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HST.161 Molecular Biology and Genetics in Modern Medicine  
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## Lecture 17

## Facioscapulohumeral Dystrophy

### FSHD; Deletion and Expansion Syndromes

#### FSHD

- autosomal dominant inheritance pattern
- deletions in a non-coding region of chromosome 4 (tip of long arm)
- phenotype: muscle weakness in face, all skeletal muscles; inability to smile, inability to bring arms up to shoulder height - scapular muscles “wing” out of place.
- Initial genetic linkage made in 1990; by 2007, about 95% of FSHD families had been linked to one locus
- 3.3 kb D4Z4 repeats; these are deleted in discrete units in FSHD, but at least one unit of D4Z4 is necessary for the disease phenotype (zero repeats does produce abnormalities but not FSHD). These don't code for genes, but maybe they affect expression of surrounding genes.
- DUX4 isn't usually expressed into anything; however, some studies showed that under some circumstances, DUX4 might be convinced to be transcribed into a protein that travels to the nucleus and instigates apoptosis
- One group reported that FRG2, FRG1, and ANT1 were overexpressed in FSHD; however, other groups have not found the same thing.
- Three proteins bind to D4Z4 binding element; this suggests repression of surrounding genes.

#### Why is this disease considered “epigenetic”?

- these deletions, in mouse models, don't actually produce FSHD phenotype; suggesting a gain-of-function disease
- similar sequence on chromosome 10q; deletions here don't do anything. Exchanging sequences between 10q and 4q also doesn't do anything.
- There's a mystery sequence between D4Z4 and the telomere on chromosome 4 that is critical to producing the phenotype, but we don't know what it is or exactly where it is.

No anticipation is really observed. Repeats are conserved; there's some mosaicism, but anticipation really doesn't happen.

Number of repeats is theorized to be the same in affected and unaffected muscle.