

## An overview of current research in FSH

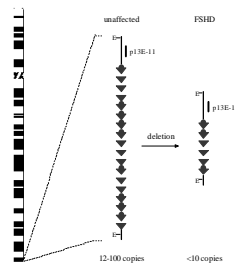
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## Outline of talk

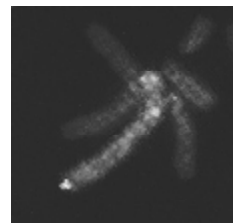
- Give an overview of current FSH research areas
  - FSH Workshop in San Diego (part of American Society of Human Genetics meeting)
  - Attended by researchers from around the world
- Provide information about research in my group in Nottingham

## Why has progress been slow?

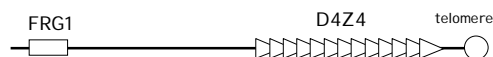
- A major problem in understanding FSHD is that the mutation in FSH is unique
  - Few clues from other diseases
- For technical reasons, this region of the genome was difficult to sequence
- Similarity to other regions of the genome can make data difficult to interpret



## Visualising D4Z4 on chromosomes

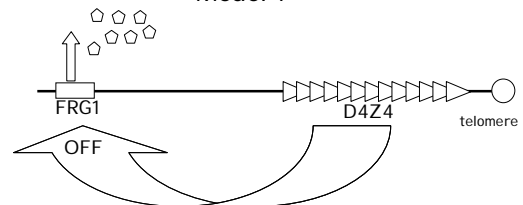


## How do deletions in D4Z4 cause FSHD?



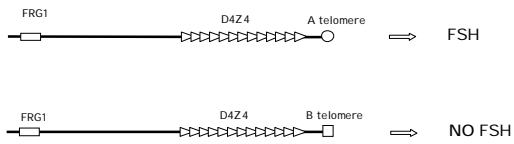
- There are a number of different models
  - None yet proven

## How do deletions in D4Z4 cause FSH? Model 1



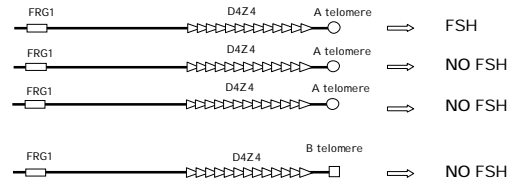
D4Z4 normally causes the FRG1 gene to be switched off and make little product  
When the deletion occurs, FRG1 is turned on inappropriately  
However, there is not consistent data to support this model. In San Diego, there was more data that did not support it

The particular version of chromosome 4 that carries the deletion is critical for FSH



D4Z4 deletions cause FSHD only on chromosomes 4 that have an A-type telomere (about 45% of chromosomes 4 in the general population are A-type).

The particular version of chromosome 4 that carries the deletion is critical for FSH



Just this year, the research group in Leiden showed that D4Z4 deletions cause FSHD only when they occur on one variant of A-type chromosomes 4. This chromosome variant accounts for about 86% of A-type chromosomes in the population.

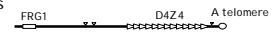
### What does this mean?



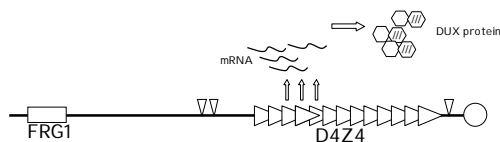
- We think that this means that one or more specific DNA changes on this chromosome are responsible
- These might be within D4Z4
- Current efforts now aimed at identifying these differences in DNA sequence

### Research aim 1 in Nottingham

- Determine the DNA sequences of full D4Z4 arrays
- Not yet done
  - Technically difficult
  - Not part of Human Genome sequence
  - Until recently assumed that all arrays equivalent
- Collaboration with Prof John Armour in Nottingham



### How do deletions in D4Z4 cause FSH? - Model 2



Perhaps D4Z4 produces an mRNA encoding the DUX protein. We think that normally, production of this mRNA is very strictly controlled.


When the deletion occurs, DUX mRNA and protein is produced inappropriately and is harmful to cells.

At the moment, there is limited evidence for this model

### Research Aim 2: Does D4Z4 contain a gene?

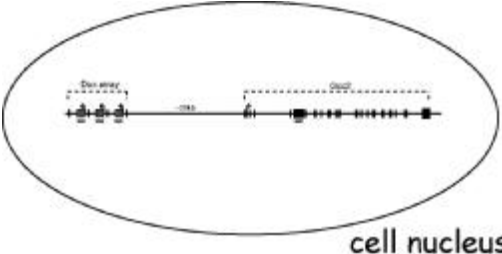
- We have recently identified sequences equivalent to D4Z4 in other mammals
  - Elephants
  - Mice and Rats
- We used information in sequence databases
- The first demonstration that such sequences (homologues) exist
- The properties of these sequences indicate they encode a protein (DUX)

### The mouse D4Z4 (DUX) array




- Like human D4Z4, this is a tandem array of repeated sequences
- Not located at the end of the chromosome
- We know that an mRNA is produced and this encodes a protein similar to the predicted human DUX protein
  - This has not yet been proven for human D4Z4
- We don't know if the human and mouse arrays have equivalent functions

### We used RNA-FISH to test if the mouse DUX array is transcribed



cell nucleus

### Results of experiment confirm mouse array produces an mRNA and is a gene



### What we need to do now

- Determine whether the human D4Z4 repeat makes a protein
- Test whether the human and mouse repeats have equivalent functions
  - § If they do, we should be able to make a mouse model of FSH by mimicking the mutation

### Future prospects in FSH research

- This year there have been some significant new findings
  - Data from different groups are now starting to point in the same direction
  - These have identified new areas of research to investigate that should help us to understand the underlying disease mechanism

This greater understanding will be necessary before we can study therapeutic approaches efficiently

Research into therapeutics in other MDs will help inform strategies for FSH