An expansion in the ZNF9 gene causes PROMM in a previously described family with an incidental CLCN1 mutation

In 1997 Mastaglia *et al* described a two generation family of Macedonian origin with phenotypic features of PROMM and an incidental CLCN1 mutation.[1] Affected individuals had mild myotonia, predominantly proximal muscle weakness, and cataracts, compatible with a diagnosis of proximal myotonic myopathy (PROMM). Molecular genetic studies showed that the proposita did not have the chromosome 19 myotonic dystrophy (DM1) CTG expansion, but did have the R894X mutation in exon 23 of the muscle chloride channel gene (CLCN1). However she had only passed the R894X mutation to one of her two affected offspring. Thus the CLCN1 gene mutation did not segregate with the disease. We can now confirm that a definite genetic cause for PROMM has been identified in this family.

In 1998 a locus for a second type of myotonic dystrophy (DM2 or PROMM) was mapped to chromosome 3q21.[2] In 2001 it was shown that DM2/PROMM was caused by a CCTG repeat expansion located in intron 1 of the zinc finger protein 9 (ZNF9) gene.[3] Inheritance of the microsatellite markers D3S1589, D3S3606, D3S1541, and D3S3684—flanking the DM2 locus—was compatible with DM2 being the disease in the family described by Mastaglia *et al*. The DM2 repeat expansion is difficult to demonstrate because of its very large size, but the presence of an expansion can be inferred by the non-inheritance of the normal sized allele from the affected parent, as in other expansions. The proposita of the family reported by Mastaglia *et al* shows only one normal sized allele for the tetranucleotide repeat region of the ZNF9 gene, and by inference she has an expanded allele. This may occur through the proposita either being homozygous for the same sized normal allele or through having one normal sized allele and one expanded allele. Her two affected offspring also only have one normal sized allele, and in both of them this is different in size from the normal sized allele in their mother. Thus they have not inherited a normal sized allele from their mother, but have inherited different normal sized paternal alleles. This family is thus suffering from DM2/PROMM.

The proband was 49 years old when initially described, and had been symptomatic for 15 years. In the six years since that description, there has been minimal worsening of symptoms, with the patient reporting a little more difficulty in climbing stairs and rising from low chairs. However, there was no deterioration in strength or increased myotonia on examination. Repeat psychometric testing has not shown further reduction in either verbal or performance IQ (74 and 75, respectively), but she had become significantly depressed, requiring treatment. A second brain magnetic resonance image (MRI), five years after the initial one, showed some increase in the extent of the periventricular white matter disease, but this was still considered mild and there was no atrophy of the parenchyma. Some subtle signal abnormality was seen for the first time in the pons.

The proband's offspring remain clinically asymptomatic with respect to cataracts, muscle problems, and cognition, at the ages of 34 and 24 years. In the initial description both were shown to have myotonic discharges on electromyography, and this has not been repeated. However, they have now each had brain MRI, in both cases reported as being within normal limits. The younger sibling has the incidental CLCN1 mutation. The R894X mutation has been described in association with the autosomal recessive form of myotonia congenita, and so—without a mutation on the other CLCN1 allele—would not be expected to cause a disease phenotype.[4] However, some CLCN1 mutations can cause either a recessive or a dominant mode of transmission depending on supplemental genetic factors.[4] Thus the coexistence of the ZNF9 and the CLCN1 mutations may conceivably cause a more severe phenotype. At the present time, neither sibling has any abnormality; thus this theory cannot be proven or disproven.

As well as confirming the genetic basis of the disease in this family, this report also confirms PROMM as being a very slowly progressive and relatively benign disease. Although the MRI changes in other neurodegenerative diseases such as CADASIL can predate the clinical signs by more than 10 years (personal observation), this would not appear to be the case in PROMM. Although there has been a recent report of a patient with PROMM and schizophrenia who was intolerant of neuroleptics and susceptible to malignant hyperthermia,[5] the proband has had several general anaesthetics without mishap. However, she had developed a psychiatric disorder in the form of depression, which is the third report of psychiatric dysfunction in PROMM patients.

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The validity of using the mini mental state examination in NICE dementia guidelines

The mini mental state examination (MMSE) is widely used as a rapid means of quantifying cognitive function.[1] The National Institute for Clinical Excellence (NICE) guidelines concerning the use of cholinesterase inhibitors (CI) in Alzheimer's disease recommend using the MMSE as quantifiable measure to inform decisions regarding initiation and continuation of drug treatment.[2] Our study questions whether poor interrater reliability of the MMSE makes it an inappropriate tool for monitoring drug response.

A postal survey evaluating the MMSE section termed ''attention and calculation'' was conducted among all consultant neurologists in the UK. The original instructions regarding this section involve asking the patient to count backwards in sevens from 100 for five subtractions, or, if the patient ''cannot or will not perform this task'' to spell ''WORLD'' backwards, scoring the number of letters in the correct order.[1]

Of the 407 questionnaires sent, there were 234 (58%) responses.

The MMSE was used in clinical practice by 91% of respondents, with 51% of respondents describing their use as ''frequent''. Test choice and method of scoring this section of the MMSE are shown in fig 1.

Only 10% of respondents were aware of schemes describing standardised scoring of mistakes when spelling WORLD backwards. Raters were asked to score a sample incorrect response ''DRLOW''. We did not allocate a ''correct'' score for this example since we believe the original guidance on how to score errors[1] is imprecise. Out of a maximum of five points, 51% assigned a score of three and 25% a score of one. Other scores included two respondents assigning a score of five. When scoring ''93–85–78–71–64'', 59% assigned a score of four points and 23% a score of one.

This survey of consultant neurologists confirmed substantial variability in the use and scoring of the serial sevens/WORLD backwards section of the MMSE. This interrater error leads to a potential score difference of up to four points for this section alone. We focused on this section of the MMSE alone to ensure brevity of the survey, as we perceived that the scoring method assigned to these questions is particularly dependant on the rater's interpretation. Rogers *et al* found the mean improvement in MMSE score after 12 weeks of treatment with CI to be 1.3 points.[3] NICE guidelines for CI prescription in Alzheimer's disease give specific recommendations to stop these drugs if a patient's score deteriorates when the MMSE is repeated two to four months after commencement, or if the score falls below 12 points. Our results show that typical patterns of scoring the MMSE are too inconsistent to detect such small improvements in cognition and so may lead to inappropriate cessation of CI treatment.

The findings are in keeping with the large interrater variability previously demonstrated among a small group of psychiatrists,[4] suggesting that the results likely to be generalisable to most doctors. Our study's incomplete response rate and finding that only half the respondents use the MMSE frequently introduces sources of selection bias, however, we believe that numbers were large enough to derive meaningful conclusions.

Should NICE use the MMSE as their recommended cognitive rating scale in Alzheimer's disease? Few of the studies showing benefit from CI use in Alzheimer's disease use the MMSE as a primary outcome