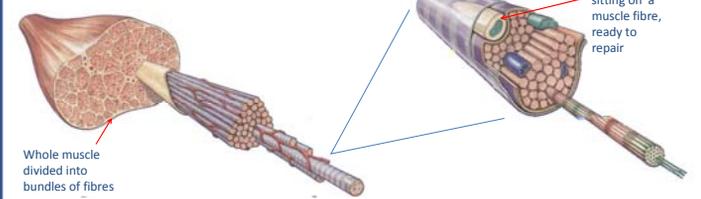


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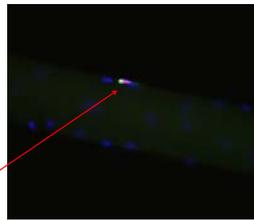
## What is a satellite cell?



Each muscle is made of many long muscle fibres, which generate force by contracting. Skeletal muscle is maintained and repaired by resident stem cells, called satellite cells. Muscular dystrophies are characterised by muscle weakness and wasting, indicating gradual failure of this stem cell-mediated repair.

## Does DUX4 affect stem cells in FSHD?

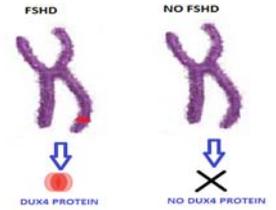
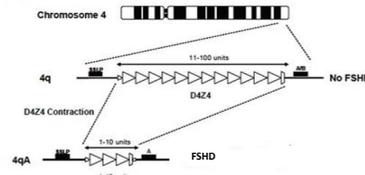
FSHD is characterised by a weakness and wasting of certain muscles. It is also a late onset disease, implying a problem with muscle repair. Satellite cells play a key role in muscle maintenance and repair, so even a minor defect in their function (e.g. due to 'unnatural' and toxic DUX4 expression) could cause major problems in a muscle.



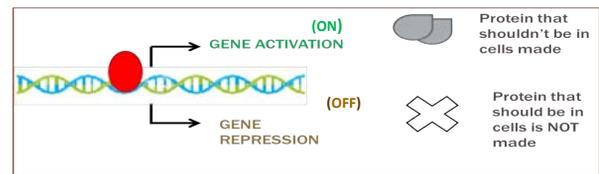
Satellite cell (highlighted) sitting on a muscle fibre.

Our lab studies satellite cell function and how it is controlled by proteins

## What causes FSHD?



Each cell contains 23 pairs of chromosomes, which contain **genes**. Genes encode **proteins**, which have many important roles in the body. FSHD is caused by the loss of a critical number of repeat units on the end of Chromosome 4 (arrows indicate units). This loss means that a protein (**DUX4**) is made in some muscle cells that is not normally present in muscle. DUX4 protein is toxic and causes cells to die. This is why many now believe that this causes the muscle weakness in FSHD. DUX4 is a **transcription factor**, which means that it can bind to other genes and control their production of proteins. It can do this in two ways:



Evidence shows that the alteration in gene activity caused by DUX4 is toxic to muscle cells and satellite cells.

## How is our lab studying FSHD?

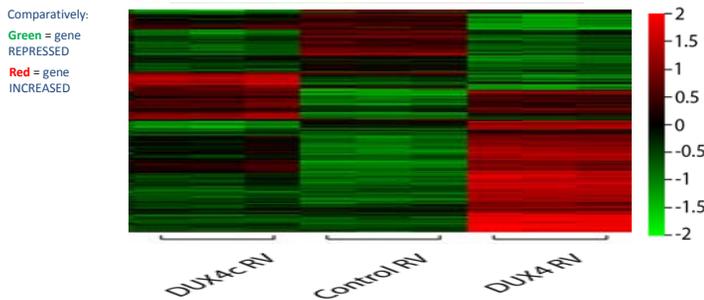
To investigate the effects of DUX4 on satellite cells, we have put DUX4 into satellite cells and measured the changes in gene activity that occur. Several versions of DUX4 were made, to determine which parts are crucial for FSHD pathology.



Although all versions of DUX4 are different, they all contain the area that allows them to act as transcription factors (green boxes)

Satellite cells that were made to express the different versions of DUX4 were analysed on a microarray. The microarray measures whether genes activity was increased (red) or repressed (green). The satellite cells with DUX4 were compared to cells where no DUX4 is present, so we can see the specific changes.

### Multivariate analysis: Heat map



This heat map shows gene activity. From this we can directly compare genes that were activated (red) and genes that were repressed (green) by DUX4.

For example:

Gene Name	Fold change compared to control				
	tMALDU X4-ERD	tMALDU X4	DUX4c	DUX4	tMALDU X4-VP16
Spry1	1.017786	0.910775	0.949715	1.551504	1.817977

## Aim of my PhD project:

My PhD project is to analyse key genes/proteins affected by DUX4, and to see if the toxic affects could be blocked, with the aim of ameliorating muscle weakness and wasting

### Key words/phrases:

- Gene:** A section of DNA on a chromosome which codes for a protein.
- Chromosome:** A condensed bundle of DNA, coding for several thousand genes. Humans have 23 pairs of chromosomes, with each cell containing an identical set.
- Protein:** A large molecule consisting of a specific sequence, determined by DNA. Proteins are essential components of muscle and the body as a whole- approximately 15% body weight is protein.
- FSHD:** Facioscapulohumeral muscular dystrophy
- Satellite cell:** an adult muscle stem cell
- DUX4:** (Gene name) Double homeobox 4, a toxic protein only expressed in FSHD
- DUX4c:** (Gene name) Double homeobox 4 centromeric
- Microarray:** A chip which can measure the relative amounts of different genes
- Stem cell:** an unspecialised cell which can both produce specialised cells (such as muscle) and self-renew so that you have a constant supply.
- Transcription factor:** a protein which can bind to DNA and turn ON or OFF other genes

## What are the next steps?

1. Identify pathways that could cause muscle wasting
2. Manipulate these pathways to see if they do affect muscle function
3. See if manipulation of a pathway can make DUX4 less toxic

Ultimately this work will contribute to understanding how DUX4 causes FSHD, and suggest protein networks that could be targeted (e.g. by drugs) to ameliorate the symptoms of FSHD.

## Acknowledgments and Further Reading

This research was part funded by the MDC (Muscular Dystrophy Campaign) and part funded by the MRC (Medical Research Council).

Further reading on FSHD pathology and our research at [http://www.muscular-dystrophy.org/about\\_muscular\\_dystrophy/conditions/99\\_facioscapulohumeral\\_muscular\\_dystrophy\\_fsh](http://www.muscular-dystrophy.org/about_muscular_dystrophy/conditions/99_facioscapulohumeral_muscular_dystrophy_fsh)