity of the enzyme. In mouse cochlea, the $\alpha 2$ isoform is expressed in the spiral structures: ligament, limbus, and ganglion¹⁴, where it is believed to play an important role in the development

Table 1 Two point lod scores between 1q microsatellite markers and DFNA49

Marker	Recombination fractions (θ)							Z _{max}	θ _{max}
	0.00	0.01	0.05	0.10	0.20	0.30	0.40		
D1S394	~∞	3.93	4.27	4.11	3.38	2.40	1.20	4.27	0.05
D1S1600	~∞	3.34	3.72	3.59	2.98	2.11	1.04	3.72	0.05
GDB:190880	~∞	0.97	1.51	1.60	1.44	1.09	0.62	1.60	0.10
D1S3780	5.72	5.63	5.27	4.80	3.78	2.62	1.29	5.72	0.00
D1S3783	5.42	5.34	5.00	4.55	3.58	2.48	1.21	5.42	0.00
D1S1167	3.31	3.26	3.04	2.76	2.16	1.49	0.76	3.31	0.00
D1S3784	6.02	5.93	5.55	5.06	3.99	2.77	1.37	6.02	0.00
D1S2707	5.42	5.34	5.00	4.55	3.58	2.48	1.21	5.42	0.00
D1S3785	6.02	5.93	5.55	5.06	3.99	2.77	1.37	6.02	0.00
D1S3786	~∞	3.93	4.27	4.11	3.38	2.40	1.21	4.27	0.05
D1S484	~∞	3.34	3.72	3.59	2.98	2.11	1.05	3.72	0.05

and maintenance of the fluid and electrolyte balance. *CASQ1* has 11 exons¹⁵ and codes for calsequestrin, a calcium binding protein found in the cytoplasm of outer hair cells where it is thought to store and release calcium from membrane bound intracellular storage sites.¹⁶ Calcium is believed to play a major signalling role in outer hair cells by controlling metabolism, cytoskeletal integrity, cell shape, and cell excitability. *KCNJ10* consists of two exons¹⁷ and encodes an inwardly rectifying K⁺ channel subunit that is strongly expressed in the cochlear stria vascularis, where it is crucially involved in the generation of the endocochlear potential,^{18, 19} and in the satellite cells that surround the neurones and axons of the cochlear and vestibular ganglia.²⁰ Knockout mice for *KCNJ10* present a profound deafness and severe structural degeneration of the cochlea.^{21, 22} *KCNJ9* has three exons²³ and codes for a K⁺ channel with structural and functional similarity to *KCNJ10*,²⁴ although its expression has not been reported in the inner ear so far.

The exons and flanking regions of the four genes were investigated by heteroduplex and DNA sequencing in two affected subjects (I:1 and II:2). These analysis only revealed the non-pathogenic polymorphisms, 1097T→C in exon 3 of *KCNJ9* (NCBI SNP cluster id: rs3001040) and the IVS1-84T→C intronic change in *KCNJ10*, which was present in several control individuals with normal hearing. This last polymorphism allowed us to verify the presence in affected subjects of the two intact copies of *KCNJ10* exon 2, which include the entire coding region, so excluding the deletion of, or insertions in, this exon as the cause of deafness (data not shown).

Reports of more families with hearing deficit linked to DFNA49 may enable a further refinement of the critical interval facilitating the identification of the responsible gene. We are now searching for novel candidate genes at the DFNA49 interval.

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Authors' affiliations

M Angel Moreno-Pelayo, S Modamio-Høybjør, A Mencía, I del Castillo, F Moreno, Unidad de Genética Molecular, Hospital Ramón y Cajal, Madrid, Spain
S Chardenoux, C Petit, Unité de Génétique des Déficits Sensoriels, CNRS URA 1968, Institut Pasteur, Paris, France

M Fernández-Burriel, Laboratorio de Genética Molecular, Hospital Universitario Materno Infantil, Las Palmas de Gran Canaria, Spain
M Lathrop, Centre National de Génotypage, Evry, France

*The first two authors contributed equally to this work and the order of authorship is arbitrary.

Correspondence to: Dr F Moreno, Unidad de Genética Molecular, Hospital Ramón y Cajal, Carretera de Colmenar Km 9, 28034, Madrid, Spain; fmoreno.hrc@salud.madrid.org

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ECHO.....

Susceptibility to Crohn's disease may lurk in enzyme mutation

Please visit the *Journal of Medical Genetics* website [www.jmedgenet.com] for a link to the full text of this article.

A preliminary study of genetic polymorphisms affecting transforming enzymes in the gut has singled out for the first time microsomal epoxide hydrolase as a likely candidate for susceptibility to Crohn's disease (CD).

Homozygous Tyr 113 substitution for His 113 in exon 3 of the microsomal epoxide hydrolase (*EPXH*) gene was the only one of seven variants in a series of genes coding for detoxifying enzymes with a significantly higher frequency in patients with CD than controls (47% v 21%, respectively). Tyr/Tyr genotype was also more common within the patient group than in the control group (allele frequency 0.67 v 0.61, respectively), and the odds of having the Tyr 113 allele were almost three times higher. This variant and another, in exon 4 of the same gene, were not associated with disease site, disease onset, fistulas, or history of bowel resection.

The variants were identified by PCR-RFLP (restriction fragment length polymorphism). They included those in cytochrome *P-450* 1A1C (*CYP1A1* 3' flanking region, *CYP1A1* exon 7); glutathione S-transferases mu-1, pi-1, and theta-1 (*GSTM1*, *GSTP1*, *GSTT1*); and epoxide hydrolases (*EPXH*) in exons 3 and 4. Screening was performed on 151 consecutive outpatients at a hospital clinic in the Netherlands and age and sex matched healthy controls; all were Caucasian.

Reactive oxygen species and their toxic metabolites have been implicated in inflammation of the gut in CD. Detoxifying enzymes, such as glutathione S-transferases and epoxide hydrolases, may also have a role, so polymorphisms affecting their activity may affect risk of developing CD.

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REVIEW

Mulibrey nanism: clinical features and diagnostic criteria

N Karlberg, H Jalanko, J Perheentupa, M Lipsanen-Nyman

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Mulibrey nanism (MUL) is an autosomal recessive disease caused by mutations in the *TRIM37* gene encoding the peroxisomal TRIM37 protein of unknown function. In this work, we analysed the clinical characteristics of 85 Finnish patients with MUL, most of whom were homozygous for the Finn major mutation of *TRIM37*. The patients' hospital records from birth to the time of the diagnosis at age 0.02–52 years (median 2.1 years) were retrospectively analysed. All except four of the patients (95%) had a prenatal onset growth failure without postnatal catch up growth. The mean length standard deviation score (SDS) was –3.1 and –4.0 at birth and at diagnosis, respectively. In infancy, feeding difficulties, and respiratory tract infections were the most common problems. Congestive heart failure and pericardial constriction were diagnosed during infancy in 12% and 6% of the patients, respectively. At the time of the diagnosis, characteristic craniofacial features of scaphocephaly, facial triangularity, high and broad forehead, and low nasal bridge were evident in over 90% of the patients. In addition, practically all patients were gracile and had thin extremities. Other findings included a peculiar high-pitched voice (96%), yellowish dots in ocular fundi (79%), cutaneous naevi flammei (65%), hepatomegaly (45%), and fibrous dysplasia of long bones (25%). Mild muscular hypotonicity (68%) was the only neurological abnormality. The clinical features of the Finnish patients with MUL formed a distinct entity. The most consistent findings were growth failure and characteristic craniofacial features. However, organ manifestations varied considerably in early childhood. Based on these findings, we propose new diagnostic criteria for MUL.

and Turkish (c.855_862delTGAATTAG).¹² All five mutations result in a shift of the reading frame, resulting in a truncated TRIM37 protein.¹³ TRIM37 is a 130 kDa protein expressed in many tissues¹⁴ and located in the peroxisomes, suggesting that MUL is a peroxisomal disease.¹⁵ TRIM37 belongs to a new subfamily of zinc finger proteins (previously designated RBCC for ring-B box-coiled coil). The function of the TRIM37 protein and the pathogenetic mechanisms underlying MUL are unknown.

Diagnostic evaluation and clinical care of the patients with MUL in Finland has been centred in our institution. Here we report the clinical findings from birth to the time of the diagnosis in all known Finnish patients, and present revised diagnostic criteria.

PATIENTS AND METHODS

Patients

The series included all the known 85 Finnish patients with MUL diagnosed by the original criteria.² DNA was available from 80 patients; 78 of them homozygous for the Finn major mutation, and two compound heterozygotes for the two Finnish mutations. The other five patients had died before mutation analysis became available. In four of those five cases, DNA was obtained from family member(s); one parent couple, two single parents, and one sibling, all carriers of the Finn major mutation. The phenotype of the remaining patient left no doubt about the diagnosis.

Collection of data

The hospital ethics committee approved the study. We retrospectively analysed the patients' hospital records from birth to the time of diagnosis. We recorded data on their clinical events and on their appearance and dysmorphic features. The patients were photographed, and x rays of the skull, thorax, and long bones as well as appropriate laboratory assays were obtained on the first visits. The obstetric and growth histories were collected from hospitals and child welfare centres. The patients' parents, relatives, and physicians were interviewed for missing details. Birth size and subsequent lengths/heights were expressed as standard deviation scores (SDS) according to the Finnish standards, and postnatal weights as percentage deviations from the mean weight for height and sex.

See end of article for authors' affiliations

Correspondence to:
Dr M Lipsanen-Nyman,
The Hospital for Children
and Adolescents,
University of Helsinki,
00029 HYKS, Finland;
marita.lipsanen@hus.fi

Mulibrey nanism (*muscle-liver-brain-eye* nanism, MUL; OMIM #253250) is an autosomal recessive disorder with severe growth failure and multiple organ manifestations first described in the early 1970s.^{1,2} Today we know of some 110 patients, 85 of them from Finland. Sporadic cases have been reported from various ethnic groups all over the world.^{3–12}

MUL is caused by mutations in the *TRIM37* gene on chromosome 17q22–q23.¹³ Five different mutations have been reported in patients with MUL. Two of them are Finnish, the Finn major (c.493–2A→G) and the Finn minor mutation (c.2212delG). The others are Czech (c.838–842delACTTT), American (c.1346–1347insA)¹³

Abbreviations: SDS, standard deviation score; SGA, small for gestational age; SRS, Silver-Russell syndrome

RESULTS

The clinical data on the 85 Finnish patients with MUL were systematically analysed from birth to time of the diagnosis. The age at the diagnosis varied from 0.02 to 52 years (median 2.1 years). A third of them were younger than 1 year and two thirds were younger than 5 years.

Pregnancy and delivery

Most of the pregnancies were uneventful. Complications included pre-eclampsia (three cases), anti-Rhesus immunisation (a pair of siblings), gestational diabetes (one), and varicella zoster infection (one). Nineteen of the pregnancies (23%) had been monitored because of poor fetal growth. Fifteen mothers (18%) had had miscarriages in previous pregnancies. Length of gestation varied from 32 to 42 weeks (median 39 weeks); 90% of the children were born at full term. Labour was uncomplicated in all but three cases, in which an urgent caesarean section was performed because of threatened asphyxia. Apgar score at 5 minutes was on average 8 (range 2–10).

Newborn period

Of the newborns, 81 (95%) were small for gestational age (SGA), with birth length SDS below –2.0 for gestational age (fig 1). Birth length SDS was on average –3.1 (range –6.4 to 0.7), and mean birth weight SDS was –2.8 (range –4.0 to 0.5). Occipitofrontal head circumference SDS ranged from –0.9 to 0.8 (mean –0.5) indicating macrocephaly relative to length in the majority of children.

Figure 1 Length SDS at birth and at the age of 2.0 years in 85 infants with MUL, 39 boys and 46 girls. The growth failure progressed postnatally in 74% of the patients.

Table 1 Problems in infancy in 85 patients with Mulibrey nanism

Feature	Frequency (%)
Neonatal problems	
Respiratory problems	31
Ventilatory assistance needed	20
Cyanosis while crying	15
Feeding difficulties	30
Nasogastric feeding tube needed	17
Suspicion of hydrocephalus	6
Suspicion of sepsis	6
Cardiac arrhythmia	1
Growth failure	96
Infections	
Upper respiratory infections >4/year	51
Pneumonia	47
Necessitating hospital care	30
Three or more pneumonias	27
Ventilatory assistance needed	25
Intubation needed	14
Middle ear infections >4/year	38
Feeding difficulties	
Vomiting	39
Difficulties in sucking	31
Nasogastric feeding tube needed	31
Delay in switching to solid foods	24
Fatigue during eating	21
Percutaneous gastrostomy needed	6
Muscular hypotonicity	46
Suspicion of hydrocephalus	16
Hypoglycaemia	15
Congestive heart failure	11
Resuscitation during first year of life	11
Due to infection	9
Due to aspiration	1
Due to arrhythmia	1
Death during infancy	5
Due to infection	2.5
Due to congestive heart failure	2.5

The newborn period was relatively normal in most cases. MUL was diagnosed in only one of the patients who had no affected siblings (table 1). Fourteen babies needed supplementary oxygen. Respiratory distress syndrome was diagnosed in three; two of them were born prematurely. Cardiac involvement was evident in only one baby with Wolff-Parkinson-White syndrome causing paroxysmal supraventricular tachycardial attacks. One third of the newborns had serious feeding difficulties; 14 of them needed a nasogastric tube. Twelve babies were hospitalised from 14 to 55 days because of feeding difficulties or pulmonary problems.

Later infancy

The growth failure progressed over the first 2 years of life in 63 patients (74%) with an SDS decrease of more than 1.0 (range –1.0 to –3.5). Catch up growth with a gain in length SDS of more than 1.0 (range 1.1 to 2.9) occurred in five (6%) of the infants. One boy and two girls reached a length SDS above –2.0 at the age of 2.0 years; one girl grew steadily from birth staying at an SDS of –1.4. At the age of 2.0 years, length SDS was on average –4.4 (range 0.1 to –7.8) (fig 1). Weight gain was also poor. Mean relative weight for height at the age of 2.0 years was –21% (range –35 to 3%).

Half of the patients failed to thrive. Feeding difficulties were the most common clinical problem such that one third needed nasogastric feeding and five children needed a percutaneous gastrostomy (table 1). A high frequency of upper respiratory infections and middle ear infections was evident; pneumonias were diagnosed in nearly half of the infants by the age of 2.0 years (table 1). Episodes of respiratory failure induced by an infection occurred in 25% of the infants. Nine infants had to be resuscitated (table 1).

Four and nine patients had congestive heart failure by the age of 1.0 and 2.0 years, respectively; four of them died.

Psychomotor development was normal or slightly delayed in a great majority of the infants. Mild hypotonicity was evident in nearly half of the infants, and a delay in both motor development and speech was noted in nearly one third. Age at the first steps and the first words ranged from 0.8 to 2.6 years (mean 1.2 years) and 0.9 to 3.1 years (mean 1.3 years), respectively. A mildly hydrocephalic skull with frontal bossing and abnormally wide fontanelles evoked suspicion of hydrocephalus in 15% of the infants (table 1).

Findings at the time of diagnosis

Clinical findings

At the time of the diagnosis all but four (96%) of the patients were below length SDS of -2.5. Nearly all the patients were gracile with relative macrocephaly, and thin extremities with proximal relative shortness and narrow shoulder (fig 2). The characteristic triangular face with high, broad forehead and low nasal bridge was present in over 90%, and scaphocephaly with occipitofrontal bossing was seen in over 80% of the patients (table 2, fig 3).

Fifteen patients (18%) had signs of heart disease (table 3). Ten of them met the criteria of congestive heart failure, and four had pericardial constriction necessitating pericardiectomy. One woman had been pericardiectomised at the age of 32 years (12 years before the diagnosis) due to constrictive pericarditis. Eighteen patients (15%) had structural heart anomalies (table 3).

Thirty eight patients (45%) had hepatomegaly and six of them had liver tumours. Wilms' tumour was detected in two patients before MUL was diagnosed. Both patients had non-symptomatic haematuria with a palpable abdominal mass as the only signs. Renal and genital anomalies were observed in 18% and 9% of the patients, respectively (table 3).

A peculiar voice characterised by high pitch and slight coarseness was noted in nearly all of the prepubertal patients. Characteristic ocular findings¹⁶ were yellow dots in the midperiphery of ocular fundi, seen in 80% of the patients. Additional ocular findings were retinal hypopigmentation and pigment dispersion with clusters of pigment in the

Table 2 Dysmorphic features of appearance at the time of diagnosis in 85 patients with Mulibrey nanism

Feature	Frequency(%)
Head	
Characteristic face: triangular face, high and broad forehead; low nasal bridge and telecanthus	90
Scaphocephaly	81
Hypoplastic tongue	80
Low set located posteriorly rotated ears	54
Dental crowding	50
High hairline	45
Wide fontanelles and sutures in infancy	37
Abnormally wide metopic suture	31
Cleft palate	2
Body	
Thin extremities	99
Accentuated lumbar lordosis	96
General gracility	95
Narrow shoulders	94
Small bell shaped thoracic cage	94
Barrell-like trunk	92
Cutaneous naevi flammei	65
Hypoplastic buttocks	52
Constitution	
Relative proximal shortness of limbs	90
Large head relative to stature	81
Large hands and feet relative to stature	67
Skeletal asymmetry	15

retina. Two thirds of the patients had cutaneous naevi flammei, most commonly in the lower limbs (80%).

Radiological findings

Slender long bones with thick cortex and narrow medullary channel (fig 4) and a low, shallow (J shaped) sella turcica (fig 5) were the characteristic radiological findings present in nearly all patients (table 4). More than half of the patients had true orbital hypertelorism. The orbital fossae were slightly upward slanting with laterally rotated axis (fig 5). Fibrous dysplasia was present in 15% of the patients, mostly in the lower limbs (fig 4). Six patients had fibrous dysplasia in more than two locations (range 2 to 4). A slight asymmetry

Figure 2 The characteristic craniofacial features; triangular face, low nasal bridge, high and broad forehead, and scaphocephaly with occipitofrontal bossing.

Figure 3 The characteristic appearance; triangular face, relative macrocephaly, general gracility, small bell shaped thoracic cage, and thin and proximally short limbs.

of extremities was noted in 17 patients (20%), which in two thirds was due to shortening by fibrous dysplasia. The thoracic cage was small and bell shaped with unusually thin ribs in nearly all patients (table 4, fig 6). Twelve patients had an enlarged heart on chest radiography.

Laboratory findings

Serum levels of the aminotransferases were slightly elevated in nearly half of the patients, AST up to 110 U/l (mean 61 U/l) and ALT up to 193 U/l (mean 41 U/l). Blood haemoglobin, white cells and platelets, glucose, gas analysis, and serum concentrations of electrolytes and creatinine were within the normal limits in the majority of patients. No other laboratory parameters were commonly abnormal.

DISCUSSION

In this work, we analysed retrospectively the clinical characteristics of patients with MUL in all 85 known Finnish patients at the time of diagnosis. At least 79 were homozygous for the Finn major mutation of the *TRIM37* gene. The results confirm that MUL is a distinct but variable entity. The most consistent findings were intrauterine onset growth failure and characteristic craniofacial features. Organ manifestations varied considerably in early childhood. In seven of the families, there was an affected sibling. In five of

Table 3 Organ manifestations at the time of diagnosis in 85 patients with Mulibrey nanism

Feature	Findings in age groups			Frequency (%)
	<1 year (n = 29)	1–5 years (n = 29)	>5 years (n = 27)	
Heart				
Signs of heart disease	6	4	5	18
Cardiomegaly	4	2	6	14
Dyspnoea	4	1	5	12
Prominent veins on upper body	3	1	5	11
Cardiac anomaly	6	2	4	15
ASD	3	1	2	8
VSD	1	1	2	5
Open ductus arteriosus	2	0	0	3
Heart failure (CHF)	4	1	5	12
Pericardial constriction	2	1	2	6
Liver				
Hepatomegaly	16	9	13	45
Hepatosplenomegaly	4	1	4	11
Ascites	3	0	6	11
Liver tumours	2	2	2	9
Urogenital				
Renal anomaly	4	4	6	18
Hydronephrosis	2	0	3	6
Abnormally located kidney	1	1	2	5
Hypoplastic kidneys	1	2	1	5
Horseshoe kidney	1	1	0	2
Male genital anomaly*				6
Cryptorchidism	1/13	3/15	1/11	6
Female genital anomaly†				2
Hyperplastic labiae	0/16	1/14	0/16	1
Prominent clitoris	0/16	1/14	1/16	2
Wilms' tumour	0	1	1	3
Benign renal neoplasia	1	0	1	3
Nervous system				
Yellowish dots in the ocular fundi	20	17	24	79
Muscular hypotonicity	23	19	15	68
Large cerebral ventricles and basal cisterns	16	13	8	44
Slow speech development	7	9	5	30
Slow motor development	5	9	6	29
Skin				
Cutaneous naevi flammei	16	20	19	65

*Males (n = 39); †females (n = 46)

these, the clinical findings were quite similar in the siblings, but in two families the phenotype showed great variation.

The clinical features have been previously reported.^{1 2 10 16 17} These reports, however, were based on small numbers of genetically unconfirmed patients. In our present series we verified the *TRIM37* mutations and concentrated on the phenotype in infancy and at the time of diagnosis.

The clinical diagnosis of MUL is a challenge during the first months of life. Infants with intrauterine growth failure are a heterogeneous group, and the facial features of patients with MUL are not unique in this group. In addition, relative macrocephaly with wide fontanelles might give a false impression of prematurity or hydrocephalus. However, the pre- and post-natal growth characteristics narrow the group in which MUL should be looked for. Generally, infants with MUL are both abnormally short and light for length. Additionally, they not only fail to catch up in postnatal growth, but their growth failure progresses. Of all newborns, 5% are born SGA, but only 1.5% are both short and light for length.¹⁸ Further, most (>70%) healthy infants born SGA show a good catch up growth during the first few months of life.^{18 19} Consequently, it is in the small subgroup of children born SGA and lacking postnatal catch up growth that the possibility of MUL should be considered.

Figure 4 The characteristic x ray findings: slender long bones with thick cortex and narrow medullary channel (big arrow). Fibrous dysplasia in the middle third of left tibia (small arrow).

Silver-Russell syndrome (SRS) is the other dysmorphic growth disorder characterised by severe intrauterine growth failure with absence of postnatal catch up growth. The fact that patients with MUL and SRS both are gracile with similar facial dysmorphism makes SRS the most important differential diagnosis. In early infancy, feeding difficulties occur in both MUL and SRS. These two conditions, however, develop their own distinct characteristics. Clinodactyly, small face with marked triangularity, micrognathia, downturned mouth corners, and skeletal asymmetry with hemihypertrophy are

Table 4 Radiological findings in 85 patients with Mulibrey nanism

Feature	Frequency(%)
Head	
Occipitofrontal bossing	90
Low and shallow (J shaped) sella turcica	89
Laterally rotated orbital fossae	80
Small hypoplastic face	71
Orbital hypertelorism	64
Large cerebral ventricles and cisterns	43
Body	
Accentuated lumbar lordosis	96
Bell shaped thorax with unusually thin ribs	94
Extremities	
Slender long bones	93
Fibrous dysplasia of long bone	25

characteristics of SRS.^{20–22} Hepatomegaly, heart failure due to pericardial constriction or cardiomyopathy, yellow dots in ocular fundi, cortical thickening, and fibrous dysplasia of long bone do not occur in SRS. SRS, however, is considerably variable both clinically²¹ and genetically.²³ A mild phenotype, for example, is observed in SRS patients with maternal uniparental disomy of chromosome 7.²² Furthermore, atypically mild cases with MUL have been diagnosed in three Finnish infants since the analysis of *TRIM37* became available.

The *TRIM37* protein is localised to peroxisomes, but its function is unknown. It is expressed in several tissues.¹⁴ Thus, it is no surprise that MUL shares features with other peroxisomal disorders. These include growth failure, facial dysmorphism with midface hypoplasia, retinal pigmentary changes, skeletal dysplasia, skin changes, cardiac involvement, muscular hypotonicity, and hepatomegaly. In particular, Refsum's disease, with its cardiac manifestations such as cardiomyopathy leading to congestive heart failure, resembles many of the features of MUL.²⁴ Lack of major neurological manifestations and mental retardation are the most notable differences between Mulibrey nanism and the known peroxisomal disorders. The only neurological dysfunctions occurring in MUL are mild muscular hypotonicity and slight delay in motor and speech development.

Constrictive pericarditis²⁵ with restrictive cardiomyopathy, when present, dominates the clinical state as well as the prognosis.²⁶ However, only 12% of our patients had congestive heart failure at the time of diagnosis (median 2.1 years) and even half of the adult patients were free of major heart problem.²⁶ In contrast, almost all patients

Figure 5 A characteristic cranium with high and broad forehead, small face, orbital hypertelorism, and scaphocephaly with occipitofrontal bossing and J shaped sella turcica (large arrow). Note the characteristic slightly upward slanting orbital fossae with the laterally rotated axis (small arrow).

Figure 6 The small bell shaped thoracic cage with thin ribs (arrow). Note the characteristically rounded heart shadow frequently seen in children with MUL.

reported from outside Finland were notably compromised by the heart disease. Presumably, while MUL is relatively well known to Finnish paediatricians, it is elsewhere mostly recognised by its characteristic heart disease. As the heart involvement is critical for the prognosis, its early diagnosis is of major importance.

Hepatomegaly was obvious in half of the patients at the time of the diagnosis. Histopathological studies showed chronic passive congestion, indicating that the liver enlargement is an early clinical sign of the heart disease. At the time of the diagnosis, 10% of the patients had liver tumours as detected by radiological examinations or autopsy. The tumours differed in size and were often multifocal. Histopathological analysis of the tumour samples revealed hamartomas with fibrosis and lipid degeneration. To reveal these lesions, abdominal ultrasonography is regularly performed, and if suspicion of liver tumours arise, MRI is indicated. Beside liver tumours, two of the patients had Wilms' tumour as published previously for one Finnish and one non-Finnish patient.^{6 11} The biological basis of the tumour development remains to be solved.

Feeding difficulties are a major clinical problem during infancy. In general, swallowing is poorly coordinated in infants born prematurely or SGA and the degree of dysfunction is inversely related to the degree of immaturity and growth failure.^{27 28} The oral anatomy of mature infants are particularly well suited for eating by sucking, with the tongue being relatively large, filling the oral cavity.^{27 29} Infants with MUL, however, have a hypoplastic and anteriorly triangular shaped tongue. This is evident in nearly 70% of these infants. The craniofacial hypoplasia, maturational delay,¹⁷ and muscular hypotonicity all probably contribute to the feeding difficulty. Early recognition and management are important because dysphagia poses a threat to the child's respiratory function and nutrition, and may also contribute to the failure of catch up growth.

Patients with MUL are prone for respiratory tract infections and have an exceptionally high risk for pneumonia. No immunological defects have been demonstrated in MUL and the basis of this susceptibility is not known. Possibly, the pneumonia may result from aspiration. Interestingly, infections quite easily lead to respiratory failure, suggesting that the ability to cope with the stress of an infection is subnormal. In our study, two patients

Table 5 Diagnostic signs and their prevalence in 85 patients with Mulibrey nanism (46 females and 39 males) For the diagnosis, three major signs with one minor sign are required, or two major signs with three minor signs

Signs	Frequency(%)
Major signs	
Growth failure (A or B or C)	
A) small for gestational age (SGA)	95
lacking catch up growth	
B) height in children 2.5 SDS below	94
population mean for age	
C) height in adults 3.0 SDS below population	90
mean	
Characteristic radiological findings (A or B)	
A) slender long bones with thick cortex	93
and narrow medullar channels	
B) low and shallow (J-shaped) sella turcica	89
Characteristic craniofacial features	90
Scaphocephaly, triangular face, high and	
broad forehead, low nasal bridge and telecanthus	
Characteristic ocular findings	
Yellowish dots in retinal mid peripheral region	79
Mulibrey nanism in a sibling	17
Minor signs	
Peculiar high pitched voice	96
Hepatomegaly	70
Cutaneous naevi flammei	65
Fibrous dysplasia of long bone	25

died in infancy from an infection. At autopsy, both were found to have adrenal cortical hypoplasia. Subnormal stress tolerance could be due to adrenal hypoplasia with adrenocortical failure.

While growth failure, the craniofacial features, and hepatomegaly are important clinical consequences of MUL, they are also common features of other dysmorphic conditions. Hence, the characteristic ocular and radiological findings, cutaneous naevi flammei, fibrous dysplasia of the long bones, or signs of the Mulibrey heart disease are confirmatory of the MUL diagnosis. Based on our present findings and clinical experience, we propose revised diagnostic criteria for Mulibrey nanism (table 5). Importantly, while none of the clinical features was constant, 99% of our patients presented with at least three of the major and one of the minor signs. One patient had only two major signs, but he had three of the minor signs (table 5).

In conclusion, we have delineated the phenotype and defined the clinical diagnostic criteria in the genotypically homogenous series of all known Finnish patients with Mulibrey nanism. Different *TRIM37* mutations may not lead to exactly the same phenotype. However, it is important that infants born SGA, lacking postnatal catch up growth, and having poor weight gain, hepatomegaly, and characteristic craniofacial features should evoke suspicion of Mulibrey nanism. Although rare, this condition might also underlie congestive heart failure and failure to thrive in absence of a clear characteristic dysmorphology.

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Authors' affiliations

N Karlberg, H Jalanko, J Perheentupa, M Lipsanen-Nyman, The Hospital for Children and Adolescents, Biomedicum Helsinki, University of Helsinki, 00029 HYKS, Finland

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CORRECTION

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DFNA49, a novel locus for autosomal dominant nonsyndromic hearing loss, maps proximal to DFNA7/DFNM1 region on chromosome 1q21-q23 (*J Med Genet* 2003;**40**:832–836).

Owing to a fault in the production process an error was introduced to figure 2 of this paper. The last gene at the bottom of the figure should correspond to CASQ1, and not to ATP1A2, which is mapped just above it. We apologise for this error.