



MYOTONIC DYSTROPHY
SUPPORT GROUP

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**Why do we get new families
with
myotonic dystrophy ?**

By

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Why do we get new families with 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 only 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 though, are not recognised until a severely affected child is born.

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 on 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. 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 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 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. Most people have two versions of this CTG repeat (one from each parent) with differing numbers of repeats. The exact number of repeats is usually in the range of from 4 to

approximately 40 CTG repeats, with 5, 11, 12, 13 and 14 repeats being very common. People with myotonic dystrophy have an increased number of repeats from 50 up to many thousands. 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 only very rarely in the general population. However, the expansions associated with myotonic dystrophy 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 a larger repeat and hence are almost always more severely affected than their parent. This phenomenon, known as 'anticipation', is very unusual and does not occur in most 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 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 genetically 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, 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 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, much research has been done by many groups throughout the world trying to understand how myotonic dystrophy is maintained in the general population. One of the earliest observations made was that in addition to the large CTG repeat, everybody with myotonic dystrophy shares the exact DNA sequence around the repeat. This strongly suggests that everybody with myotonic dystrophy shares a common ancestor at some point in human evolution. The fact that myotonic dystrophy is found 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 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 families might be. Initially it was suggested that myotonic dystrophy is much more common than previously recognised with 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 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 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 a man he passes on much larger repeats to his offspring, usually in the range associated with mid-life onset of the 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 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 been investigating the inheritance of the myotonic dystrophy 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. Thus, in simple terms of DNA content, each egg and sperm are genetically equivalent to children. Thus, by analysing individual eggs and sperm we could 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 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 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 families, including the unaffected relatives, has recently revealed that indeed such repeats do exist at low frequency. Although these repeats are not associated with detectable symptoms, there 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 families, they appear to be too unstable to connect widely disparate myotonic dystrophy 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 comes from 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 - 40 repeats. Although the occasional mutation events 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 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 ancestor, who lived 100,000 years ago, probably had in order of 20 CTG repeats.

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