

## SHORT REPORT

## Dominantly inherited proximal myotonic myopathy and leukoencephalopathy in a family with an incidental CLCN1 mutation

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### Abstract

**A two generation family of Greek origin with mild myotonia, predominantly proximal muscle weakness, and cataracts compatible with the syndrome of proximal myotonic myopathy, is reported. In addition, brain MRI showed a diffuse leukoencephalopathy in the proband. Molecular genetic studies showed the R894X mutation in exon 23 of the muscle chloride channel gene in the proband but in only one of her two clinically affected offspring, indicating that it is not the mutation causing disease in this family.**

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Most patients with myotonia can be readily identified as having myotonic dystrophy, myotonia congenita, or paramyotonia congenita on the basis of the clinical characteristics of the condition and the specific gene defects responsible for these conditions are now well recognised. In myotonic dystrophy, the mutation causing the disease is an abnormally expanded CTG trinucleotide repeat sequence on chromosome 19q13.3,<sup>1,2</sup> with a positive correlation between the repeat size and the clinical severity of the disease.<sup>3</sup> The CTG repeat lies within the 3' untranslated region of a protein kinase gene, DMPK, but also disrupts the CpG island of a homeodomain encoding gene DMAHP.<sup>4</sup> Expression of the homeodomain gene is down regulated in correlation with the extent of the triplet repeat expansion<sup>5,6</sup> whereas the effect on DMPK expression remains controversial.<sup>7</sup> Thus the exact pathophysiological mechanism in myotonic dystrophy remains unclear.<sup>7</sup>

In myotonia congenita, multiple mutations have been identified in the human skeletal muscle chloride channel gene (CLCN1) on chromosome 7q32, which encodes the skeletal muscle chloride channel protein CIC-1, some being associated with the dominant (Thomsen) and others with the recessive (Becker) form of myotonia congenita.<sup>8</sup> In paramyotonia congenita, mutations have been found in the gene for the  $\alpha$ -subunit of the muscle sodium channel

on chromosome 17 and mutations in this gene may also cause hyperkalaemic periodic paralysis and myotonia fluctuans.<sup>8</sup>

In 1994 Ricker *et al*<sup>9</sup> described three families with a dominantly inherited condition, characterised by myotonia, proximal muscle weakness, and cataracts, in which there was no abnormal expansion of CTG repeats in the DMPK gene or linkage to the loci for myotonic dystrophy or for the muscle chloride or sodium channel disorders. They suggested that this may represent a new disorder and referred to the condition as proximal myotonic myopathy (PROMM). The same group subsequently reported a further 14 families with this condition, drawing attention to the multisystemic nature of the disorder and its similarity to myotonic dystrophy in some families.<sup>10</sup> There have subsequently been reports of other families<sup>11</sup> and of isolated cases with a similar condition.<sup>12</sup> The phenotypic range of this condition has been further extended by the recent report of three families with dominantly inherited PROMM in which a distinctive form of leukoencephalopathy was also present in some affected people.<sup>13</sup>

We report a further family with dominantly inherited PROMM, associated leukoencephalopathy, and a mutation in the CLCN1 gene which did not segregate with the disease.

### Case reports

#### PATIENT 1-1

The proband was a 49 year old Greek woman who was first seen in April 1994 with a 15 year history of lower limb weakness. This had resulted in difficulty in climbing steps and rising from low chairs or from the squatting position. She denied muscle pain, cramps, or difficulty in relaxing her grip. She had also noted a gradual deterioration in visual acuity. A diagnosis of polymyositis had been made previously but there had been no improvement during a three month course of prednisolone therapy. The patient's mother and three siblings are alive and well and living in Greece. Her husband is from the same region of northern Greece but the families are not known to be related.

Physical examination showed reduced visual acuity in both eyes (right 6/12, left 6/18). There

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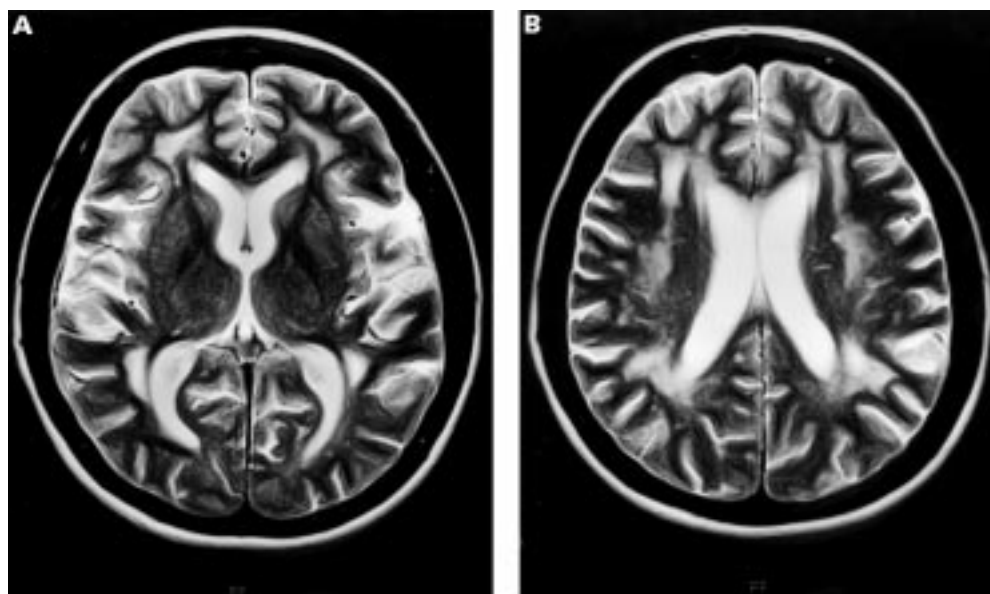
was no evidence of cognitive impairment on clinical examination but psychometric testing showed a reduced verbal IQ of 73 and performance IQ of 76. There was weakness and mild atrophy of the sternomastoid (3+/5) with 4–4+/5 power in the other neck muscles. There was a diffuse essentially symmetric pattern of weakness in the upper limbs (shoulder abduction, elbow extension 4+/5, elbow flexion, wrist and finger flexion and extension 4/5) and lower limbs (hip flexion 4/5, knee extension 4+/5, other groups 5/5) with mild atrophy of the thigh muscles and hypertrophy of the anterior tibial muscles. Percussion myotonia was elicited in the thenar muscles and tongue but there was no eyelid myotonia or myotonia on gripping. She was unable to rise from a squat or to sit up from the lying position. The tendon reflexes were all present with flexor planter responses. Sensory testing was normal.

The serum creatine kinase concentration was increased at 295–583 U/l (normal <200) on various occasions. There were also mild increases in serum  $\gamma$ -glutamyl transferase (56 U/l, normal <40) and alanine transaminase (46 U/l, normal <40). Other biochemical studies were normal. Slit lamp examination showed small punctate lens opacities in both eyes which were not of the typical polychromatic type seen in myotonic dystrophy. Fluorescein angiography showed widespread disruption of the pigment epithelium at the left macula but not the right. Concentric needle EMG showed increased insertional activity and prolonged myotonic discharges in the multiple proximal and distal upper and lower limb muscles examined. Motor unit morphology was normal in most muscles apart from a few short duration, low amplitude motor unit potentials in the biceps brachii. Motor and sensory nerve conduction studies were normal.

An open muscle biopsy taken from the left vastus lateralis showed non-specific chronic myopathic changes on light microscopy. There

was a wide variation in fibre size with numerous hypertrophic fibres measuring 100–125  $\mu$  in diameter and atrophic fibres measuring 20  $\mu$ , some of which were angulated. Histochemical stains demonstrated that the hypertrophic fibres included both fibre types, type 1 fibre predominance and atrophic type 2 fibres. On Quantimet analysis the ratio of type 1 to type 2 fibres was 80%:20% and the mean fibre size was 85  $\mu$ . Other light microscopical features included 28% central nucleation and focal fibre splitting. Central nuclei were particularly prominent in the larger fibres, in which up to 20 such nuclei could be found in cross sections. In those fibres with central nuclei, the average number was eight. In longitudinal sections short chains of four to eight internal nuclei were found. No inflammation, necrosis, or vasculitis was noted. The neural cell adhesion marker for regenerating fibres was negative. Mitochondrial stains—namely, the modified Gomori, NADH, succinate dehydrogenase and cytochrome c oxidase—gave normal results. Results from other stains, including myophosphorylase, phosphofructokinase A and B, adenylate deaminase, non-specific esterase, acid and alkaline phosphatases, periodic acid Schiff, and oil red O were within normal limits. Immunoperoxidase stains for dystrophin, adhalin ( $\alpha$ -sarcoglycan),  $\beta$ -dystroglycan, and merosin all showed complete well defined sarcolemmal labelling of normal intensity in all fibres. Spectrin was used to monitor sarcolemmal integrity. Electron microscopy showed retention of the myofibrillar architecture within most of the muscle fibres and no structural abnormalities in mitochondria.

Brain MRI showed mild prominence of the cortical sulci and ventricles and pronounced symmetric multifocal areas of hyperintensity in the periventricular and subcortical white matter of the cerebral hemispheres (figure). The white matter changes extended into the peri-



Brain MRI of patient 1–1. Axial dual echo T2 weighted images, showing mild cerebral atrophy and pronounced symmetric, multifocal areas of hyperintensity in the periventricular and subcortical white matter of both cerebral hemispheres.

atrial white matter regions of both temporal lobes (figure A). The grey matter and posterior fossa white matter were normal.

#### PATIENT 2-1

This 28 year old woman, who is the daughter of the propositus, admitted to occasional difficulty in relaxing her grip but had not been aware of any other muscular problems, or visual or other symptoms. On examination her visual acuity was normal and there was no evidence of cognitive impairment. There was 4/5 weakness of the sternomastoid muscles, which were not atrophic. There was a diffuse but predominantly proximal and symmetric pattern of weakness in the upper limbs (shoulder groups 4/5, elbow extension 4/5, flexion 4+/5, wrist and finger flexion, and finger extension 4/5). She had large calves and thighs with 4+/5 weakness of hip flexion and normal power in other muscle groups in the lower limbs. She was able to sit up from the lying position and to rise from a squat, but had difficulty in doing this repetitively. There was no grip or percussion myotonia of the hands or tongue or eyelid myotonia.

Needle EMG showed a pronounced increase in insertional activity with myotonic discharges and trains of positive waves in the deltoid, biceps, EDC, vastus lateralis, and anterior tibial muscles and increased numbers of low amplitude, short duration motor units in the last three muscles. Muscle biopsy was not performed. Brain MRI was normal.

#### PATIENT 2-2

This 17 year old man, the son of the propositus, had not been aware of muscle weakness, pain, or cramps, but had noted difficulty in relaxing his grip. On examination he was strongly built with large thighs and calves. There was mild myotonia on hand gripping, which improved with repetition, but no eyelid myotonia or percussion myotonia in the hands or tongue. There was no weakness or atrophy of the sternomastoid muscles. In the upper limbs there was mild symmetric weakness of internal and external shoulder rotation (4+/5 and 4/5), elbow extension (4+/5), and finger extension (4/5). There was no weakness of the trunk muscles or of any lower limb muscle groups. He was able to rise from a squat and to sit up from the lying position without difficulty. The tendon reflexes were normal and the planter responses were flexor. Visual acuity was normal.

Needle EMG showed increased insertional activity, including scattered myotonic discharges and high frequency repetitive discharges, and low amplitude short duration myopathic potentials in the biceps, forearm extensor, and anterior tibial muscles. Muscle biopsy was not performed. Brain MRI was normal.

#### MOLECULAR ANALYSIS

##### *Myotonic dystrophy region*

Molecular analysis for the myotonic dystrophy triplet repeat<sup>1,2</sup> did not identify an abnormal allelic expansion. The proband had two normal

sized alleles. Results showed that the affected offspring of the proband had inherited the same allele from their affected mother. Thus the disease in this family could be associated with a different mutation in this region.

##### *Sodium channel gene (SCN4A) region*

Linkage analysis to the skeletal muscle sodium channel gene *SCN4A* on chromosome 17 using primers for the two described microsatellites<sup>14</sup> could not rule out linkage to this locus, because, as with the myotonic dystrophy locus, both affected children inherited the same allele from their affected mother.

##### *Chloride channel (CLCN1) region*

Analysis of the *CLCN1* gene in the propositus disclosed a single strand conformation polymorphism in exon 23. Sequencing the polymorphic fragment identified the known R894X mutation.<sup>15</sup> This mutation has been stated to behave as a recessive mutation in some families, with clinically unaffected people carrying the mutation, and as a dominant mutation in other families. It gives results between those of definite dominant and definite recessive mutations when expressed in *Xenopus oocytes*.<sup>15</sup> The same mutation was identified in the affected son of the propositus but not, as determined by SSCP analysis, in two blood samples drawn on separate occasions from the affected daughter (2-1). Analysis of the inheritance of the T cell-receptor  $\beta$  (*TCRB*) microsatellite, which shows linkage to myotonia congenita,<sup>16</sup> supported the results of the *CLCN1* analysis, and makes linkage of the disease in this family to the chloride channel gene region unlikely. Therefore, this mutation does not segregate with the disease in the family.

In addition to the myotonic dystrophy CTG repeat, the two *SCN4A* microsatellites, and the *TCRB* microsatellite, nine other microsatellite markers (the spinocerebellar ataxia one *SCA1*<sup>17</sup> and three *SCA3*<sup>18</sup> and dentatorubral pallidol- uysian atrophy *DRPLA*<sup>19</sup> triplet repeats; the *D5S125*,<sup>20</sup> *D5S127*,<sup>21</sup> *JK53CA*,<sup>20</sup> *EF13/14*,<sup>20</sup> microsatellites from the spinal muscular atrophy region on chromosome 5, and the intron 45 and 49 microsatellites within the dystrophin gene<sup>22</sup>) were tested on the family. There was no evidence of sample errors.

#### Discussion

Since the first reports,<sup>9,23</sup> at least 30 families with PROMM have been reported.<sup>24</sup> Many of these have been from Germany and others have been from the United States, Italy,<sup>11</sup> and Spain.<sup>25</sup> The core phenotypic features comprise mild myotonia which may fluctuate, a proximal pattern of weakness particularly in the lower limbs, which may also vary in severity, and cataracts, which in some patients are indistinguishable from those found in myotonic dystrophy.<sup>24</sup> Other less constant features include muscle pain and stiffness, calf muscle hypertrophy, cardiac conduction defects, mild hypogonadism, and leukoencephalopathy which has recently been reported in three German families.<sup>13</sup>

The clinical picture in the present cases was considered to be compatible with PROMM. The myotonia was mild, being detected on EMG examination in all three cases but in only two cases on clinical examination and was asymptomatic in the propositus. There was a proximal pattern of weakness in the lower limbs, with severe weakness of the trunk muscles in the propositus and a more diffuse pattern of weakness in the upper limbs. Hypertrophy of the calf and thigh muscles was also a feature. EMG and muscle biopsy confirmed the myopathic nature of the disorder and did not show any other specific features.

Involvement of the CNS was not mentioned in the early reports of PROMM apart from reference to mental retardation in one patient in the families reported by Ricker *et al.*<sup>9</sup> The first report of cerebral MRI findings was that of Meola *et al.*<sup>11</sup> Of four affected cases in their family, three had normal MRI whereas the fourth, a 71 year old man, was stated to have multiple ischaemic lesions which were considered to be unrelated. In the recent report of three German families<sup>13</sup> six affected members from three different families were found to have diffuse involvement of the white matter of both cerebral hemispheres with pronounced hyperintensity on T2 weighted images in four cases. Possible clinical correlates included stroke-like episodes, seizures, hypersomnia, and parkinsonism but cognitive function was not formally assessed in affected patients. In the present family, a similar pattern of leukoencephalopathy was found in the oldest patient (the propositus), who had a low IQ, but not in her two affected children. As it seems unlikely that cerebral MRI was performed in any of the early PROMM families reported in the medical literature, it is possible that involvement of cerebral white matter is a more common feature of this multisystemic disorder than previously appreciated. The table shows that all six affected cases with white matter changes in the German families were over 33 years of age and all had cataracts, whereas these changes were absent in the two younger cases in the present family. It is possible, therefore, that both the cataracts and leukoencephalopathy in these families are age related phenomena.

The possibility of a mitochondrial encephalomyopathy and of merosin deficiency, both of which may be associated with cerebral white matter disease in adult life, was considered in the present family but was excluded on the basis of the histological and immunohistochemical findings in muscle from the propo-

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tus. It is of interest that changes in cerebral white matter have also been reported in myotonic dystrophy<sup>26</sup> but are not usually as extensive or as symmetric as in the PROMM families.

The nature of the genetic defect in PROMM remains unknown and awaits the identification of further candidate genes and linkage studies in informative families. It is of interest that in the present family a coincidental R894X mutation in exon 23 of the CLCN1 gene was found in the propositus and was initially suspected of being the disease causing mutation. However, when the offspring were tested, both of whom were clinically affected, the mutation was found in one but not in the other, indicating that the mutation does not segregate with the disease in this family. If, as seems likely, the leukoencephalopathy in the propositus is part of the disease phenotype, a search for candidate genes should involve those which are expressed both in skeletal muscle and cerebral white matter. This family is too small on its own to allow determination of linkage of this new disease, but could be used in conjunction with other such families<sup>13</sup> to localise the gene(s).

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Comparison of clinical features in the present cases and previous cases of PROMM with leukoencephalopathy reported by Hund *et al.*<sup>13</sup>

Clinical features	Present cases			Previous cases (n=6) with leukoencephalopathy
	1-1	2-1	2-2	
Age (y)	49	28	17	33-62
Age at onset	34	—	—	3-6th decades
Weakness	Moderate	Mild	Mild	Mild to severe
Muscular hypertrophy	Yes	Yes	Yes	Not reported
Myotonia (clinical)	Mild	Mild	Mild	Mild
Cataracts	Yes	No	No	Yes
White matter changes	Yes	No	No	Yes
IQ	76	NT	NT	NT

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## HISTORICAL NOTE *continued*

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In the first book the poem points to the latent, incubation period between acts of venerie, and the onset of the primary stage characterised by the genital chancre. Fracastoro observes the lessening of symptoms with the passage of time. In the second book he describes the infective nature of the semen: *seminaria contagiosum*, which logically informs his advice on prevention. Treatment with mercurials, and with guaiac obtained from the sacred wood of the American Indians is included in his consideration of a variety of regimens.

The source of the name syphilis is disputed; it has been suggested that it is a corrupt mediæval form of Sipylus, the son of Niobe (so called after a mountain) in Ovid.<sup>3</sup> Niobe was in Greek legend, the daughter of Tantalus, supposed to have been changed into stone while weeping for her children. The alleged origins of syphilis were reflected in its many other names: the Spanish pockes; the Neapolitan itch; morbus Gallicus, the French disease; and pockis (pocks or pox). Pock-royal was the satirical name for a pustule of the great pox (syphilis) as opposed to the small pox. The association with illicit intercourse and the notion of sin was well described in 1662 by W Gurnall: “What a beauty Man was, till he was pock-broken (if I may say so) by sin.”<sup>4</sup> Pockwood was the wood of a tree of the genus *Guaiacum*, in use for the cure of syphilis in the 16th century.

Many euphemisms developed to conceal the sinful rewards of venerie. It is still referred to as “Lues” from *lues* the plague and *Lues venerea* (syphilis). Spirochaetes, twisted, coiled organisms were described in 1876, being found in Weil’s disease, relapsing fever, and in syphilis. The more specific name *treponema* was coined in German by F Schaudinn in 1905,<sup>5</sup> from the word for thread. The specific disease was caused by *Treponema pallidum* (*Spirochaete pallida*) and communicated by sexual connection

or accidental contact (acquired form) or by infection of the child in utero (congenital form).

Three stages of the disease were distinguished, primary, secondary, and tertiary syphilis; the first characterised by chancre in the part infected, the second by affections of the skin and mucous membranes, the third involving the aortic valve, bones, muscles, and brain. Diagnosis remained difficult for it is a multisystem disease, “the great mimicker.” August Paul Wassermann (1866–1925) devised a test for syphilis in 1906, in which antibodies to the organism were detected by a complement fixation test. John Kolmer (1886–1962), an American pathologist, modified the test using beef heart cardioliipin as the antigen. Many more “specific tests” evolved.

During the first half of the 19th century, the authorities on the treatment of syphilis by mercury compounds were divided into mercurialists and non-mercurialists. Iodopin was introduced at the turn of the 20th century. By 1910 Arsphenamine (Salvarsan) was used by Paul Ehrlich for use in syphilis and yaws.<sup>6</sup> In the pre-penicillin era, Julius Wagner Ritter von Jauregg (1857–1940) introduced malaria-therapy in 1918.

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