

Original articles

Paternal transmission of congenital myotonic dystrophy

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Abstract

The congenital form of myotonic dystrophy is reported to be almost exclusively, if not exclusively, maternally transmitted. We present a case of congenital myotonic dystrophy which was inherited from a mildly affected father. This family illustrates that the congenital form of myotonic dystrophy can occur without intrauterine or other maternal factors related to the disease. The possibility of paternal transmission of the congenital form of myotonic dystrophy could be considered when counselling myotonic dystrophy patients and their families.

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Myotonic dystrophy (DM), an autosomal dominant multisystem disorder, is the most common form of adult muscular dystrophy, with a prevalence of about 1/8000.¹ The severe congenital form of the disease has been recognised for over 30 years.² Major clinical features of congenital DM are reduced fetal movement, hydramnios in later pregnancy, neonatal respiratory distress and feeding problems, facial weakness, hypotonia, congenital talipes, delayed motor development, and mental retardation, with IQs in the range of 40 to 80. After the neonatal period, the patients may have improved muscle strength and respiratory status. The typical findings associated with adult onset DM, such as myotonia and cataracts, may not be present in infancy, but occur later in childhood or adolescence.^{1,3,4}

The DM mutation has been identified as an expanded trinucleotide repeat in a putative protein kinase gene at 19q13.3.⁵ The degree of repeat expansion correlates with the severity and age of onset of the disease and the length of the repeat may increase in successive generations,⁶ therefore providing a basis for the phenomenon of anticipation in myotonic dystrophy.

According to published reports, congenital DM is exclusively or almost exclusively inherited from an affected mother.^{3,4,7-10} The reason for maternal transmission is unclear. It has been suggested^{7,10} that an intrauterine maternal factor may be responsible for the manifestations of

congenital DM in a fetus carrying the gene defect.

We present a case of congenital DM inherited from a mildly affected father. This case illustrates that congenital DM can occur without intrauterine or other maternal factors.

Family report (fig 1)

Family members were examined at The Children's Hospital of Philadelphia and The Hospital of the University of Pennsylvania where blood samples were obtained. Electromyography was performed on the proband (III·2) and his paternal aunt (II·1).

CASE 1

The proband (III·2) was born to a 34 year old woman and a 39 year old man after 36 weeks'

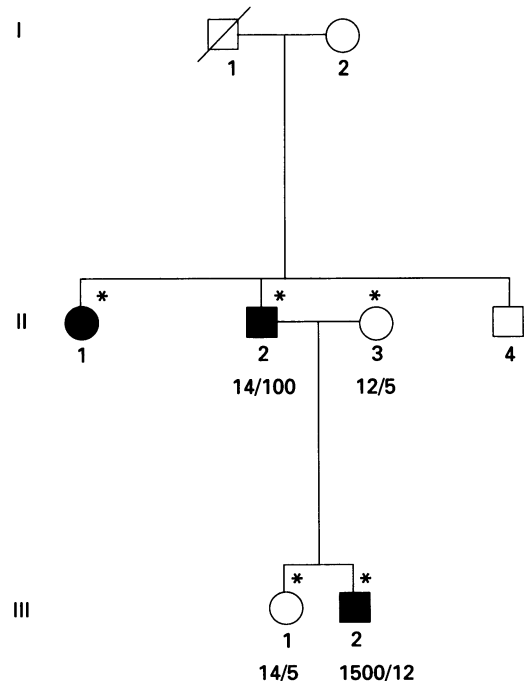


Figure 1 Pedigree of the family where the proband (III·2), father (II·2), and paternal aunt (II·1) have myotonic dystrophy, represented by shaded symbols. Unaffected members are represented by open symbols. The asterisk indicates that the person has been seen by a neurologist at The Children's Hospital of Philadelphia or The Hospital of the University of Pennsylvania. The numbers below the pedigree symbols are the results of molecular analysis of the CTG repeat containing region of the myotonin gene and indicate the number of CTG repeats found on each chromosome.

gestation. The pregnancy was complicated by bleeding at the end of the first trimester and by polyhydramnios. The patient was hypotonic and developed problems breathing at birth. His Apgar scores were 8 at one minute and 8 at five minutes. He was given supplemental oxygen in the delivery room and within one hour was in respiratory distress requiring up to 60% oxygen. Worsening respiratory status led to intubation (by a transport team). He continued to fare poorly, a pneumothorax was discovered, and a chest tube was placed. He required mechanical ventilation for three to four weeks and his five week stay in hospital was complicated by repeated pneumothoraces and feeding difficulty.

His development was delayed. He was first able to hold his head up when prone at 6 to 7 months, sit unsupported at 11 months, crawl at 12 months, walk at 14 months, walk up steps one at a time at 8 years, and with alternating feet at 10 years. Speech difficulties were noted at an early age, and he continues to have a severe communication deficit. Psychometric testing with the Wechsler Intelligence Scale for Children-Revised (WISC-R) showed a full scale IQ of 50 at the age of 11 years. An MRI brain scan showed generalised diffuse cerebral atrophy. Chromosome analysis showed a normal male karyotype. Testing for fragile X yielded a negative study by cytogenetic techniques.

His history is also remarkable for recurrent otitis media and a cholesteatoma, which was removed from the left ear. He has chronic lung disease, with asthma and recurrent pneumonia; he has tight heel cords bilaterally which required surgical release on the left.

Physical examination at the age of 14 showed a head circumference of 56 cm (>98th centile), narrow elongated face, downward slanting palpebral fissures, mild symmetrical ptosis, tent shaped mouth, high arched palate, mild scoliosis, and hyperextensible joints. Neurological examination was remarkable for facial weakness, dysarthria, percussion and grip myotonia, and decreased muscle tone with generalised symmetrical weakness. Electromyography (EMG) showed myopathic motor unit potentials and myotonic discharges characteristic of DM.

CASE 2

The proband's father (II-2) has no definite symptoms of muscle weakness at the age of 53, but he reports some fatigue and decreased exercise tolerance. His general examination is remarkable for cataracts and frontal hair loss. Neurological examination showed mild facial weakness. Neck and extremity muscles had normal strength. No percussion or grip myotonia could be elicited. He was unavailable for EMG testing.

CASE 3

The proband's mother (II-3) is a 48 year old woman with no symptoms of DM or signs of the disease on neurological examination. EMG

of the proximal and distal upper extremity muscles was normal.

CASE 4

The proband's paternal aunt (II-1) is a 54 year old woman with a 10 to 12 year history of drooping eyelids and weakness of the extremities. Her history is also remarkable for cataracts and non-insulin dependent diabetes. Neurological evaluation showed bilateral ptosis, neck and proximal extremity weakness, and percussion myotonia. EMG showed widespread myotonia consistent with the diagnosis of DM.

CASE 5

The proband's sister (III-1) is a 24 year old woman with no symptoms of DM or signs of disease on neurological examination.

OTHER FAMILY HISTORY

By history, the proband's paternal uncle (II-4) is a 43 year old man with no symptoms of DM. The proband's paternal grandfather (I-1) died at the age of 70 from a myocardial infarction and had no history of symptoms of DM. The proband's paternal grandmother (I-2) is an 80 year old woman with a history of cataracts and diabetes.

Molecular analysis of CTG repeat in the myotonin-protein kinase gene

Genomic DNA extracted from peripheral blood cells was digested with *EcoRI*, *BglI*, and *BamHI* and studied by Southern blot hybridisation with a probe directed against the CTG repeat containing region of the myotonin gene, amplification of which has been associated with DM.^{6,11-13} This region was also studied using polymerase chain reaction (PCR) amplification with flanking primers.¹³

Results

Molecular analysis of the CTG repeat containing region of the myotonin gene is shown in fig 2. III-2 had one allele with 12 CTG repeats by PCR analysis and a second allele on Southern blots showing heterodisperse amplification with approximately 1500 to 1600 repeats. II-2 had alleles with 14 and 100 CTG repeats by PCR analysis. II-3 had alleles of five and 12 CTG repeats. III-1 had alleles of five and 14 repeats.

Discussion

Our patient's clinical presentation is typical of congenital DM, and the size of the CTG repeat expansion is within the range reported in other congenital patients. Hunter *et al*¹⁴ observed a trend of earlier age of onset, increasing disease severity, and poorer school performance with increasing CTG repeat size in 109 DM gene carriers from 17 families. The correlation between CTG repeat length and disease severity is not exact, however. Tsilfidis *et al*¹⁵

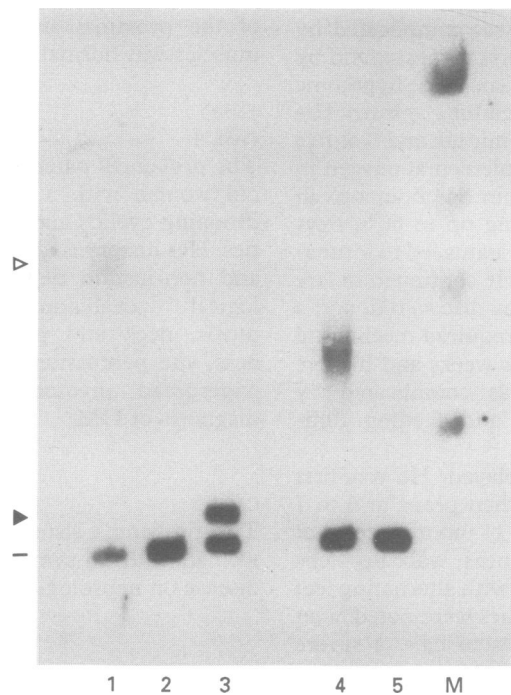


Figure 2 A Southern transfer of *Bgl*I digested genomic DNA was probed with probe PM10M6. Lane 1 = affected proband, lane 2 = proband's mother, lane 3 = proband's father, lane 4 = positive control, lane 5 = negative control, and M = molecular size standards. The germline band at 3.4 kb is marked with a dash, the expanded paternal allele (100 CTG repeats) with a shaded arrowhead, and the proband's heterodisperse expanded allele (1500 CTG repeats) with an open arrowhead.

reported a proportion of severe congenital DM children (4/22) with only modest CTG amplification and some patients with non-congenital disease who have very large CTG repeat lengths. These studies were done with white blood cells, and persons with DM are mosaic with respect to CTG length.¹¹ Tsilfidis *et al*¹⁵ suggest that tissues which have the most effect on the development of congenital DM, such as muscle and brain, may show a better correlation between repeat length and disease severity. Anvert *et al*¹⁶ compared the lengths of CTG repeats in blood and muscle samples from the same affected persons and found somatic heterogeneity with greater repeat length in the muscle samples. Most reported congenital DM children have CTG repeats which are demonstrably larger than those of their respective affected parents. However, Cobo *et al*¹⁷ reported a case where the mother had "classic" features of DM with a CTG repeat band of 7 kb, and her affected son, born with congenital DM, has a CTG band of 4 kb.

Our patient differs from others in published reports in that he inherited the disease from his father. The reason for maternal preponderance

in transmission of congenital DM is unclear, and it is not known why our patient is an exception. Imprinting has been suggested as a factor in this maternal transmission, but a recent study has shown that the DM protein kinase gene is not imprinted in the mouse.¹⁸ It may be that males do not normally pass on the more expanded repeats because of effects on sperm viability. This family and another case recently reported in abstract form¹⁹ illustrate that the congenital form of DM can occur without intrauterine or other maternal factors related to the disease. Our report shows that large expansions can occur with paternal transmission of the disease. The possibility that this could lead to severe congenital onset could be considered when counselling myotonic dystrophy patients and their families.

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