Myotonic dystrophy is an inherited disease that is passed from one generation to the next through a faulty gene. It is not caused by an infectious agent such as a virus or bacteria.

How genes work

DNA is the genetic material found in the nucleus of nearly every cell. A gene is a stretch of DNA that carries a set of instructions on how a protein should be made. These proteins carry out the functions of the body. Scientists estimate that humans have about 25,000 different genes. For example, there are genes that control eye color, genes that make proteins to break down food in the stomach, and genes that encode enzymes that regulate how cells grow.

When the DNA of a gene is altered, a mutation is said to have occurred. Some mutations have little effect on how the body functions. Others are more serious, causing the production of defective proteins that result in disease symptoms.

How myotonic dystrophy is inherited

Both DM1 and DM2 are passed from parent to child by *autosomal dominant* mutations. This means that the faulty gene is located on one of the chromosomes that does not determine sex (autosome) and that one copy of the mutated gene is enough to cause the disease (dominant). Because the gene is not located on the X or Y sex chromosomes, it can be passed to male and female children with equal frequency.

In nearly all cases, patients with DM have one normal copy of the DM gene and one copy with the mutation. This means an affected parent has a 50% chance of passing on the mutated gene to an offspring. Individuals who receive the mutated gene will have the disease, although they may not show symptoms for many years. Children that do not inherit the mutated gene will never develop DM.

A recent study suggested that all affected individuals can be traced back to just one or two people who had the original mutations, thousands of years ago. Unlike some genetic diseases, for example, the types of genetic changes that come from exposure to radiation or toxic chemicals, the mutations causing DM do not occur spontaneously.

Causes of DM

In patients with myotonic dystrophy, there is a problem with a particular gene that causes it to convey faulty instructions. This mistake results in the symptoms of DM. The two forms of myotonic dystrophy are caused by mutations in different genes. Although DM1 and DM2 show similar symptoms, the two forms have fundamentally different origins. Scientists are currently looking into the possibility that there may be additional forms of DM caused by mutations at different sites.

- **DM1.** The genes responsible for myotonic dystrophy type 1 (DM1) are found on chromosome 19. Each chromosome consists of a long chain of chemicals that form the units of DNA. These units are called nucleotide bases. The disease is characterized by stretches of DNA (abbreviated CTG) on the *DMPK* (dystrophia-myotonic protein kinase) gene that are repeated several times. It is sometimes referred to as a *trinucloetide repeat disease* because of the repetition of these three DNA base pairs. In healthy people, there are between 5 and 37 repeats of the CTG sequence. People with myotonic dystrophy type 1 have expanded repeats which can contain anywhere from 50 to more than 4,000 repeats of the CTG sequence.

- **DM2.** The genes responsible for myotonic dystrophy type 2 (DM2) are found on chromosome 3. The repeat sequences contain stretches of DNA in which four chemicals (abbreviated CCTG) on the *Znf9* (zinc finger protein 9) gene are repeated. As in DM1, the disease occurs after the number of repeats exceeds a certain threshold. Healthy individuals will have fewer than 75 CCTG repeats. People with DM2 can have anywhere between 75 and 11,000 repeats.

Distinctive genetic mechanisms in DM

Myotonic dystrophy is one of the most complex disorders known. In addition to the incredible variability of clinical symptoms, the disease also has several unique mechanistic features:

- **Autosomal dominant inheritance.** The genes for DM1 and DM2 are dominant, meaning that a person can inherit the disease even if only one parent carries the gene. Also, a child has the same risk of inheriting DM regardless of whether it is the father or the mother who carries the gene.

- **Variable penetrance.** This term refers to the fact that the number and severity of DM symptoms varies widely among people with the disease. This is true even among people with the same subtype, and among individuals in the same family.

- **Somatic mosaicism.** A key characteristic of DM is that different cells in different tissue types will show varying numbers of genetic repeats. This is due at least in part to the fact that the number of repeats changes, is different in different cells and increases in number throughout the lifetime of the individual. Thus, the number of repeats reported in a diagnostic test will depend on how old the individual was when sampled, which tissue was tested and then, will only measure the average number of repeats.

- **Anticipation.** The number of repeats in the DM genes tends to increase with each affected generation. As a result, the symptoms of the DM1 appear earlier in life and are more severe in each successive generation. These changes are often dramatic. For example, a person whose only symptom was cataracts that appeared later in life can have a child with life-threatening symptoms present at birth. This effect indicates that the number of times the gene sequence is repeated has a bearing on the severity of the disease symptoms. Anticipation appears to be less pronounced in DM2.

- **Transmission of congenital form through mother.** The most severe form of myotonic dystrophy (congenital myotonic dystrophy: DM1) is almost always passed to the child from an affected mother. Scientists think that this occurs because the number of repeated sequences expands greatly during the process when the egg cells are created.