Manifesting carriers

What is a "carrier"?

Diseases that are inherited (passed down from generation to generation) are described as genetic conditions. Typically one or both copies of a gene are not working properly (affected by a mutation) and the effect that this dysfunction has on the body is what causes the various presentations of the different genetic conditions.

There are several mechanisms by which genetic diseases can be inherited. To be a carrier one functional copy needs to be enough for normal function. These types of inherited conditions are described as recessive.

In autosomal recessive inheritance the affected gene is on a chromosome inherited equally by males and females. Both copies of the gene need to have a mutation for the disease to present. In this situation it is likely that both parents have one functioning gene and one faulty gene for a condition and that, through chance, the baby has received a dysfunctional copy of the gene from each parent. Because having one functioning gene is enough for the disease to not be present the parents are described as "carriers" for that condition. It is very unlikely that either parent was aware that they were a carrier until the baby is born. In each pregnancy there is a 25% chance that the child will be affected, 50% chance they will be a carrier like their parents and a 25% chance that they have received the two functional genes and are not affected nor a carrier.

The sex chromosomes X and Y determine if a baby will be a boy or a girl. X-Linked conditions are caused by a defect in a gene on the X chromosome. One functioning copy is enough to prevent the condition. Girls receive an X from mum and an X from dad and are described as XX. Boys receive an X from mum and a Y from dad and are described as XY. As boys have only one X chromosome if they inherit an X chromosome with the defective gene then they will have the condition. The mother is described as a "carrier" and with one functioning gene is usually unaffected. A carrier mother has a 25% chance in each pregnancy of having an affected male child.

How does a carrier become a "manifesting carrier"?

Basically if one functional copy is enough to prevent the condition a manifesting carrier has lost functionality in their one copy and cells with this lack of functionality will be presenting the condition. This loss can be similar to the normal presentation of an affected person (severe), mild because most functionality is preserved or anywhere in between.

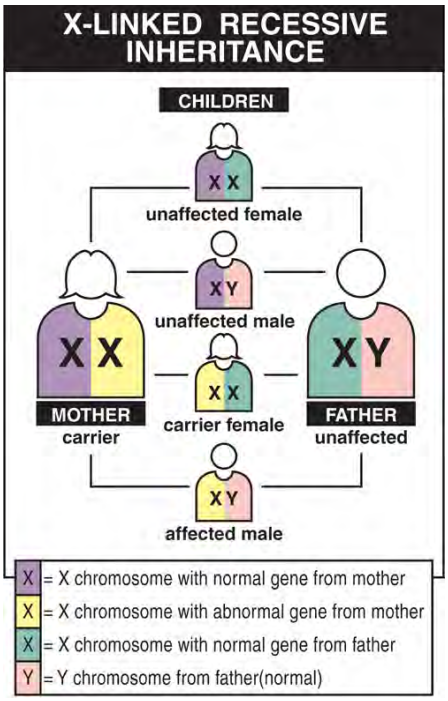

Chart showing the genetic inheritance pattern of X-linked Duchenne muscular dystrophy

Mechanisms that cause a carrier to manifest

X-inactivation (also called lyonisation):

Although females have two X chromosomes in each cell only one is needed as demonstrated by males who only have one X chromosome. To prevent too much genetic information, one X chromosome is turned off or inactivated in each of the females cells. Typically this is random and leads to the female being a mosaic (if a gene is mutated then you would expect approximately 50% of cells with and 50% of cells without the functioning gene). In some females there is skewed X-inactivation. Around 35% of women have skewed ratio of 70:30, and 7% of women have an extreme skewed ratio of over 90:10. If this is in favour of the chromosome with the dysfunctional gene, the result is the condition presenting potentially similarly to an affected male. It is the individual's inactivation pattern that leads to the variable presentation found in female manifesting carriers of X-linked conditions such as Duchenne and Becker muscular dystrophy.

Any other mechanism that prevents the functional gene from being expressed in the cell will cause disease presentation in those cells. This includes allelic exclusion and deletion of the functional gene.

Diagnosis

Diagnosis will depend on the condition that is being manifested. For neuromuscular conditions the following tests would be normal to help the medical professional come to a diagnosis.

- Muscle Biopsy – looks at an individual's muscle cells for characteristic patterns of dystrophin
- Blood Testing – looks for non-random X-inactivation patterns and elevated levels of creatine phosphokinase (CPK)
- Electromyography (EMG) – observes the electrical activity of muscles and its consistency with activity typical of Manifesting Carriers.
- Electrocardiogram (ECG) – can identify abnormal heart rhythms
- DNA Testing – can identify the presence of the abnormal gene in the individual

Genetic counseling is available to families once a genetic condition has been determined. This service provides information, helps families understand inheritance patterns and what this means

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in their family, as well as enabling people to make more informed family-planning decisions. You can access this via your GP, self-refer or an MDA Fieldworker.

Management

Once a condition has been determined it is important to be aware of any hidden symptoms such as underlying heart conditions or anesthetic reactions that are a part of the typically presenting disease. Because of the variable nature of the presentation in each person and the fact that most neuromuscular diseases have no cure, symptom management is focused on prevention and treatment of the presenting symptoms.

Typically, regular exercise and stretching and a good diet that helps maintain a healthy weight will be of benefit.

A neurologist, cardiologist, respiratory physician, physiotherapist, occupation therapist, orthopaedic surgeon and a dietitian may all be needed at some point. Due to the progressive nature of these conditions, make sure you are given referrals as things change so that the new symptoms are getting the best treatment available.

Support

The MDA Fieldworkers are available for support. They have in-depth knowledge of a range of neuromuscular conditions, and will have a better understanding of your needs and challenges. Have a chat over the phone or they can come to you for a kanohi ki te kanohi/face-to-face visit. They may have some real practical suggestions that have worked for others to offer as well. This service is offered free of charge to MDA members and is funded through donations and grants. Contact your local MDA Branch to be put in contact with your fieldworker.

The MDA Support Network allows people with similar circumstances or challenges to come together to share their experiences and provide emotional and moral support, in addition to practical advice and information. By bringing together people with common experiences, support networks can provide an invaluable addition to medical care. The MDA of New Zealand Support Network currently has over 700 members throughout New Zealand who want to be in touch with others livings with neuromuscular conditions.

Please see the MDA website www.mda.org.nz for contact details and more information that you might find relevant for you and your whanau.

The information contained above was largely sourced from the following websites:

http://ghr.nlm.nih.gov/glossary=xchromosomeinactivation

http://www.musculardystrophyuk.org/app/uploads/2015/02/manifesting-carriers.pdf