

MD

Myotonic Dystrophy  
SUPPORT GROUP

Why do we get  
new families  
with Myotonic  
Dystrophy?

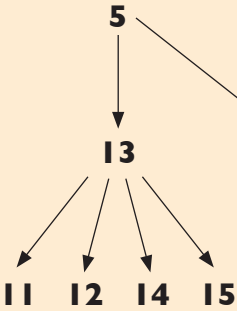
by

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## 5 to 20 mutation

This mutation event probably only occurred once in human evolution in the shared common ancestor of all Myotonic Dystrophy families.



### 5 to 15 repeats

Repeats in this range are not associated with any symptoms and are present at high frequency in the general population. They are genetically very stable when transmitted changing only very rarely. There is essentially zero risk of new Myotonic Dystrophy families arising from individuals with such repeats.

### 20 to 35 repeats

Repeats in this range are not associated with any symptoms and are present at quite high frequency in the general population. They are genetically unstable when transmitted, but increase in length quite slowly. There is definite risk of new Myotonic Dystrophy families arising from individuals with such repeats, but it may take many hundreds of generations.

20

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25

27

30

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35

### 40 to 50 repeats

Repeats in this range are not associated with any symptoms, but are present at only very low frequencies in the general population. They are though genetically unstable when transmitted, increasing in length very rapidly and leading to new Myotonic Dystrophy families within a few generations.

40

45

50

### 60 to 3000 repeats

Repeats in this range are associated directly with Myotonic Dystrophy symptoms. The repeat is genetically very unstable and expands rapidly in successive generations giving rise to the increased severity and decreased age of onset observed in Myotonic Dystrophy families.

80

300

1000

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# Myotonic Dystrophy

Myotonic dystrophy affects a wide range of body systems and varies dramatically in the relative severity of the symptoms and the age at which the first symptoms appear. Some individuals have a very mild form with perhaps no muscle involvement and the development of cataracts in old age as their only symptom. More usual is the development of muscle weakness and stiffness in adult life. Many families with myotonic dystrophy type I though, are not recognised until a severely affected child is born with congenital myotonic dystrophy.

Myotonic dystrophy is an inherited condition being transmitted from one generation to the next. Each individual has two copies of each gene, one inherited from each parent, and passes either one of these to their own children. Only one copy of the defective gene is required to develop myotonic dystrophy, thus all individuals carrying the mutation usually have some symptoms and usually only one parent is affected. Both sexes are equally affected by the

symptoms and the condition can be inherited from parents of either sex, although the most severe congenitally affected individuals usually inherit the condition from their mother.

For some years now we have known the nature of the basic defect at the level of the DNA that results in myotonic dystrophy type I. The genetic material, DNA, that is contained within every cell is comprised of four chemical letters A, C, T and G. These letters form a complex code containing all of the information needed to create a human being. The order, or sequence, of these letters, is very important, but at first glance appears to be mostly random. However, there are regions of the DNA where a simple sequence is repeated a number of times. Myotonic dystrophy type I is associated with one such region where the sequence CTG is repeated several times. The number of copies of the CTG repeat varies within the general population. Everybody has two versions of this CTG repeat (one from each parent), often with differing numbers of

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repeats. The exact number of repeats is usually in the range of from 5 to approximately 40 CTG repeats, with 5, 11, 12, 13 and 14 repeats being very common. People with myotonic dystrophy type 1 have an increased number of repeats from 50 up to many thousands. Individuals with more repeats have a more severe form of the disease and an earlier age of onset. Variation in the number of repeats accounts for much of the wide variation in symptoms associated with myotonic dystrophy type 1. Individuals with 50 to 100 repeats usually have the mild late onset form of the disease. Two hundred to 500 repeats are associated with onset in the third and fourth decade of life, whilst congenitally affected children often have more than 1,000 repeats.

The number of repeats can change when passed from one generation to the next, but this happens relatively rarely in the general population. However, the expansions associated with myotonic dystrophy type 1 are very

unstable and nearly always change when passed from one generation to the next. Unfortunately, the repeat number nearly always increases such that children usually have more repeats and hence are almost always more severely affected than their affected parent. This phenomenon, known as 'anticipation', is very unusual and does not occur in most other genetic diseases.

Anticipation presents us with a problem in understanding the incidence of the condition in the general population. In a family with myotonic dystrophy type I the symptoms get worse from one generation to the next until the point at which no new children with the condition are born. This happens because congenitally affected individuals usually do not themselves have children and many men with the adult form are infertile. Thus, if there were a given number of families with myotonic dystrophy type I, over several generations we would expect the disease to die out. Although this seems to be true in individual families, as far as we can tell this does

The logo consists of the letters 'M' and 'D' in a white, hand-drawn, cursive style. The 'M' is on the left and the 'D' is on the right, with a small gap between them. The background is a solid orange color.

not hold true for the population as a whole in which the incidence of the condition appears to remain constant. Thus, new families with the condition must arise in order to replace those in which the disease gene is lost.

Over the years, many groups throughout the world have worked hard trying to understand how myotonic dystrophy type I is maintained in the population. One of the earliest observations made was that in addition to the large CTG repeat, everybody with myotonic dystrophy type I shares the exact same DNA sequence around the repeat. This strongly suggests that everybody with myotonic dystrophy type I shares a common ancestor at some point in human evolution. The fact that myotonic dystrophy type I is found primarily in people of European and Asian descent and is absent in sub-Saharan Africa indicates that this common ancestor probably lived in one of the populations that was migrating out of Africa approximately 60-100,000 years ago as humans spread and

colonised the planet via Europe and Asia.

Much speculation has centred on what the link between the ancient ancestor and modern myotonic dystrophy type 1 families might be. Initially it was suggested that myotonic dystrophy type 1 is much more common than previously recognised with many more individuals with the relatively mild late onset form which is usually only diagnosed in people with more severely affected relatives. Although there undoubtedly are more individuals with the mild form of the disease than we currently know about, it would require that repeats in the range of 50 to 100 could be passed from parent to child without large increases over many generations. Indeed, it has been shown that this can sometimes happen and result in the occurrence of myotonic dystrophy type 1 in quite widely separated branches of some families. However, this only tends to happen when the repeat is passed on by females. Almost invariably when a repeat in the range of 50 to 100 repeats is inherited by

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a man he passes on much larger repeats to his offspring, usually in the range associated with adult onset of symptoms, 200 to 500 repeats. This male bias in the further expansion of repeats in the 50 to 100 range explains the excess of affected grandfathers that we see in myotonic dystrophy type I families.

One of the disadvantages to studying human genetics is that humans have relatively small families. In our research group and those of our collaborators, we have investigated the inheritance of the myotonic dystrophy type I repeat by using an alternative approach to studying families. The genetic material is passed from one generation to the next in the form of the woman's eggs and the man's sperm. In simple terms of DNA content, each egg and sperm are genetically equivalent to children. Thus, by analysing individual eggs and sperm we can increase the effective number of 'offspring' that we could study. Obviously it is not possible to readily obtain eggs from females, but a single

ejaculate from a male contains millions and millions of sperm. We have developed very sensitive methods whereby we can analyse the DNA derived from individual sperm cells. This approach has enabled us to investigate in detail how the myotonic dystrophy type I repeat is inherited from males. Our results confirm that the expansions are very unstable in males and almost always become much larger. Thus, it is not possible that myotonic dystrophy type I can be maintained in the population by multiple generations of mildly affected individuals.

An alternative hypothesis was that there was a low frequency of individuals in the general population who had intermediate sized repeats, larger than usually seen, but smaller than those associated with the disease in the range of 40 to 50 repeats. A large survey of myotonic dystrophy type I families, including the unaffected relatives, revealed that indeed such repeats do exist at low frequency. Although these repeats are not associated with detectable symptoms, they are



though very unstable and highly likely to expand into the disease associated range, once again, particularly when passed on by a man. Thus, although such repeats appear to be present in the early generations of myotonic dystrophy type I families, they appear to be too unstable to connect widely disparate myotonic dystrophy type I families. Therefore, the only possible remaining explanation is that small repeats from within the range usually observed in the general population must occasionally expand into the disease associated range.

Another clue to the origins of myotonic dystrophy type I comes from the observation that a small proportion of individuals in the general population also share the same DNA sequence around the repeat. However, rather than containing the large expanded repeats directly associated with myotonic dystrophy symptoms, such individuals usually have from 20 to 40 repeats. Although changes in length for small repeats have been observed in families

from the general population, such events are rare and require the analysis of large numbers of families. However, using our sensitive single sperm approach we are able to measure the rate that the small repeats change when passed on by males in the general population. This work has revealed that the very small repeats (less than 20) are very stable and virtually never change. Repeats larger than 20, however, change 1-2% of time they are passed on and repeats larger than 30 change more than 10% of the time. In contrast to repeats in the disease range though, the changes are only usually one or two repeats. Thus, it is probable that new myotonic dystrophy type I families arise by the gradual accumulation of repeats in individuals in the general population over many generations. We can also speculate that the common myotonic dystrophy type I ancestor, who lived 60-100,000 years ago, probably had in the order of 20 CTG repeats. However, it may then have taken many hundreds or even thousands of generations



for the number of repeats to grow to the size necessary to cause myotonic dystrophy type 1 to occur in some families.

The vast majority of myotonic dystrophy families have myotonic dystrophy type 1 associated with the CTG expansion discussed above. We also know that a subset of myotonic dystrophy families have myotonic dystrophy type 2 which is associated with a CCTG expansion in another gene. It appears that all myotonic dystrophy type 2 families also share a common ancestor and that new families might arise by a similar mechanism to that proposed for myotonic dystrophy type 1.

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**Other publications available from the Myotonic Dystrophy Support Group:**

- Anaesthesia and Sedation for patients with Myotonic Dystrophy
- Basic Information for Midwives
- Bowel Problems in Myotonic Dystrophy
- Congenital Myotonic Dystrophy
- Excessive Daytime Sleepiness and Myotonic Dystrophy
- Facts for patients, family members and professionals
- Myotonic Dystrophy and the Eye
- Myotonic Dystrophy Support Group
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