X-linked conditions

If there's a known family history of an X-linked condition such as myotubular myopathy, Duchenne or Becker muscular dystrophy, Kennedy's disease or CMT1X, genetic counselling is recommended for women in the family to assess their risk of being a carrier.

Kennedy's disease, myotubular myopathy, Duchenne muscular dystrophy, CMT1X, Becker muscular dystrophy: What do these different neuromuscular conditions have in common?

They're all caused by alterations in genes we carry on our X chromosomes.

Females have two copies of the X chromosome and males just one copy so when there's a mistake in a gene that's on the X chromosome females have a got a second 'good' copy that provides back up but males don't and so will be affected by the X-linked condition.

This means that there are some special characteristics of families that carry a recessive X-linked condition – you'll never see an affected father pass the condition to his son and all the daughters of an affected male will be carriers for the condition.

That's because fathers pass the Y chromosome to their sons and the X chromosome to their daughters and in the case of a man with an X-linked condition that X chromosome carries the genetic mistake that is the cause of his condition.

Often in a recessive X linked condition there is no family history of the condition. This can be for two reasons, firstly a mistake on a gene that's on the X chromosome can be passed hidden through generations because females carry another X chromosome which has the healthy working gene on it that masks the effect of the gene with the mistake on it.

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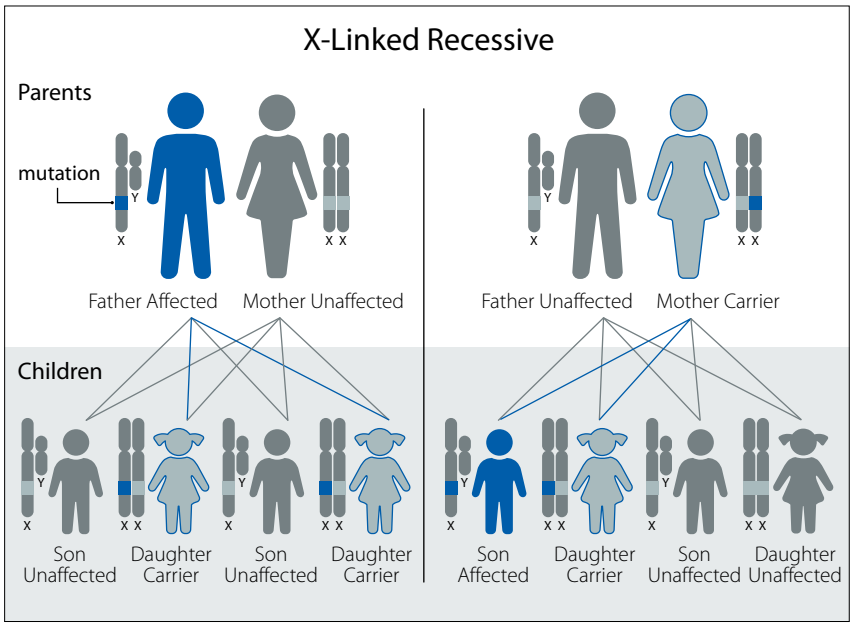
Every time a woman has a child she passes one copy of her two X chromosomes to that child – it could be the copy with the working gene or it could be the copy with the mistake on it.

If the child is a girl and she receives the copy with the mistake on it then she is a carrier for the condition (just like her mother). If the child is a boy and he receives the copy with the



Mode of inheritance.

mistake on it then he'll be affected by the condition because he lacks a second X chromosome to make up for the altered copy.

Secondly, during the process of DNA replication mistakes can be introduced. These are termed 'de novo mutations' meaning that they have occurred newly for the first time in an early stage of foetal development.

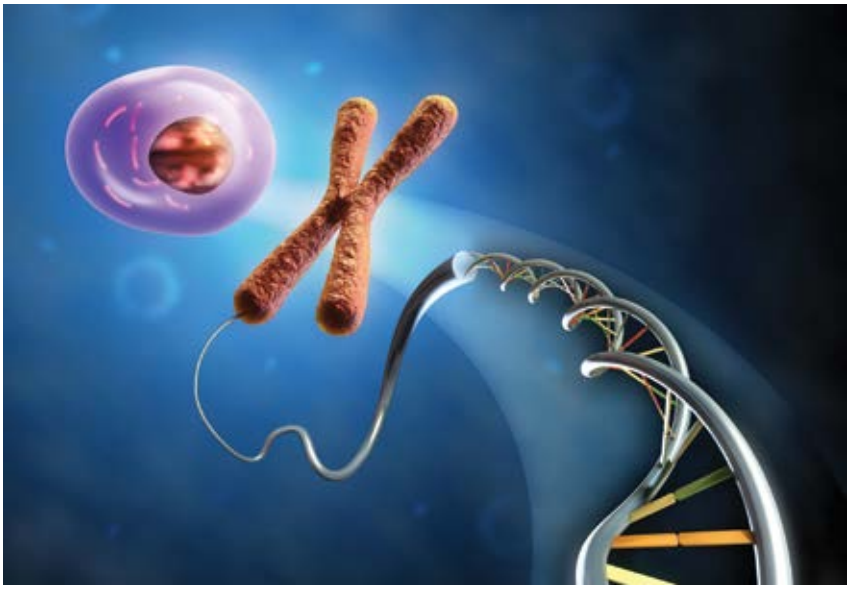
If this happens in the X chromosome of a male foetus then that male will be affected.

Some areas of the genome are more prone to becoming altered than others, for example the dystrophin gene is a particularly large gene and about one third of boys with Duchenne muscular dystrophy have the condition, not because they inherited an X chromosome with a mistake in the dystrophin gene from their mother but because the mistake in the dystrophin gene happened for the first time very early in their development.

Although recessive X-linked conditions usually occur in males these conditions do not happen exclusively in males and sometimes carrier females are affected, although usually it is considerably more mild.

One reason that some women are affected by a condition that is caused by a mistake in a gene on one of their X chromosomes is due to a skewing of the inactivation of the X chromosome that carries the working copy of the gene.

In females one of the two X chromosomes in each cell becomes genetically inactive early in development and remains untranscribed throughout life. This is termed X-chromosome inactivation. The result is that the effective amounts or dosages of products of X-linked genes are equal in males and females.



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X-inactivation occurs randomly throughout the cells in the body but sometimes the randomisation is not so random and is skewed towards the inactivation of the X chromosome that has the working copy meaning the copy containing the mistake is active in more tissues of the body.

Without X inactivation males and females would have different amounts of the proteins produced by the genes on the X chromosome.

The existence of X inactivation was first suggested by Mary Lyon in 1961. For a time this suggestion was known as the 'Lyon hypothesis,' and the inactive X chromosome was said to be 'lyonized', however these terms aren't usually used these days.

On rare occasions a female might have two altered copies of a gene present on both of her X chromosomes, in which case she will show the same signs and symptoms as an affected boy.

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Genetic counselling can be accessed by contacting Genetic Health Services New Zealand. Visit this website for more information: www.geneticheathservice.org.nz