



Exon skipping

In order to explain the concept of exon skipping, it is first necessary to explain how genes work and how mutations in the dystrophin gene can cause both Duchenne and Becker muscular dystrophy.

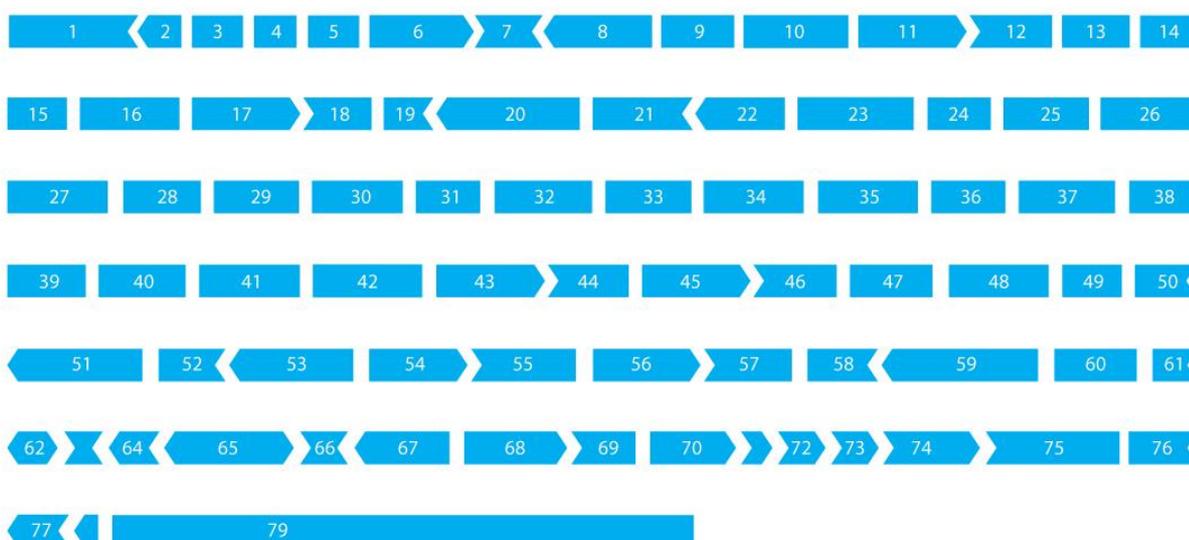
If you have any questions about exon skipping, or any other potential treatments that are being researched or in clinical trials, do get in touch with our research team. If you'd like to speak to others with the same condition as yours, we can put you in touch. Or you can visit our active and friendly online forum. To find out how we are campaigning to speed up access to potential exon skipping treatments, and to get involved, please contact our campaigns team. (You'll find contact details at the end of the factsheet.)

What are genes?

A gene is a section of DNA that contains the instructions for the production of a specific protein. Proteins are essential parts of cells and play a role in every process occurring within the cell, as well as having structural or mechanical functions which help maintain the cell's shape. It is estimated that we have about 25,000 different genes.

What are exons?

Genes are divided into sections called 'exons' and 'introns'. Exons are the sections of DNA that code for the protein, and they are interspersed with introns which are also sometimes called 'junk DNA'. The introns are cut out and discarded in the process of protein production, to leave just the exons. The dystrophin gene is our largest gene – it has 79 exons, which are joined together like the pieces of a puzzle:



What happens in Becker muscular dystrophy?

Let's zoom in on exons 68 to 75 to look at this a bit more closely:



In Becker muscular dystrophy an exon is deleted, for example exon number 74 in the diagram:



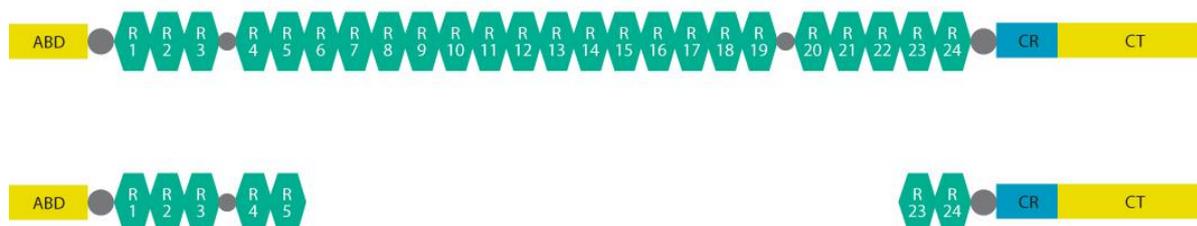
Although a part of the gene is missing, exon 73 can join up with exon 75, and the puzzle can be completed to the end of the gene:



What impact does a Becker mutation have on the dystrophin protein?

The dystrophin protein normally sits in the membrane that surrounds muscle fibres like a skin, and protects the membrane from damage during muscle contraction. Without dystrophin, the muscle fibre membranes become damaged and eventually the muscle fibres die.

Dystrophin is a very large protein with a section in the middle, consisting of lots of repeated segments (in green below). It is known that the protein can still work to some extent if some of these repeated segments are missing. Individuals with Becker muscular dystrophy have some of these repeated segments missing and have milder symptoms compared to Duchenne muscular dystrophy – often still being able to walk into their 40s and 50s.





What happens in Duchenne muscular dystrophy?

In Duchenne muscular dystrophy, an exon – or exons – are deleted, which interfere with the rest of the gene being pieced together. In our example (using exons 50-57), exon 52 illustrates this:

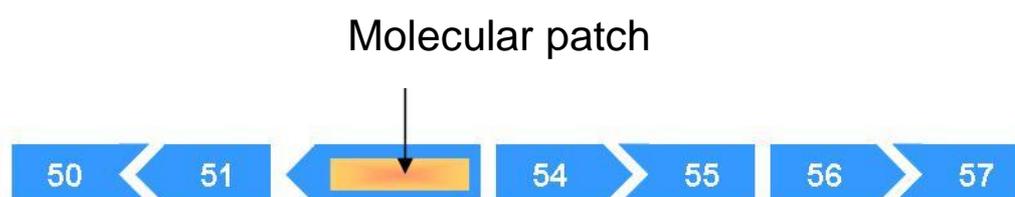


Exon 51 cannot join up with exon 53, which prevents the rest of the exons being assembled. For the dystrophin protein to work, it must have both ends of the protein. Therefore, this mutation results in a completely non-functional dystrophin protein and the severe symptoms of Duchenne muscular dystrophy.



How can exon skipping help?

As the name suggests, the principle of exon skipping is to encourage the cellular machinery to 'skip over' an exon. Small pieces of DNA, called antisense oligonucleotides (AOs) or 'molecular patches', are used to mask the exon that you want to skip, so that it is ignored during protein production. In our example, see what happens if we use a 'molecular patch' designed to mask exon 53:



Exon 51 can now join up to exon 54, and continue to make the rest of the protein, with exons 52 and 53 missing in the middle:





Does this really work?

So far, scientists have shown this technique to be effective in a mouse model of Duchenne muscular dystrophy (the *mdx* mouse), and in muscle biopsies from people with Duchenne muscular dystrophy.

Several clinical trials have taken place that show that injecting a molecular patch into the blood stream, or under the skin, results in the production of dystrophin in the muscles. On the whole the molecular patches have been well tolerated although the side effect profile of the different patches varies with some causing skin and kidney related problems. There are two companies involved in conducting clinical trials of exon skipping. The principle of exon skipping is the same for all of the clinical trials, but the molecular patch being tested has a slightly different chemical formulation.

Will it work for everyone with Duchenne muscular dystrophy?

It is thought that skipping one or two exons would be able to treat around 83 percent of the genetic errors causing Duchenne muscular dystrophy.

Will the same 'molecular patch' work for everyone?

No, the dystrophin gene is very large and the genetic errors associated with Duchenne muscular dystrophy occur in different places along this gene. There are, however, some common areas for mutations and, initially, 'molecular patches' will be made for these. For example, exon 51 skipping would be applicable for around 13 percent of children with Duchenne muscular dystrophy.

Once the technology has been shown to be effective for a particular error, it will be possible to design other 'patches'.

Are 'molecular patches' a cure?

Scientists hope that this type of therapy will halt or even reverse the symptoms of Duchenne muscular dystrophy, so that the symptoms resemble those of Becker muscular dystrophy. It will not be a cure, because if proven to be effective, this treatment would need to be repeated regularly. Just how often it would need to be repeated will become apparent during clinical trials.

A variation of "exon skipping technology" using molecular patches could be used to potentially treat other muscle-wasting conditions such as facioscapulohumeral muscular dystrophy (FSHD), congenital muscular dystrophy, and spinal muscular atrophy (SMA). Muscular Dystrophy UK is funding research that explores this avenue.

If you wish to learn more about the latest research and clinical trials, contact our research department on 020 7803 4813 or research@muscular dystrophyuk.org



We're here for you at the point of diagnosis and at every stage thereafter, and can:

- ▶ give you accurate and up-to-date information about your or your child's muscle-wasting condition, and let you know of progress in research
- ▶ give you tips and advice about day-to-day life, written by people who know exactly what it's like to live with a muscle-wasting condition
- ▶ put you in touch with other families living with the same muscle-wasting condition, who can tell you about their experiences
- ▶ tell you about – and help you get – the services, equipment and support you're entitled to.

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Here for you

The friendly staff in the care and support team at the Muscular Dystrophy UK's London office are available on **0800 652 6352** or **info@muscular dystrophyuk.org** from 8.30am to 6pm Monday to Friday to offer free information and emotional support.

If they can't help you, they are more than happy to signpost you to specialist services close to you, or to other people who can help.

www.muscular dystrophyuk.org