FSHD Genetics: Everything You Want to Know (plus some more)

Miami FSHD Family Day Conference 2019

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February 23, 2019

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What is a genetic counselor?

- Genetic counselors have a Master degree in human genetics and/or genetic counseling
- Trained to be a resource for both patients and doctors about genetic concepts
- We are involved in ordering genetic tests and disclosing these results

National Society of Genetic Counselors

Celebrating 40 Years
1979 - 2019

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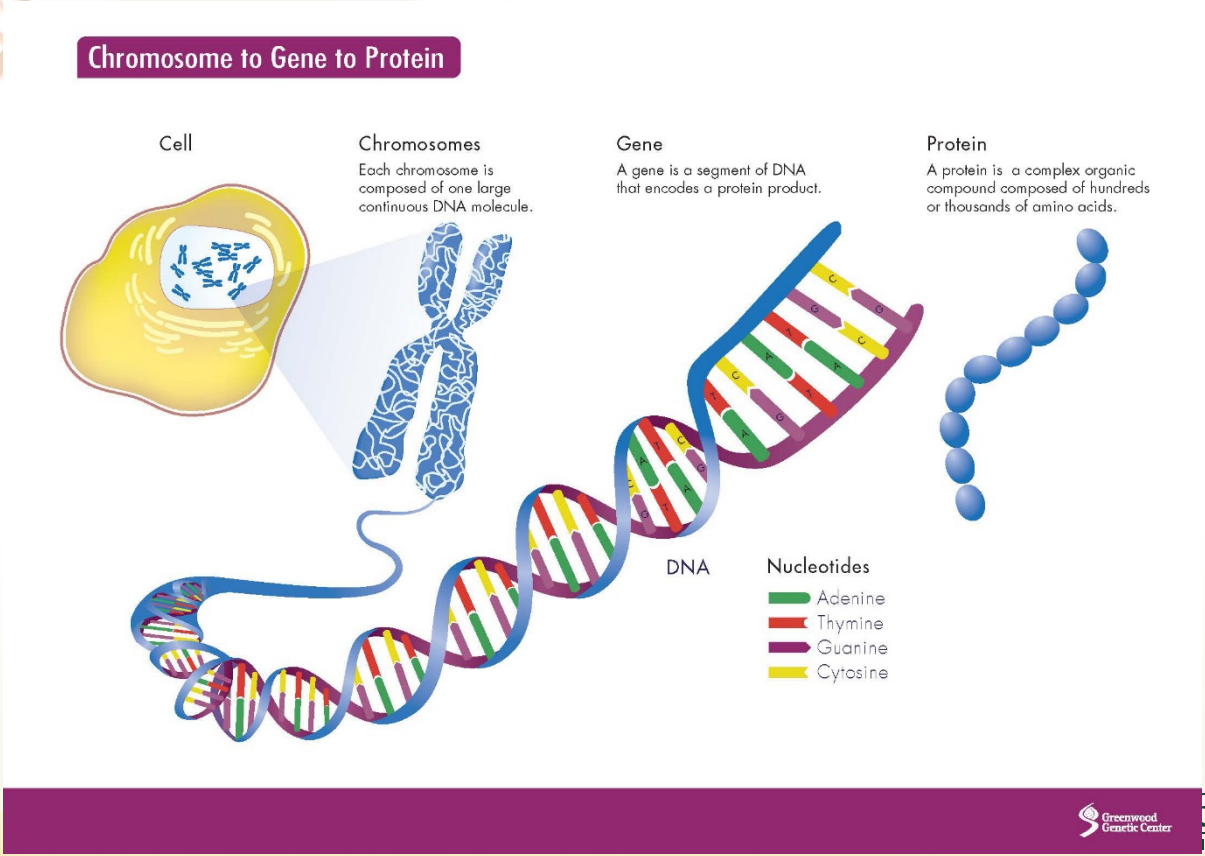
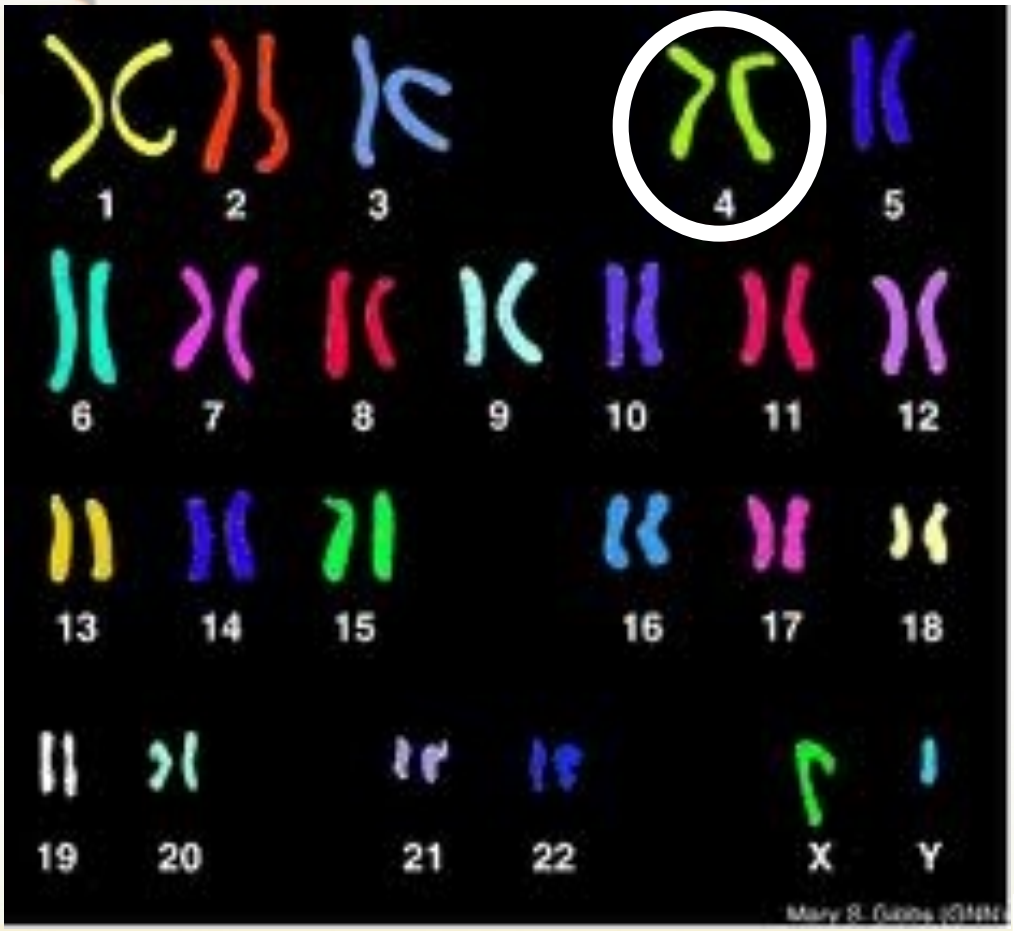
Genetics 101





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FSHD

- FSHD1 vs FSHD2
  - The main difference is underlying genetic cause
  - The symptoms of each are the same
  - FSHD1 makes up 95% of FSHD cases

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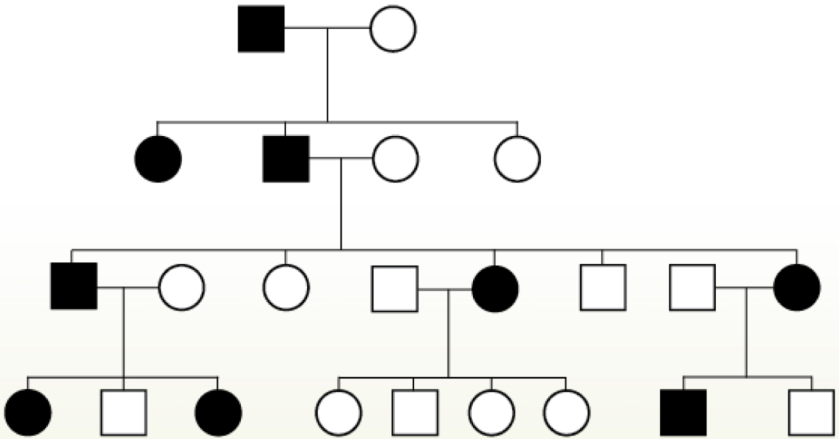
Basic Genetics of FSHD1

- Autosomal dominant
  - If an individual has the condition, they have a 50% chance of passing it on.



Source: https://www.genomicseducation.hee.nhs.uk

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Basic Genetics of FSHD1

- Autosomal dominant
  - If an individual has the condition, they have a 50% chance of passing it on
  - 10-25% of cases are de novo
    - The affected individual is the first person in their family to have the contraction
    - This is one of the reasons why a person can have FSHD without a family history for the condition

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Other reasons why FSHD might "skip" generations

- Variable expressivity
  - Not all individuals in the family will have the same symptoms of FSHD
- Possible incomplete penetrance
  - A small percentage of people who have the genetic mutation for FSHD do not ever show signs of FSHD
- FSHD2
  - We will get to this later.

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What actually causes FSHD?

- The expression (presence) of the DUX4 protein
  - This protein should NOT be present in our skeletal muscles
- The D4Z4 region helps prevent DUX4 when it is “methylated”
  - FSHD is due to a hypomethylation of the D4Z4 region

DUX4=TOXIC

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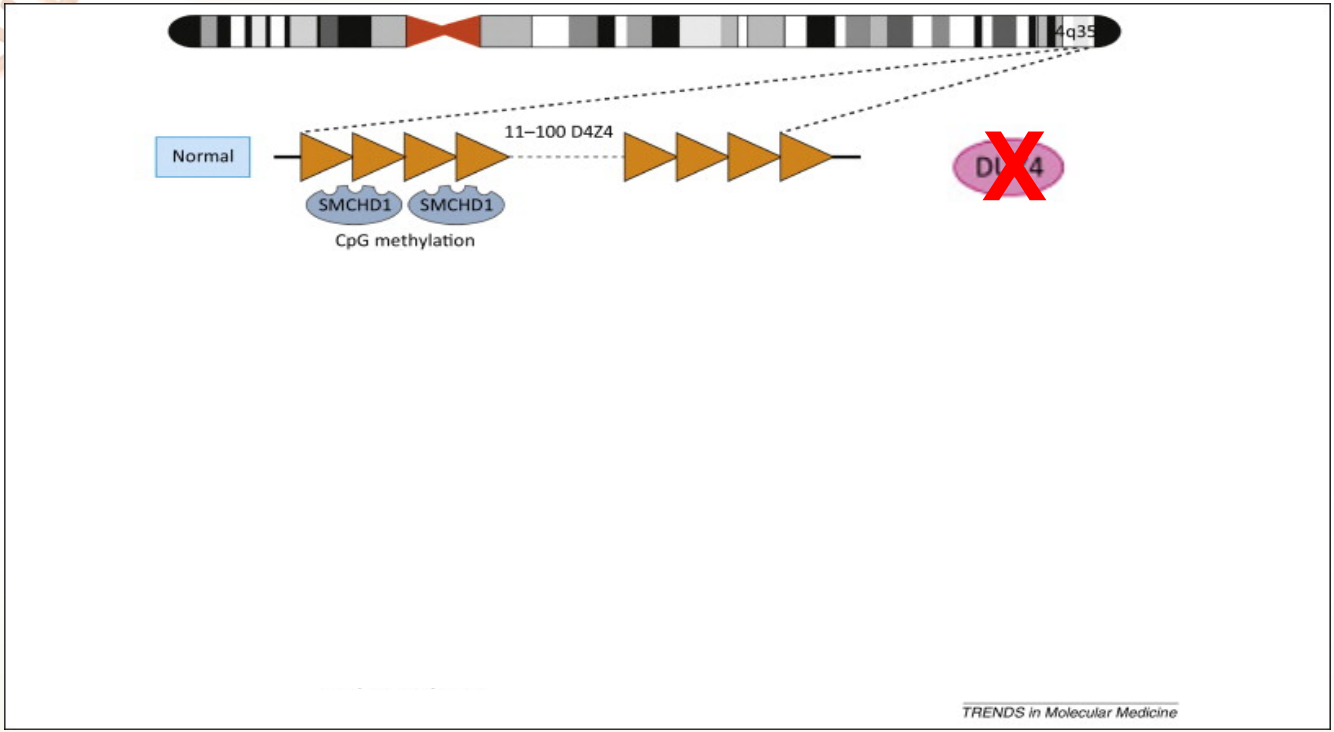
The normal D4Z4 region-No FSHD



Adapted from Fig 2. Lek et al., 2015, *Trends in Molec. Med.*

FSHD1 mechanism

- Contraction of the D4Z4 region
  - Under 11 repeats
- Hypomethylation of the D4Z4 region
- “Permissive allele”
  - 4qA
    - Allows for DUX4 to remain stable

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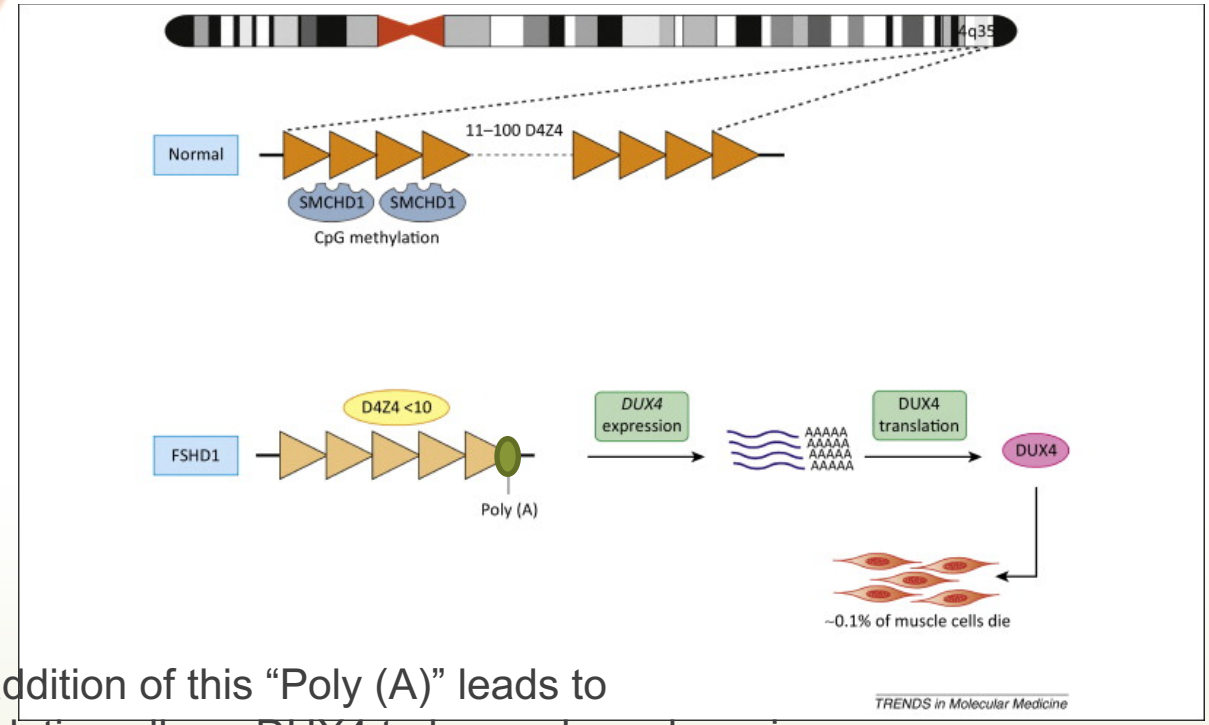
FSHD1 Mechanism



The addition of this “Poly (A)” leads to methylation-allows DUX4 to be made and survive

Adapted from Fig 2. Lek et al., 2015, *Trends in Molec. Med.*

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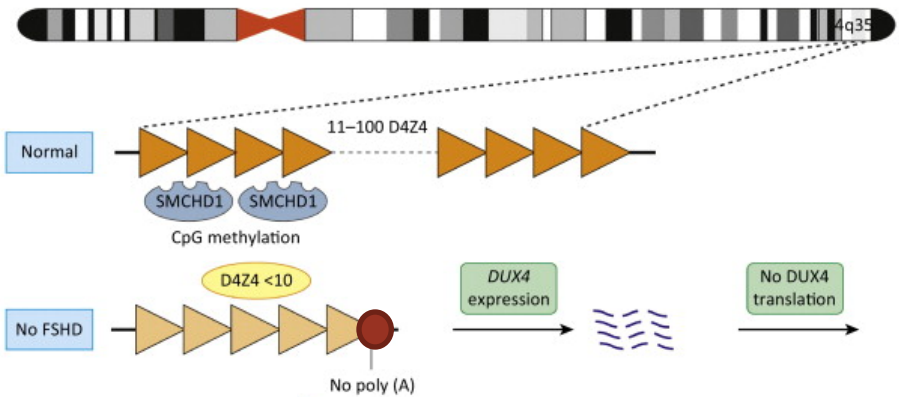
D4Z4 contractions without FSHD



Without the addition of the “Poly (A)” - DUX4 is not stable and is broken down, even with less than 11 repeats

TRENDS in Molecular Medicine

Adapted from Fig 2. Lek et al., 2015, *Trends in Molec. Med.*

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Back before FSHD2 things were so easy…

https://www.smu.edu.sg/

Why is FSHD2 so complicated?

- Digenic inheritance!

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What is digenic inheritance?

- When two different genes or genetic components are needed in order to have a genetic condition
- In the case of FSHD2 the two components needed for hypomethylation of D4Z4:
  - A mutation in the *SMCHD1* gene
  - A “permissive” D4Z4 allele

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FSHD2 Mechanism

- Permissive allele
  - 4qA
  - Only one is needed
- Mutation in the *SMCHD1* gene
  - Only 1 copy of the gene needs a mutation

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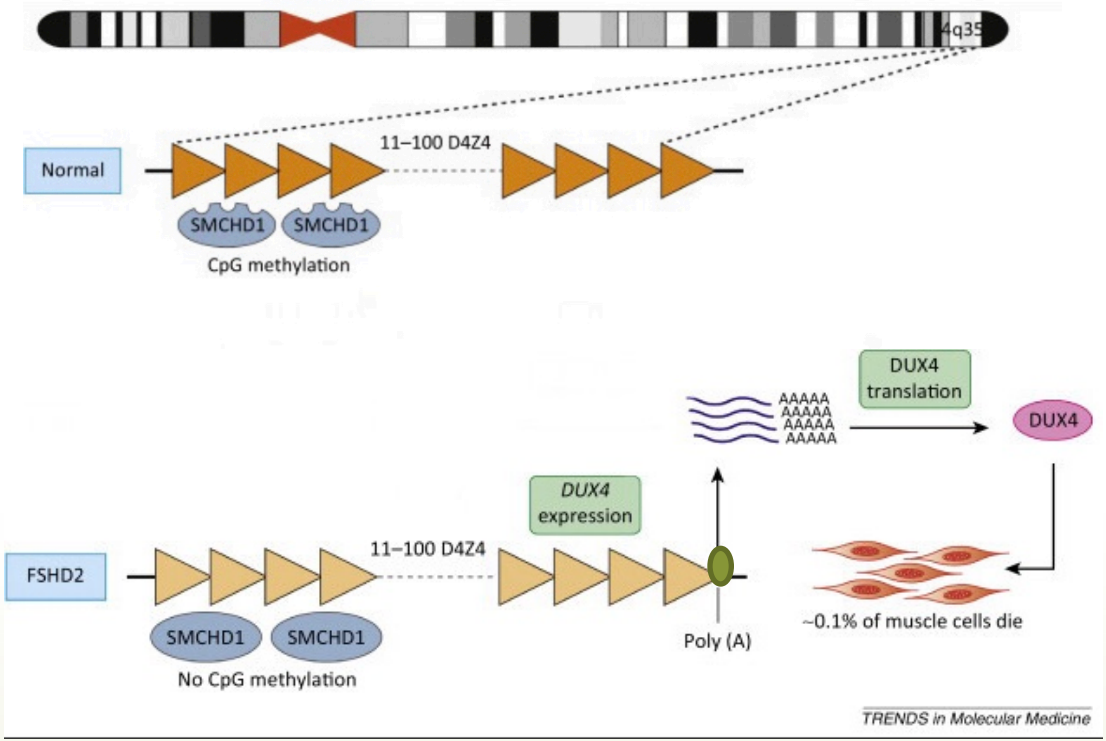
FSHD2 mechanism



Adapted from Fig 2. Lek et al., 2015, *Trends in Molec. Med.*

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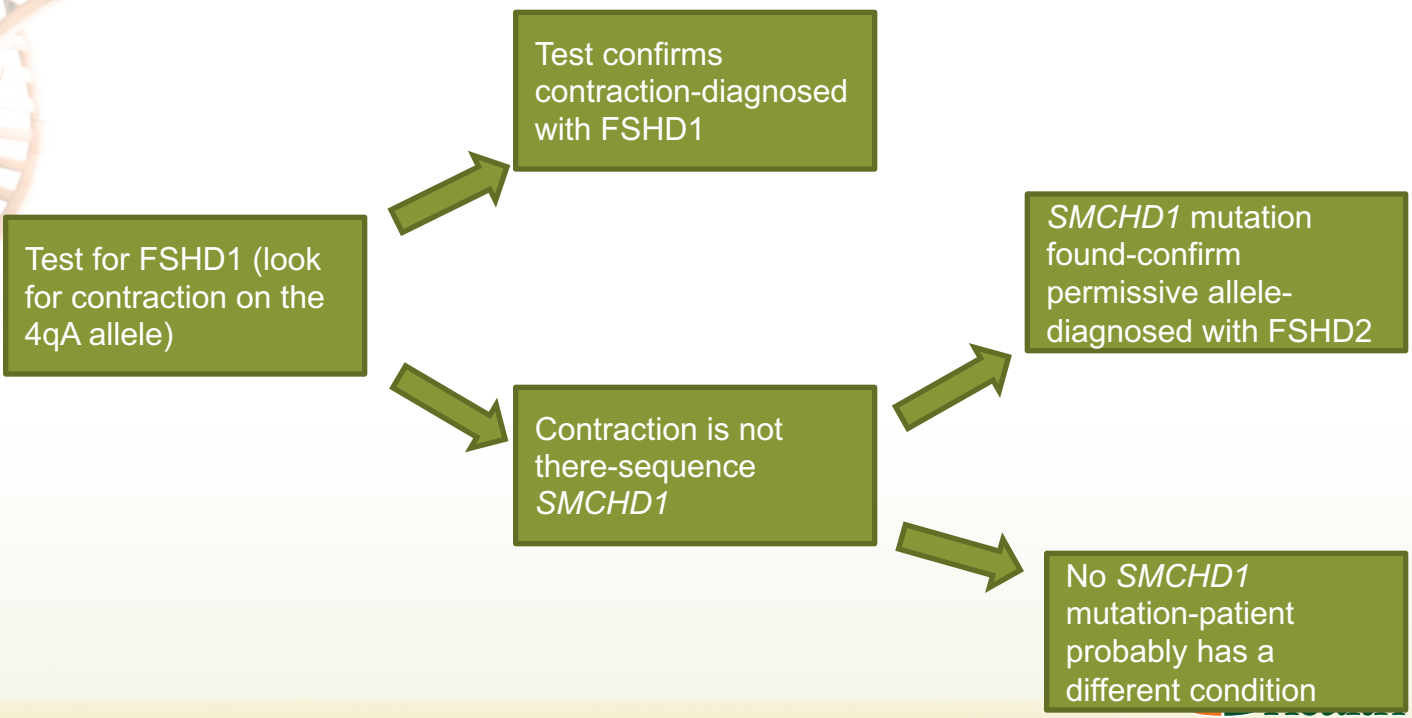
How do we test for FSHD?



Who else in the family is at risk?

- FSHD1
  - First degree relatives have a 50% chance
- FSHD2
  - 50% chance the *SMCHD1* mutation will be passed on
  - Multiply this by the chance that 4qA permissive allele will be passed on

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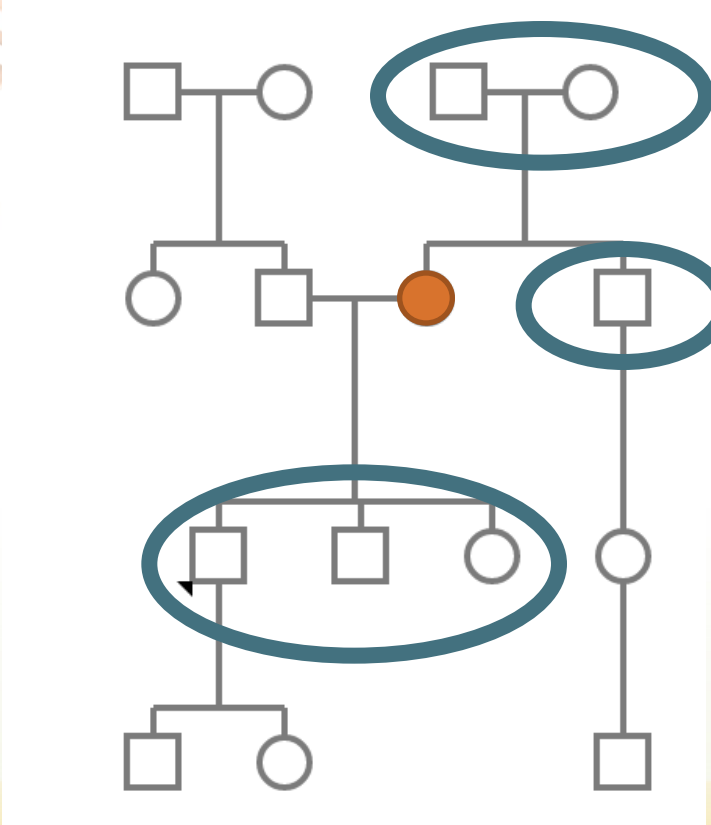
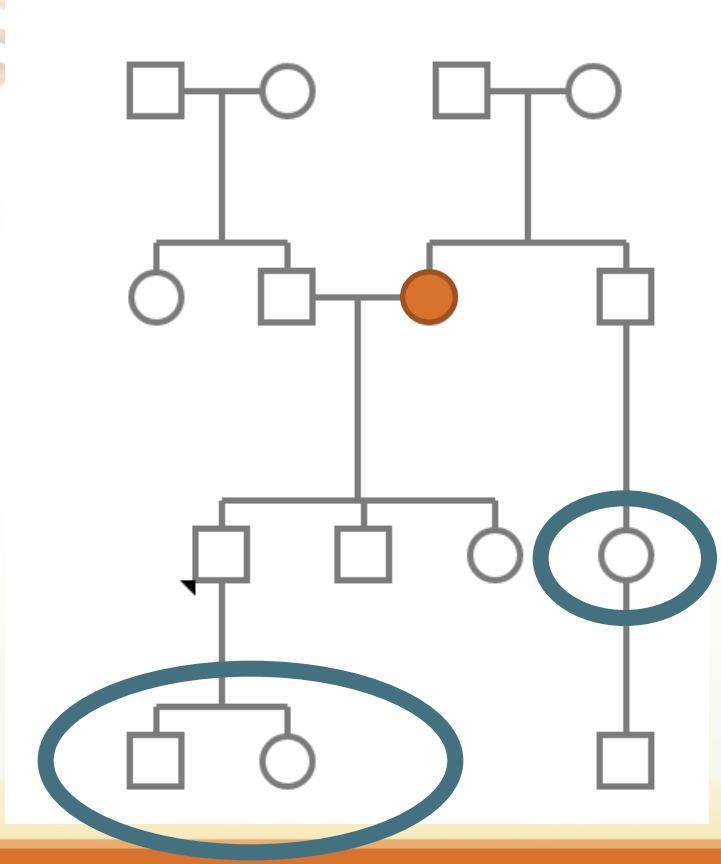
Who is at risk for FSHD1?



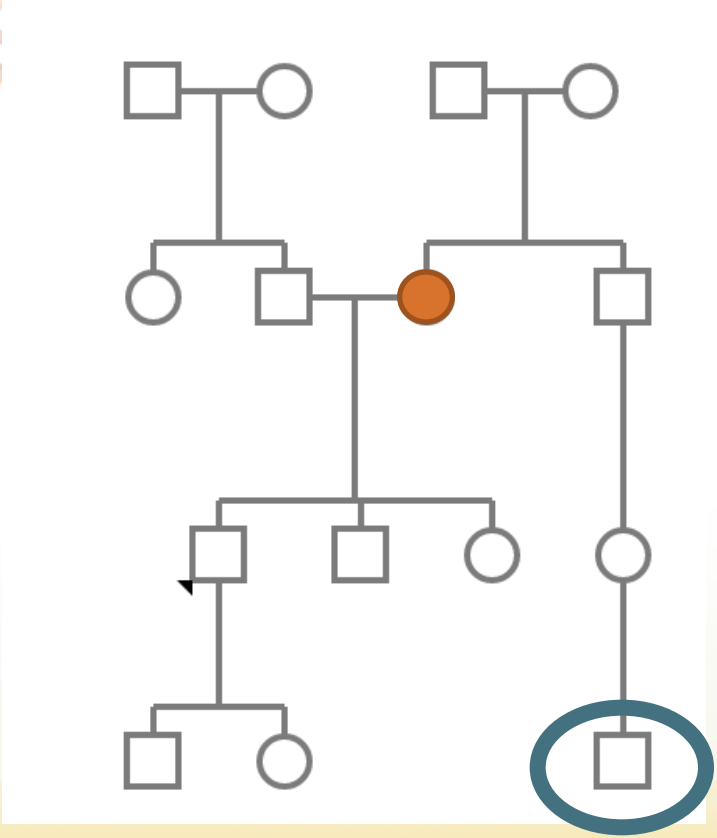
50%

Who is at risk for FSHD1?



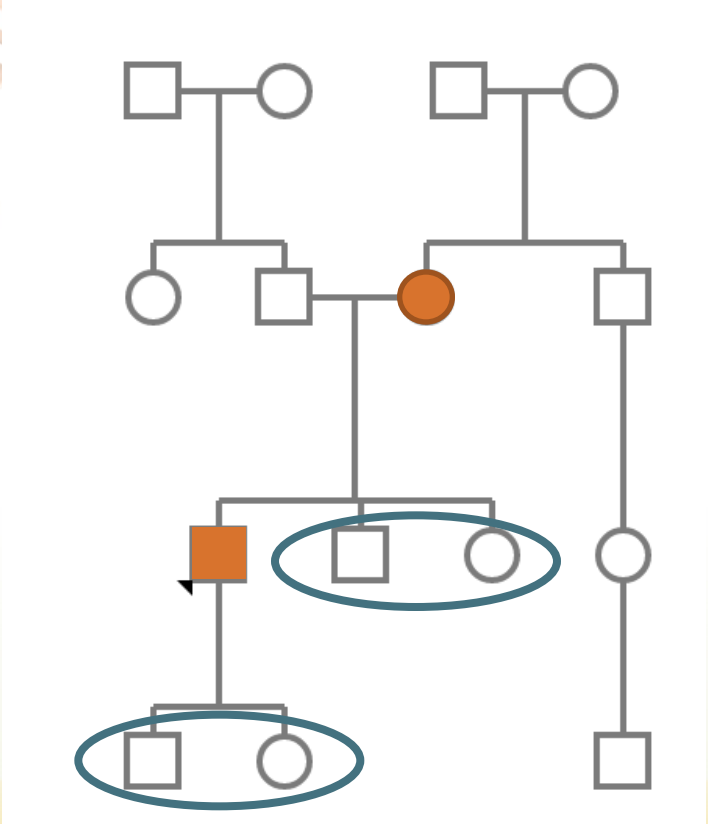
25%

Who is at risk for FSHD1?



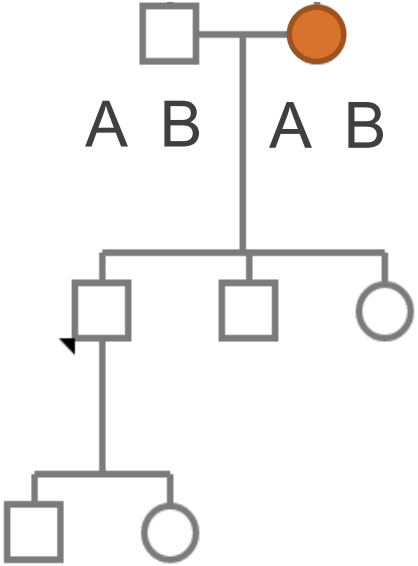
12.5%

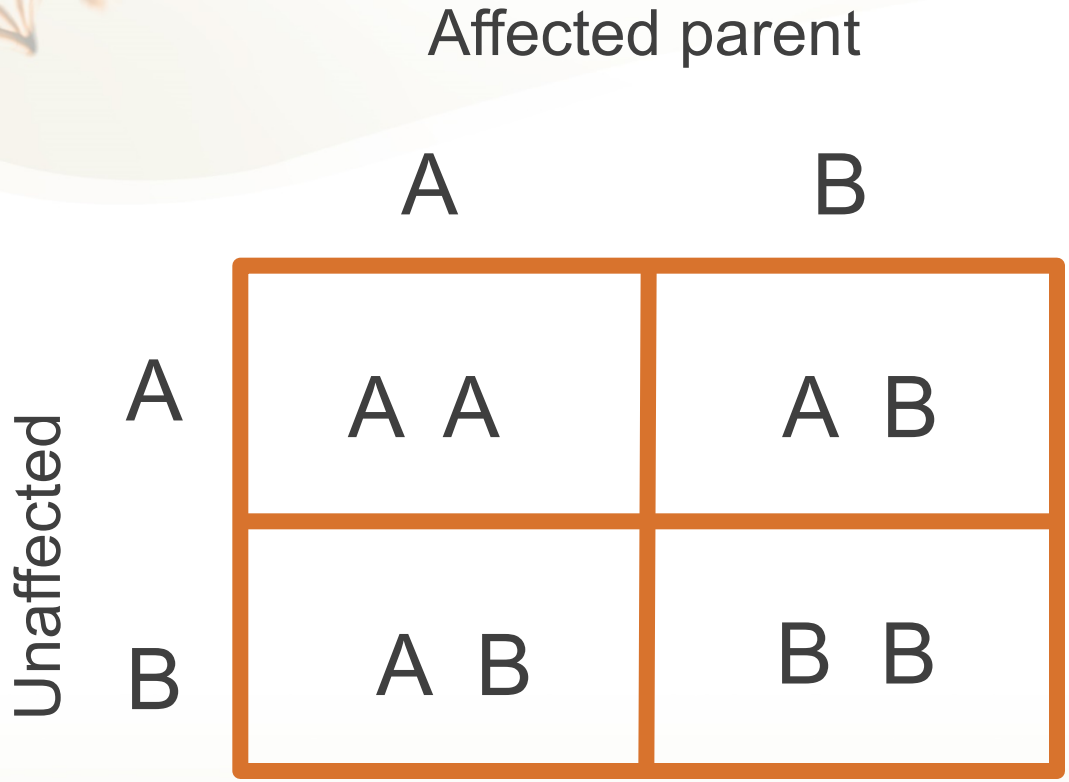
Now what are the risks for FSHD1?



50%

What chance do her kids have for FSHD2?





¾ (75%) chance child will get permissive allele

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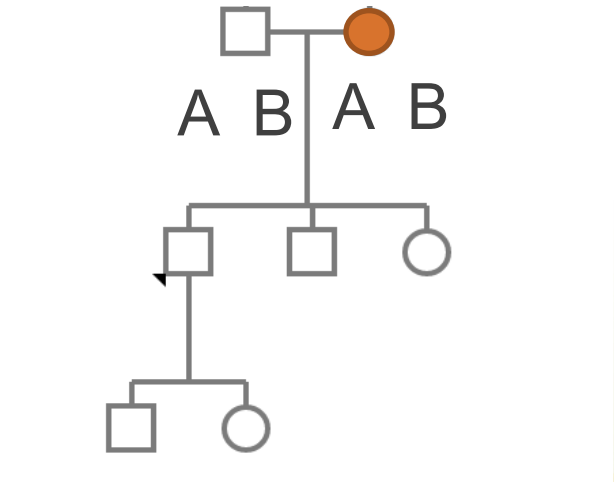
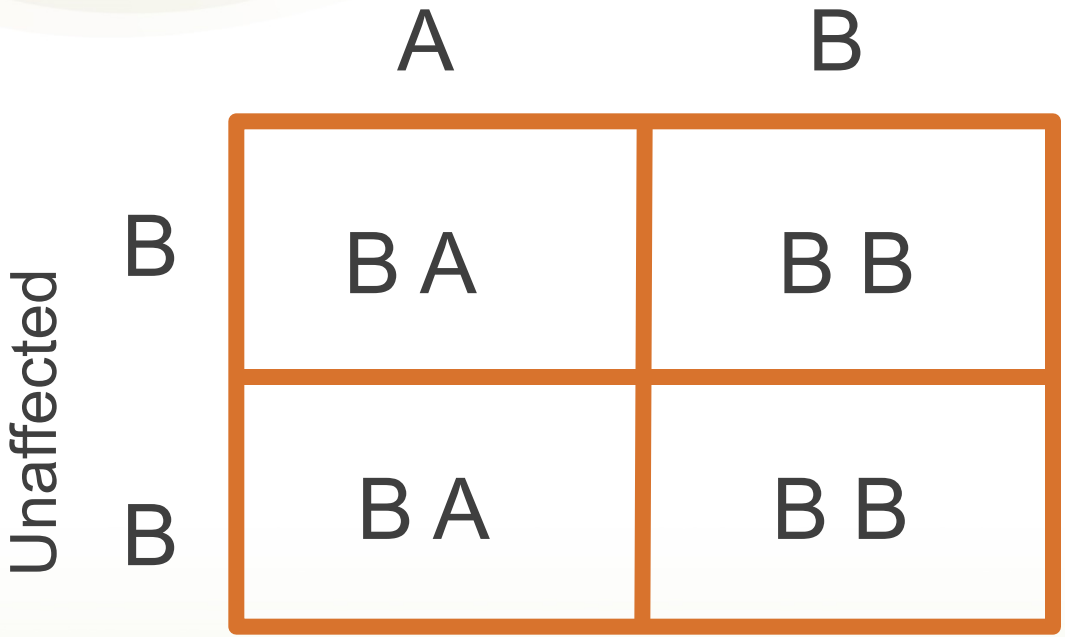
In this scenario

- 1/2 x 3/4 = 3/8 chance child will have FSHD



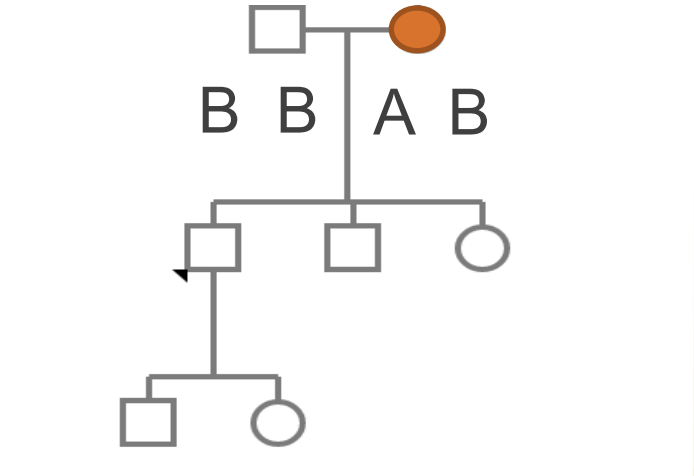
Affected parent



½ (50%) chance child will get permissive allele

In this scenario

- 1/2 x 1/2 = 1/4 chance child will have FSHD



Family planning options for FSHD

- Conceive naturally
  - No testing
- Conceive naturally
  - Test the fetus for FSHD
  - Amnio and CVS
- In vitro fertilization with preimplantation genetic testing
- Adoption, sperm/egg donation, etc.

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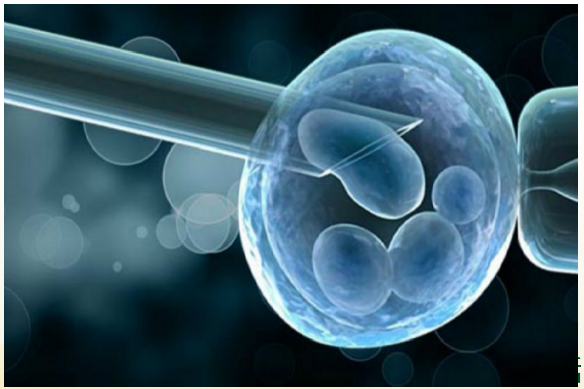
IVF with Preimplantation Genetic Testing- FSHD1

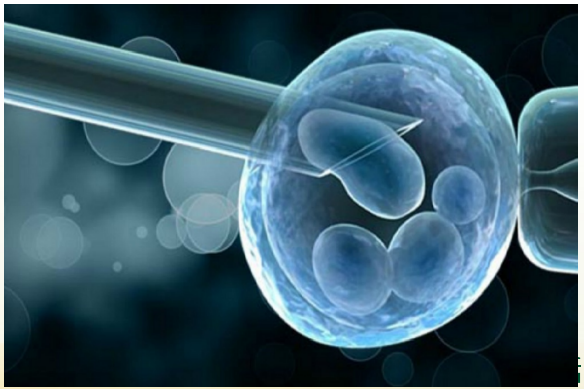
- Go through the IVF procedure
- Once embryos are obtained they are tested for FSHD contraction
  - Lab may ask for samples from additional family members
- Those embryos that test negative for FSHD are implanted
- Cons
  - Cost
  - No guarantee



https://www.iasoivf.com

IVF with Preimplantation Genetic Testing- FSHD2

- Go through the IVF procedure
- Once embryos are obtained they are tested for *SMCHD1* mutation
  - Lab may ask for samples from additional family members
- Those embryos that test negative for *SMCHD1* are implanted
- Cons
  - Cost
  - No guarantee



https://www.iasoivf.com

How can I or someone else be tested for FSHD?

- www.nsgc.org/findageneticcounselor
- Consult a neurologist

FIND A GENETIC COUNSELOR

A searchable directory of genetic counselors

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Thank you!

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