MUSCULAR DYSTROPHIES

Inherited disorders causing progressive muscle weakness and atrophy due to a genetic defect
Multiple types of MD with a common theme of muscle weakness
Some forms also cause cardiac dysfunction and cognitive deficits

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Remember steps in muscular activation

- Brain→nerves→muscles→contraction
- Lots of little details in there involving action potentials, neurotransmitters, myelin, gated ion channels, etc… should probably understand some of that stuff
- Disruptions anywhere along this pathway will result in inhibited muscle contraction
- With Myopathies, the nerve sends the signal to the muscle, but the muscle is unable to respond normally—muscular dystrophies are disorders of the muscles

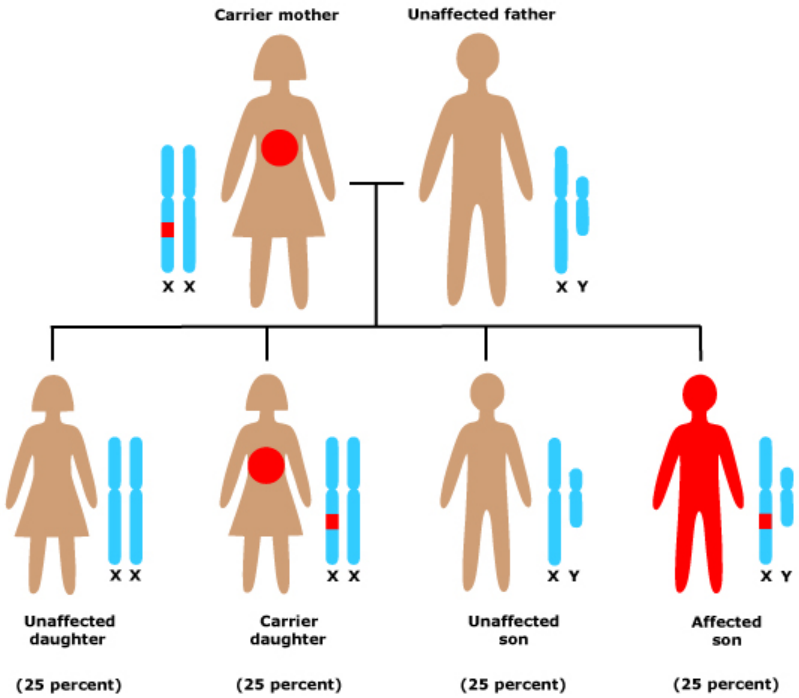
As genetics are the underlying problem behind MD, a review of genetics will facilitate understanding of different forms of MD.

- Reproduction=sex (review on your own)
- Male sperm XY chromosomes
- Women's egg XX chromosomes
- In reproduction, a woman contributes an X. If a male contributes a Y, the offspring will be male, if he contributes an X, the offspring will be female. Men are the deciders!

X-linked inherited diseases

- Caused by a mutation in one of the mother's X chromosomes
- May not be passed on to offspring (male or female)
- May be passed on to a daughter as asymptomatic carrier
- May be passed on to a son who will develop disease

Muscular dystrophy inheritance pattern



Duchenne, Becker, and some forms of Emery-Dreifuss muscular dystrophy are carried by the female parent. These muscular dystrophies affect 50 percent of male infants of mothers who carry the genetic defect; this is called X-linked inheritance. Females who inherit their mother's defective X chromosome generally have less severe disease than males.

Autosomal Dominant

- If a disease is autosomal dominant, it means you only need to get the abnormal gene from one parent in order for you to inherit the disease. One of the parents may often have the disease.

What happens if one of the parents has a condition due to an autosomal dominant faulty gene?
When a baby is conceived, each parent has passed on one copy of each of his or her genes to the baby. Therefore, the baby is a 'mixture' of the genetic information from each of his/her parents. When one of the parents is affected by, or predisposed to developing a condition due to an autosomal dominant mutation, he/she will pass on to a child either the working, or the faulty copy, of the gene.

As shown in *Figure 9.1*, where the autosomal dominant faulty gene copy is represented by 'D' and the working copy by 'd', there are four possible combinations of the genetic information that is passed on by the parents, in every pregnancy. There is a 1 in 2 chance that the autosomal dominant faulty gene will be passed on to the child by the affected or predisposed parent. The other parent can only pass on working copies of the gene.

This means that **in every pregnancy** there is:

- 1 chance in 2 (ie. 2 chances in 4) or 50% chance that their child will inherit the **faulty copy of the gene and the working gene copy**, and will therefore be affected by, or at increased risk for developing the condition (predisposed)
- 1 chance in 2 (ie. an equal chance) or 50% that their child will inherit **both working copies of the gene**: the working copy of the gene from his/her affected or predisposed parent as well as a working copy from his/her unaffected parent. In this case, the child will not be affected by or predisposed to the condition and cannot pass on the faulty gene that causes or contributes to the condition to any of his/her children
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While *Figure 9.1* shows the father as the parent carrying the autosomal dominant faulty gene, the same situation would arise if it was the mother.

Conditions that are due to autosomal dominant faulty genes usually affect men and women equally.

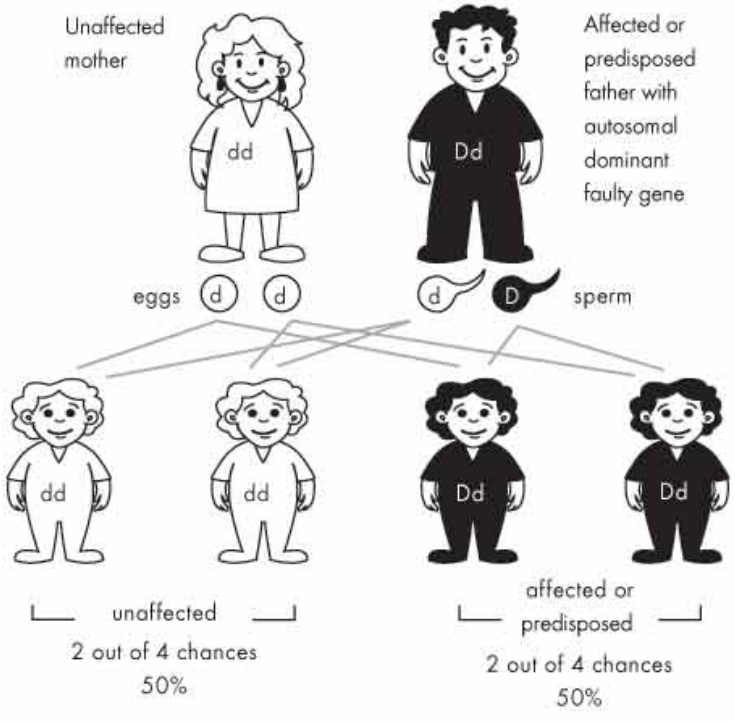

Figure 9.1: Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.

What happens if both parents have a condition due to an autosomal dominant faulty gene?
As shown in *Figure 9.2*, where the autosomal dominant faulty gene copy is represented by 'D' and the working copy by 'd', there are also four possible combinations of the genetic information that is passed on by the parents, in every pregnancy. There is 1 chance in 2 that each parent will pass on the faulty copy of the gene. There is also 1 chance in 2 that each parent will pass on the working gene copy.

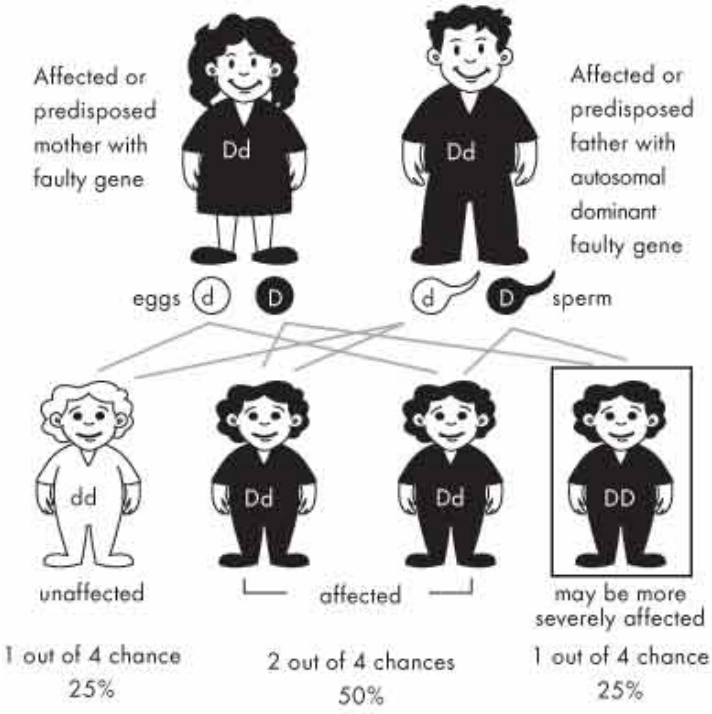

Figure 9.2: Autosomal dominant inheritance when both parents carry the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.

This means that **in every pregnancy** there is

- 1 chance in 4 or 25% chance that their child will only inherit **working copies of the gene from both parents** and be unaffected by the condition, or not at increased risk
- 1 chance in 2 (2 chances in 4) or 50% chance that the child will inherit the **faulty gene copy and the working copy** and be affected at some time in their life or be at increased risk for the condition (predisposed)
- 1 chance in 4 or 25% chance that their child will inherit the **faulty gene copy from both parents**. In this case, they will usually be more severely affected at some time in their life, depending on the condition involved. Achondroplasia and familial hypercholesterolaemia (Genetics Fact Sheets 38 & 53) are examples of conditions that are more severe when a person has inherited both copies of the faulty gene involved

What happens if both parents are unaffected carriers of the same autosomal recessive faulty gene?
When a baby is conceived, each parent has passed on one copy of each of his or her genes to the baby. Therefore the baby is a 'mixture' of the genetic information from each of his/her parents. When two carriers of the same faulty gene have a baby, each parent has a chance of passing on either the faulty gene or the working copy of the gene to the baby.

As shown in *Figure 8.1*, where the autosomal recessive faulty gene copy is represented by 'r' and the working copy by 'R', there are four possible combinations of the genetic information passed on by the parents, in every pregnancy. There is 1 chance in 2 (or 50%) that each parent will pass on the faulty copy of the gene. There is also 1 chance in 2 (or 50%) ie. an equal chance, that each parent will pass on the working gene copy.

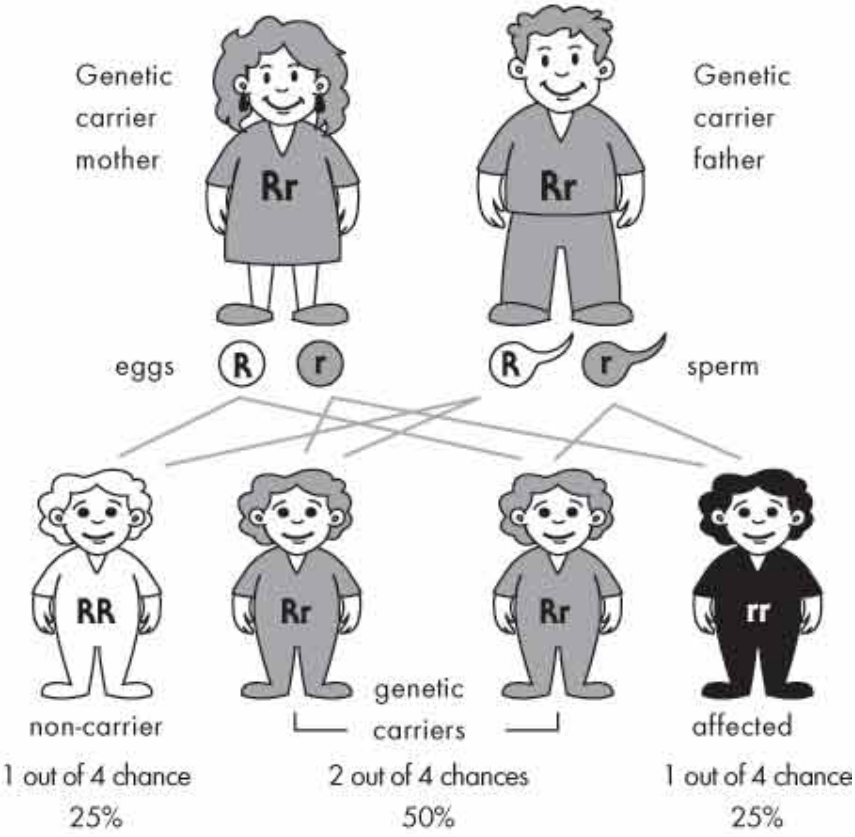

Figure 8.1: Autosomal recessive inheritance when both parents are unaffected genetic carriers for the condition. The faulty copy of the gene containing a recessive mutation is represented by 'r'; the working copy of the gene by 'R'.

This means that in every pregnancy there is

- 1 chance in 4 (25% chance) that they will have a child who inherits **both copies of the faulty gene** from his/her parents. In this case, no working gene product will be produced and their child will be affected by the condition
- 1 chance in 4 (25% chance) that their child will inherit **both copies of the working gene** and will be unaffected by the condition
- 1 chance in 2 (ie. 2 chances in 4; 50% chance) that their child will inherit the **faulty copy of the gene and the working copy of the gene** from each parent and he/she will be an unaffected carrier of the faulty gene, just like the parents; ie. a genetic carrier for the condition

What happens if only one of the parents is an unaffected carrier of an autosomal recessive faulty gene?

As shown in *Figure 8.2*, where the autosomal recessive faulty gene copy is represented by 'r' and the working copy by 'R', there are four possible combinations of the genetic information passed on by the parents, in every pregnancy.

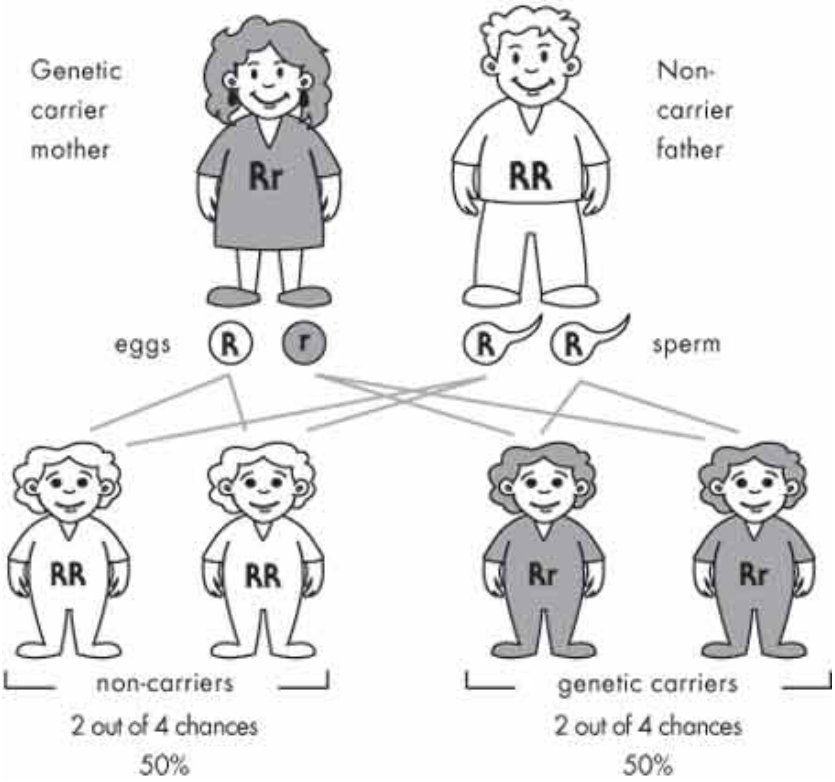

Figure 8.2: Autosomal recessive inheritance when only one of the parents is an unaffected genetic carrier for the condition. The faulty copy of the gene containing a recessive mutation is represented by 'r'; the working copy of the gene by 'R'.

This means that in every pregnancy, there is:

- No chance that the couple will have a baby affected with the particular condition
- 1 chance in 2 (ie. 2 in 4 chances; 50% chance) that they will have a child who inherits **both copies of the working gene** from his/her parents. In this case, the child will be unaffected by the condition
- 1 chance in 2 (ie. 2 in 4 chances; 50% chance) that their child will inherit the **faulty copy of the gene and the working copy of the gene** and he/she will be an unaffected carrier of the faulty gene; ie. a genetic carrier for the condition

WHEW!

Duchenne Muscular Dystrophy (DMD)

- Defective gene on X chromosome responsible for producing dystrophin (a protein that protects muscles)
- A dystrophin deficit leads to enzymatic muscle breakdown
- Disease occurs in males
- Age of onset 2-3yo, may be wheelchair bound by 12, survival into late teens/20's (respiratory infections, cardiomyopathy)
- Sx/s start centrally (trunk) spread to legs first
- Will likely see elevations in CK
- May also cause cardiomyopathy, scoliosis, fractures (from falls), may have some cognitive impairment
- Treatment with corticosteroids can increase strength, will not change prognosis
- Females may be asymptomatic carriers, may have mild symptoms
- Women with a family hx should perhaps consider genetic testing prior to becoming pregnant.

Becker Muscular Dystrophy—SIMILAR to DMD, but those affected make ***some*** dystrophin

- Defective gene on X chromosome responsible for producing dystrophin (a protein that protects muscles)
- A dystrophin deficit leads to enzymatic muscle breakdown
- Disease occurs in males
- Age of onset is later and symptoms are milder than in DMD
- Will likely see elevations in CK
- Comorbid cardiomyopathies are less common but can be more severe, survival into 40's
- Sx/s start centrally (trunk) spread to legs first
- Treatment with corticosteroids can increase strength, will likely not change prognosis
- Females may be asymptomatic carriers, may have mild symptoms
- Women with a family hx should perhaps consider genetic testing prior to becoming pregnant.

Emery-Dreifuss Muscular Dystrophy

- Can be caused by a number of different inheritance patterns, can occur in males/females
- Muscle weakness usually begins in arms in teen years, then progresses to legs and face
- Can also have cardiac abnormalities leading to malignant arrhythmias—pacemakers can be lifesaving

Myotonic Dystrophy

- Most common form of MD (in whites)
- Affects males/females
- Two genetic subtypes, originally named type 1 and type 2 (clinically the same, difference is in gene affected)
- Muscle stiffness, inability to relax muscles after contraction
- Affects different body systems causing muscle loss and weakness—facial muscles, arms, legs; also cardiac complications, cataracts, abnormal intellectual functioning, excessive daytime somnolence

Limb-Girdle Muscular Dystrophy

- Affects shoulder girdle and/or hip girdle
- May see elevations in CK
- Has multiple inheritance patterns
- Age of onset varies
- Disease progression is slow, comorbid conditions (cardiac, cognitive) are rare
- Treatment focused on stretching to prevent contractures

Fasiosapulohumeral Muscular Dystrophy

- Affects males/females
- Usually progresses slowly
- Extremely variable in age of onset and severity at onset
- Autosomal dominant—a parent with the disease has a 50% chance of passing the disease on to offspring
- Infant form—sx/s early in life—profound facial weakness (inability to close eyes, etc). Disease progresses to include shoulders, hip, etc. Most are wheelchair bound by age 9-10. May also have seizures, cognitive deficits, hearing loss.
- Classical form—sx/s between 20-30yo. Slow progression with milder weakness of facial muscles (pouting appearance), Shoulders and arms are usually involved eventually.

Congenital Muscular Dystrophy (CMD)

- Sx/s apparent at birth
- "floppy baby"
- No treatments available

References:

- **Up To Date (online)**
  - **Overview of Muscular Dystrophies**
- **2009 CURRENT Medic al Diagnosis and Treatment**
- **Centre for Genetics Education**
  - http://www.genetics.com.au/healthprof/index.html