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New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1)

The International Myotonic Dystrophy Consortium (IDMC)*

Myotonic dystrophy (DM; OMIM 160900, also known as dystrophia myotonica, myotonia atrophica and Steinert disease) is an autosomal dominant myotonic myopathy associated with abnormalities of other organs, including eyes, heart, endocrine system, central and peripheral nervous systems, gastrointestinal organs, bone, and skin.¹ The mutation underlying DM is an expansion of an unstable cytosine-thymine-guanine (CTG) trinucleotide repeat in the 3' untranslated region of the *myotonic dystrophy protein kinase (DMPK)* gene in chromosome 19q13.3.²⁻⁴ In 1994, Thornton et al.⁵ described an autosomal dominant disorder similar to DM without CTG repeat expansion at the *DM* locus. Ricker et al.⁶ named this disease "proximal myotonic myopathy" (PROMM; OMIM 600109) because of predominantly proximal muscle weakness without atrophy as opposed to the distal muscle involvement seen in DM. Subsequently, Meola et al.⁷ described a variant of PROMM with unusual myotonic and myopathic features, which they named "proximal myotonic myopathy syndrome," and Udd et al.⁸ described a PROMM-like family with dystrophic features, which they named "proximal myotonic dystrophy" (PDM). Researchers at the University of Minnesota^{9,10} found another multisystemic myotonic disorder that closely resembles DM with distal muscle weakness but no CTG repeat expansion. Because of the close phenotypic resemblance to DM, they called this disease "myotonic dystrophy type 2" (DM2; OMIM 602668). In 1998, Ranum et al.⁹ assigned the *DM2* locus to chromosome 3q in a large kindred. Shortly after that, Ricker et al.¹¹ found that the majority of German PROMM families show linkage to the *DM2* locus. PDM was also mapped to this region (Krahe and Udd, personal communication, 1999). Whether PROMM, PDM, and DM2 represent different phenotypic expressions of a disease caused by the same mutation or if they are allelic disorders remains to be determined. It is also possible that these disorders are caused by mutations in different genes that are closely linked in the

chromosome 3q region.¹² Furthermore, the disease loci in some typical PROMM families¹¹ and other families with multisystemic myotonic disorders have been excluded from both *DM* and *DM2* loci. Because of the genetic and phenotypic heterogeneity in this group of disorders, it became necessary to establish a new nomenclature foreseeing the future discovery of new disease loci and phenotypic variability.

The phenotypic resemblance between DM (mapping to 19q13.3) and PROMM/PDM/DM2 (mapping to 3q21) complicates the diagnosis of these disorders. Consequently, genetic testing must play an important role in making an accurate diagnosis. While genetic testing for diseases linked to the *DM2* locus is currently only possible by linkage analysis (which is not commercially available), DNA testing for the diagnosis of DM has been available since the discovery of the expanded CTG repeat as the genetic mutation in 1992.²⁻⁴ The increasing use of DNA testing for DM generates many questions regarding the indications and interpretations of the test with concerns of potential misuse. For accurate determination of the mutation, standardized methods readily available in molecular genetics laboratories are desirable. Confidentiality of the results and the fate of the DNA samples after the test are also important issues.

At the Second International Myotonic Dystrophy Consortium (IDMC) Conference held on April 21 through 23, 1999 in Research Triangle, NC, 83 DM investigators reached a consensus for a new nomenclature for myotonic dystrophies. The Nomenclature Committee of the Human Genome Organization (HUGO) has approved the new nomenclature. During the Conference, IDMC also discussed the genetic testing issues of DM and developed guidelines.

Consensus for the new nomenclature:

1. All multisystemic myotonic disorders including DM, PROMM, PDM and DM2 are collectively called "myotonic dystrophies."
2. The loci for these diseases will be consecutively

*See the Appendix on page 1220 for a listing of participants of the Second IDMC Conference.

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named as “DM” followed by a number (*DMn*), such as *DM1*, *DM2*, *DM3* . . . , regardless of the clinical phenotype.

3. To accommodate this nomenclature system, the chromosome 19q13.3 locus for DM (OMIM# 160900) is changed from “DM” to “*DM1*.”
4. If a new allelic disease is discovered, it will not be assigned to a new locus; instead, it will be assigned to the previously known locus. The allelic disease will be assigned to a new OMIM number with “#” in front indicating that it is an allelic disease.
5. If diseases previously assigned to one locus turn out to be caused by mutations in two different genes located close to each other, the disease assigned to the locus more recently will be assigned to a new locus using the “*DMn*” system.

Currently, only two loci (*DM1* and *DM2*) have been assigned. The nomenclature does not preclude the use of traditional clinical terms such as “PROMM” and “PDM” for clinical diagnosis. Although the term “myotonic dystrophy” may still be used as a clinical diagnosis of the disease caused by the CTG repeat expansion at the *DM1* locus, the preferred terminology is “myotonic dystrophy type 1” or “*DM1*” which is easily distinguishable from *DM2* and other myotonic dystrophies.

Guidelines for molecular genetic testing for *DM1*

1. *The DM1 mutation.* The mutation in *DM1* is expansion of a CTG repeat motif normally present in the 3′ untranslated region of the *DMPK* gene in chromosome 19q13.3.²⁻⁴ The CTG repeat is highly polymorphic in the general population. Healthy individuals have alleles between 5 and 35 repeats, and within this range the alleles are stably transmitted. When the repeat length exceeds 50 CTGs, the allele becomes unstable and leads to disease. Alleles ranging from 35 to 49 repeats have been mostly ascertained through their symptomatic offspring, which expanded into the ≥ 50-repeat range. Alleles ranging from 35 to 49 repeats are considered “premutation” alleles. These ranges should be used in DNA-based diagnosis of *DM1*.

2. *Genotype-phenotype correlation.* There is a significant inverse correlation between the age at onset and the number of repeats. The disease severity also correlates with the repeat size. Roughly, mildly affected patients have 50 to 150 repeats, classic *DM1* patients 100 to 1000 repeats, and congenital cases can have more than 2000 repeats. However, use of these ranges in predicting age at onset or clinical severity in individual patients can be misleading because of the large overlap between phenotypic classes and the somatic mosaicism of CTG repeat alleles. In *DM1* families, there is an earlier onset of the disease as well as an increase in severity of the clinical symptoms with transmission to successive generations and this genetic anticipation is accompa-

nied by an increase in the number of CTG repeats.^{13,14} The pattern of intergenerational repeat size instability is interdependent on both the sex of the transmitting parent and their repeat size. Although a further increase in repeat length is the usual situation when the repeat is transmitted by either sex, larger average intergenerational increments, leading to very large CTG expansions, were generally found to be more frequent on transmission from females than from males.¹⁵ This explains the predominant maternal transmission of congenital cases. This association of the severest form of *DM1* with maternal transmission is in contrast to the coding CAG expanded polyglutamine repeat diseases where the largest increases in expansion size, and associated severest clinical forms of the disease, occur predominantly upon paternal transmission.¹⁶

3. *Molecular diagnosis of DM1.* Direct analysis of the CTG repeat expansion has sensitivity and specificity, such that the combination of Southern blot and polymerase chain reaction (PCR) can detect all *DM1* mutations without false positives. Southern blot analysis of genomic DNA digested with one of several restriction endonucleases (*EcoRI*, *BamHI*, *NcoI*, *BglI*) is the procedure of choice for the detection of CTG repeats larger than 100. Several probes are available for hybridization: pGB2.6,³ pMDY1,² cDNA25¹⁷ and p5B1.4.¹⁸ Using Southern blot analysis, small expanded alleles often comigrating with the normal allele during agarose gel electrophoresis are difficult to resolve. PCR must be used to identify *DM1* alleles between 5 and 200 repeats usually associated with milder cases. Using synthetic oligonucleotides primers based on the sequences flanking triplet repeat,^{4,13} the unstable region can be easily amplified. If the PCR products are run on 3.5% Metaphor gel along with size standards, the length of the repeat can be accurately determined. The PCR analysis is much faster and cheaper than Southern blot, but unfortunately repeats longer than 500 bp are not reliably amplified by PCR. Therefore, this method is not suitable to make a direct diagnosis of *DM1* in all patients, but may be useful for exclusion. When the expanded allele shows a smear in these assays, the size of the allele with the highest density should be reported. The molecular diagnosis of *DM1* should only be performed in experienced laboratories that are expected to meet rigorous standards of accuracy.

4. *Indications for genetic testing.* The molecular diagnosis of *DM1* can be used for the following purposes:

Confirmatory, or symptomatic testing.

- To confirm the clinical diagnosis: the gene test will increase the physician’s confidence in diagnosing a patient with typical symptoms.
- To clarify an uncertain clinical diagnosis: the gene test will be useful for individuals in whom *DM1* is part of a wider differential diagnosis.

As the correlation between expansion size and symptom severity is not absolute, it is not appropri-

ate to offer a prediction of prognosis based on the expansion size. Because diagnostic gene test results have direct implications for other family members (siblings and children), genetic counseling should be made available to the person who had the gene test and also to any other interested family members.

Asymptomatic, or preclinical testing.

- To determine which progenitor has the DM1 gene mutation; this information is important in genetic counseling and carrier testing to the relevant side of the family.
- To modify the a priori risk of inheriting the DM1 allele.

At present, no useful information can be given about the age at onset or about the kind of symptoms, their severity, or the rate of progression based on the repeat size. Subjects who have asymptomatic testing should always have genetic counseling by a qualified counselor, including pretest counseling to assure that the subject understands the risks and benefits of testing.

Testing of minors.

- Unless there is a medically compelling reason, minors (children under the legal age) should not be tested. This is to ensure that the person tested fully understands the risks and benefits of testing.
- Exceptions might be appropriate in the case of a symptomatic minor for whom confirmatory testing is necessary.

Prenatal testing.

- If a parent has already been diagnosed with DM1, prenatal testing can be used to assess fetal risk.
- If a parent is at 50% risk and asymptomatic, a two step process by which the at-risk parent is tested first and prenatal testing done subsequently (if still necessary) is the best approach.

Prenatal DNA diagnosis should not be considered if the parents would have the child regardless the test result. Because of the overlapping ranges and the uncertainty regarding somatic mosaicism and in utero instability of the expanded CTG repeat, it is not possible to accurately predict whether the fetus will have congenital or adult-onset DM1. Although the prenatal diagnosis is based on a direct detection of the mutation, analysis of DNA from both parents may be required to exclude maternal contamination in the fetal DNA sample and, in some cases, to verify the PCR results.

5. Confidentiality. Maintaining confidentiality of the genetic information of the test subject is the ethical and legal responsibility of the care provider and the testing laboratory. Confidentiality is important for prevention of discrimination against the subject.

6. Property rights of the DNA samples. There is a consensus that the ownership of DNA research samples belongs to the individual from whom the sample was obtained. This consensus has been extended to the samples obtained for DNA diagnoses.¹⁹ For the DNA test of DM1 mutations, we recommend each laboratory develop a detailed consent form specifically addressing questions regarding handling of the DNA sample following the test. These questions include: 1) whether the subject permits the DNA sample to be stored after completion of the test(s) ordered; 2) whether the subject permits the DNA sample to be tested in the future for other diagnostic information without further consent; and 3) under what conditions the DNA sample can be used for research.

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Appendix

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