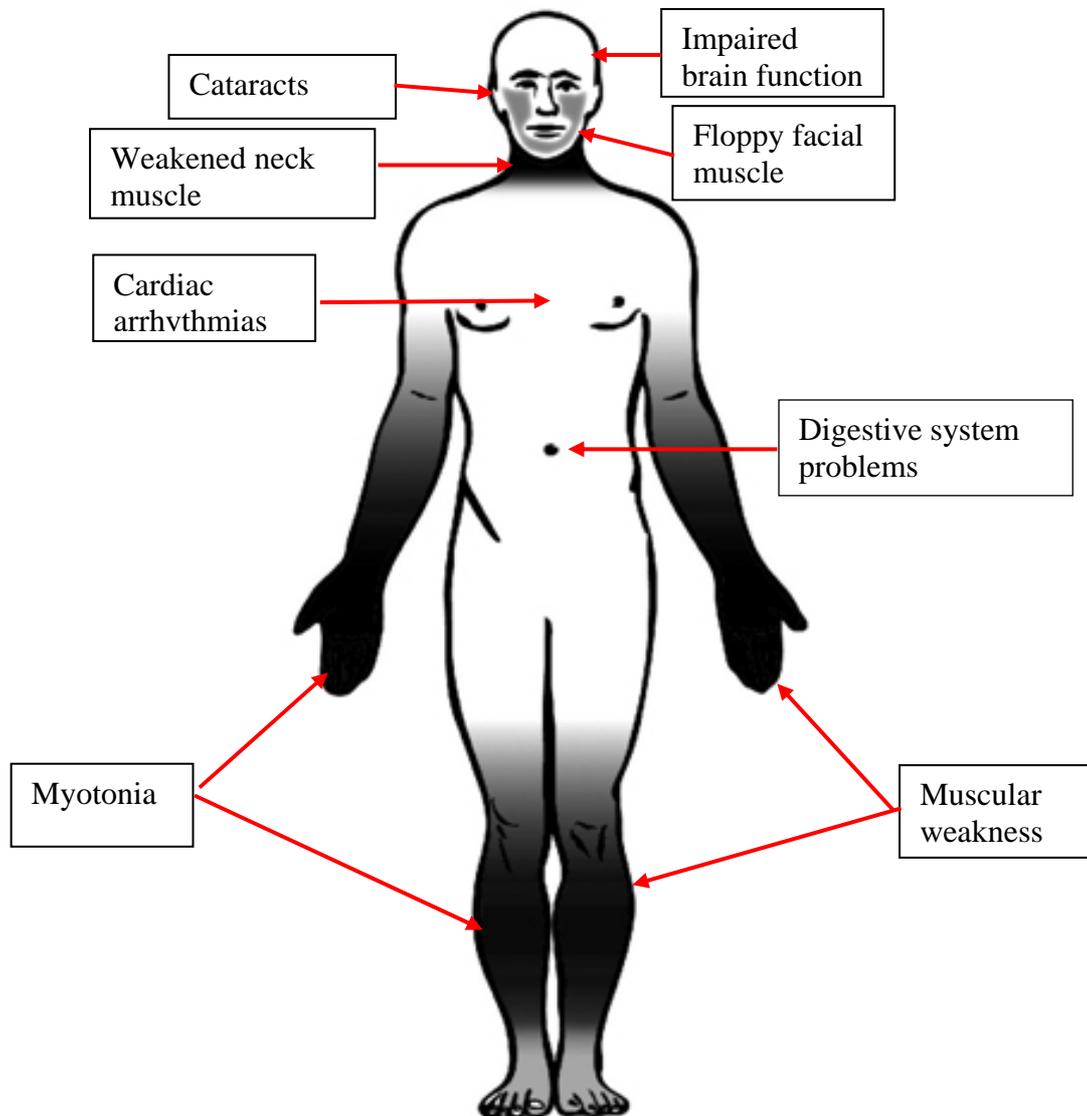


## Understanding myotonic dystrophy: a complex neuromuscular disease



**Figure 1**

### **Myotonic Dystrophy**

Myotonic dystrophy (Latin name: dystrophia myotonica) is the most common neuromuscular dystrophy in adults. The disease is dominantly inherited and affects 1:10.000 people worldwide.

Many organs are affected within myotonic dystrophy and signs and symptoms vary greatly from patient to patient (Figure 1). Typical symptoms are delayed relaxation of skeletal muscles (myotonia) and a gradually increasing muscle weakness (dystrophy). Besides muscle symptoms patients often suffer from heart failure, cataracts, diabetes, gastrointestinal problems, excessive sleepiness and learning and behavioral changes may occur. Some time ago it was discovered that there are two very similar forms of DM, namely myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2).

## Defects in the genetic material

Myotonic dystrophy is caused by a defect in the genetic material, also called DNA. Each cell in the human body contains genetic material, whether a neuron, heart cell or a muscle cell is concerned. The DNA is present in the cell in the form of chromosomes. Each cell has 46 chromosomes (Figure 2). If the DNA at a specific location on chromosome number 19 is disturbed, this will cause myotonic dystrophy type 1.

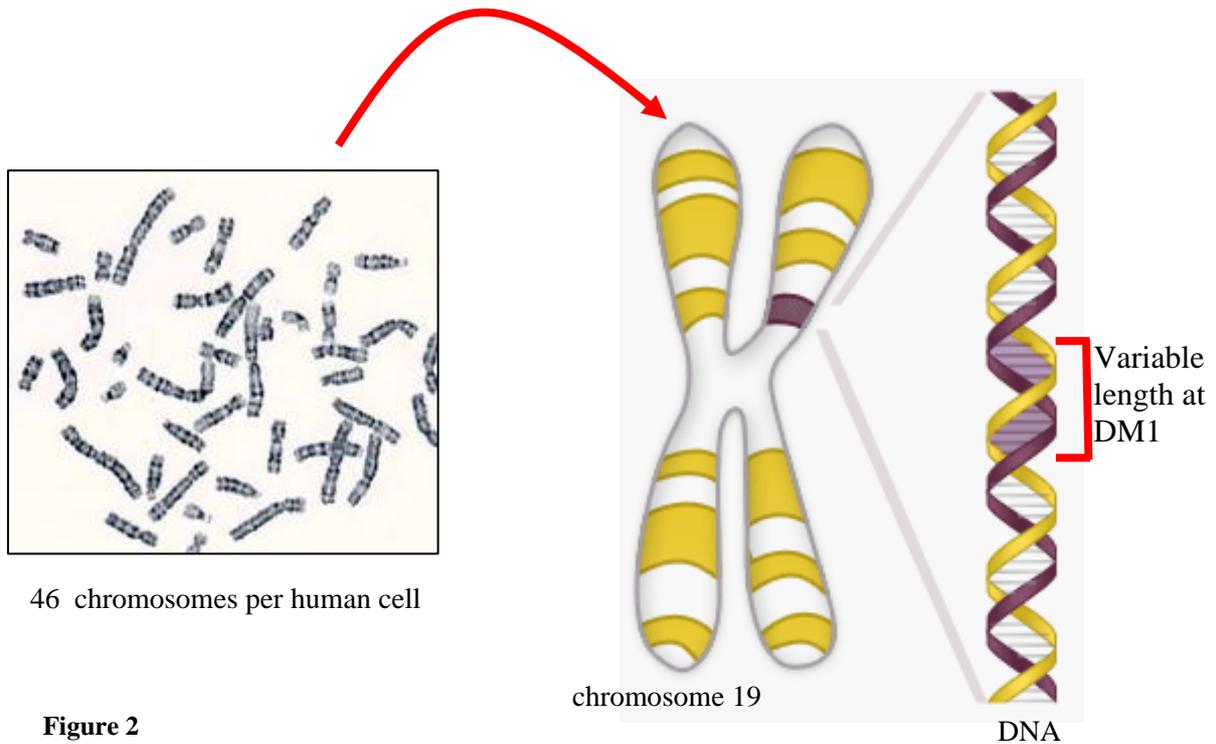
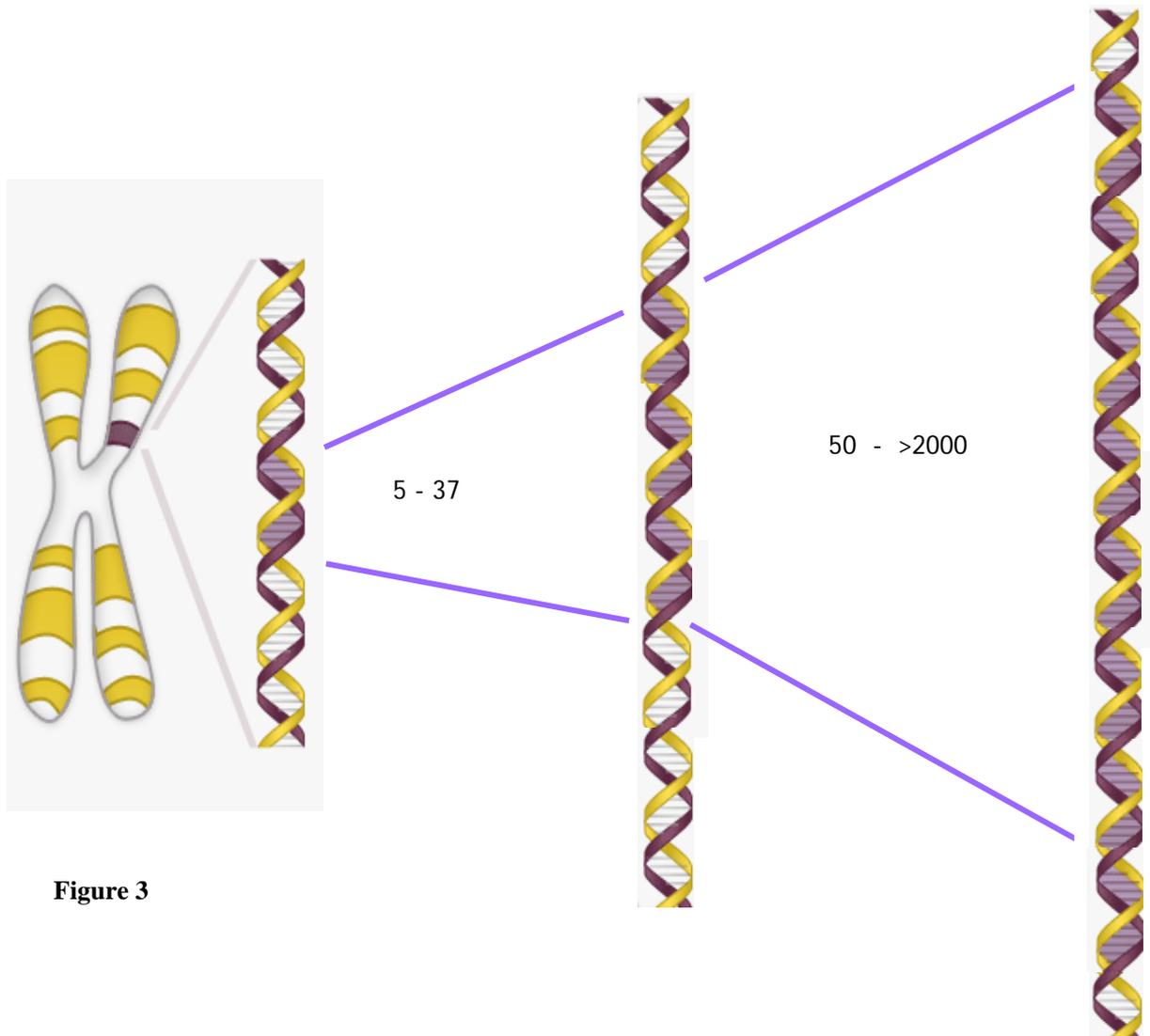


Figure 2

The disturbance is caused by a DNA segment of variable length. This segment consists of a long series of three repetitive elements, called C, T and G. In healthy individuals, the maximum range is 37 CTG triplets. A larger number of CTG triplets, which can range from 50 to 3000, will lead to the development of DM1 (Figure 3).



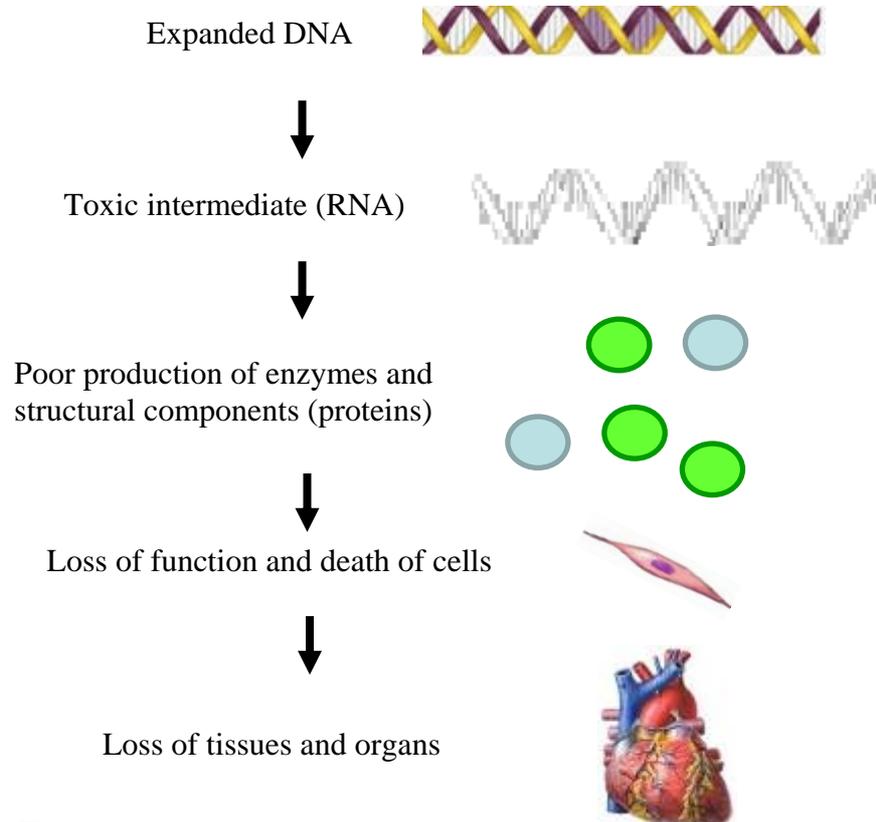
**Figure 3**

Both during the life of a patient and by inheritance from one generation to another, the length of the series CTG's usually increases. Generally speaking, a larger DNA expansion is accompanied with more severe symptoms, which occur earlier in life.

DM type 2 is also caused by a DNA expansion. In this case, however, a series of four successive components C, C, T and G is recognized. This series CCTG quartets is also unstable and is located on chromosome 3.

## How does a CTG expansion in the genetic material leads to disease symptoms?

For the proper functioning of the human body an effective cooperation between cells, tissues and organs is vital. An abnormality in the genetic material will usually lead to a change in the growth and composition of cells. The CTG-expansion, that is typical for DM1, ensures that an abnormal form of a natural intermediate, called RNA, arises. In the healthy situation, this RNA is necessary for the production of enzymes and structural proteins (Figure 4)



**Figure 4**

Research has shown that faulty RNA that is formed as a result of the CTG expansion is toxic for the cell. A specific protein, named MBNL1 (green dots, Figure 5-7), sticks to the faulty RNA. This creates insoluble complexes in the cell and MBNL1 is no longer available to perform its normal function (Figure 5). A second protein, CUGBP1 (blue dots, Figure 5-7) is on the contrary up-regulated in DM1 cells. MBNL1 and CUGBP1 function in close conjunction with each other in a cell. In DM1 the natural balance between these two factors is disrupted (Figure 5). This creates a false production of proteins causing incorrect cell- and organ functions.

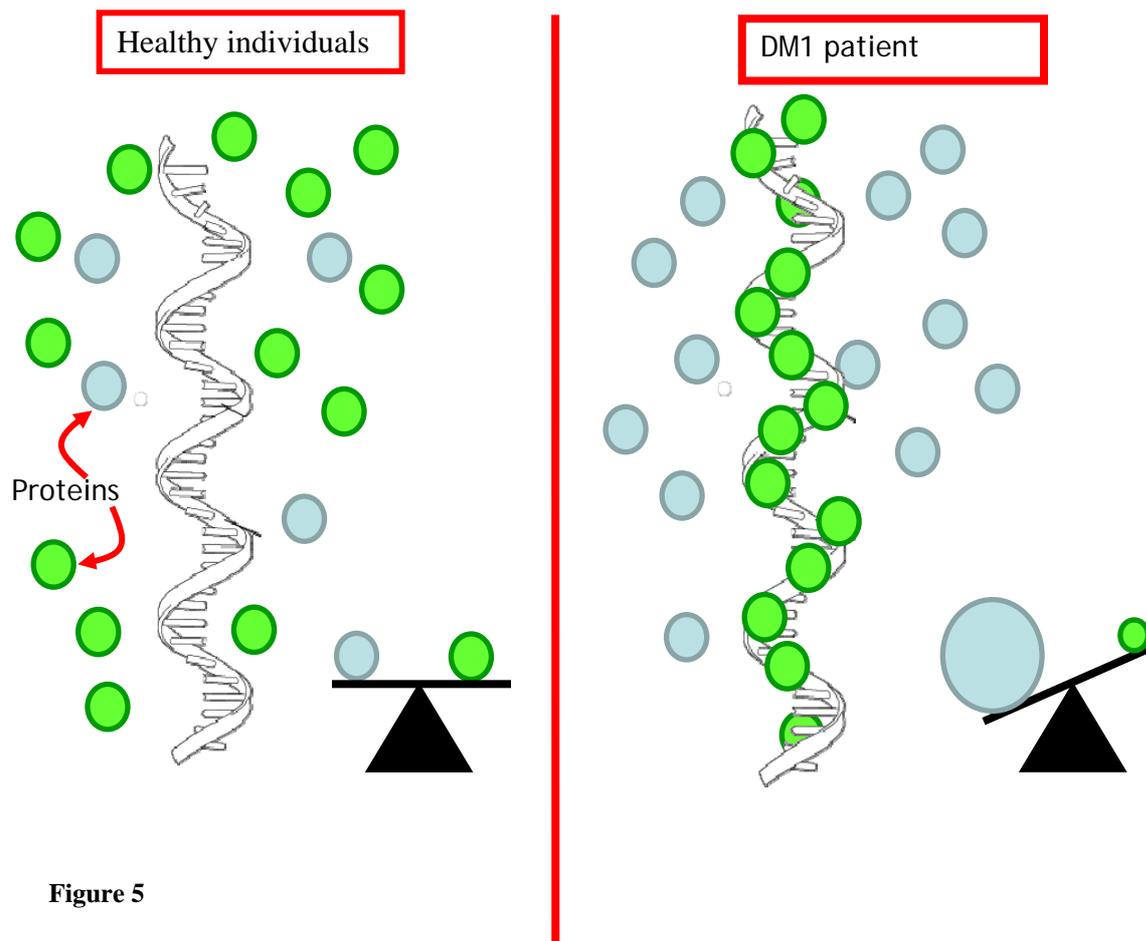


Figure 5

*Lecture by Mrs. S. Mulders associated with Nijmegen Centre for Molecular Life Sciences, University Medical Center St. Radboud, Department of Cell Biology and employed at Prosensa Therapeutics BV in Leiden. This lecture was held at the annual meeting of the VSN Myotonic Dystrophy Support Group on June 12, 2010*