

Society for  
Mucopolysaccharide  
Diseases



# Inheritance



A guide to  
understanding  
**the pattern  
of inheritance**  
in Mucopolysaccharide  
and Related Diseases  
including Fabry Disease

**Affected:** An individual who manifests symptoms of a particular condition.

**Gene:** A length of DNA which encodes for a particular protein and is known as the single unit of heredity.

**DNA** (Deoxyribonucleic acid): This is a large, double-stranded, helical molecule that contains genetic instructions for growth, development, and replication and allows for transmission of genetic information from one generation to the next.

**Chromosome:** Physical structure of a large DNA molecule organised into genes and supported by proteins called chromatin.

**Mutation:** Any alteration in a gene from its natural state; may be disease-causing or a normal variant.

**Autosomal:** Refers to any chromosomes other than the sex-determining chromosomes (i.e. the x- and y-) or the genes on these chromosomes.

**X-chromosome inactivation:** This is sometimes called lyonization. This is when one of the x- chromosomes in a female (either maternally or paternally derived) is randomly inactivated and in early embryonic cells is not expressed.

**Carrier:** An individual who has a recessive disease-causing gene mutation at a particular locus on one chromosome of a pair and a normal allele at that locus on the other chromosome.

## Introduction

MPS and related diseases are rare, inherited or genetic disorders that are passed down in families. Children affected by one of these diseases are born with it and will be affected by it for the rest of their lives.

The symptoms vary from one disease to another. There is also a wide spectrum of severity for each of the MPS and related diseases. Some individuals may be more mildly affected than others but many diseases cause severe disability. In some cases growth can be limited and mental as well as physical disabilities can develop.

For our bodies to work properly we need to constantly break down used material for disposal. Children born with an MPS or related disease are unable to produce an enzyme essential for this breakdown process. This means the used material remains stored in the cells of the body gradually accumulating over time causing the disease to progress.

MPS and related diseases are caused by faults or alterations in genes needed to produce these essential enzymes.

The diagnosis of a child or adult with an MPS or related disease often comes as a devastating shock to the individual and their parents, especially as there may be no history of anyone else in the family being similarly affected. One of the reasons for this is the way these diseases are passed down in families.

This booklet is produced by the Society for Mucopolysaccharide Diseases (the MPS Society). Its aim is to provide some background information and a simple explanation of the pattern of inheritance in MPS and related diseases that individuals and their families may need in order to make fully informed decisions. Carers and professionals working with affected individuals and their families may also find this booklet helpful.

## What are genes?

Genes are the unique set of instructions inside our bodies that make each of us as an individual. There are many thousands of different genes, each carrying a different

instruction. They are the blueprint for our growth and development and control how our bodies function.

Genes are made up of long strands of DNA tightly coiled on structures called chromosomes. DNA is made up of a sequence of four chemicals and for each gene there is a particular order that the sequence follows. Just like the order of letters and words in a sentence, the sequence of the DNA for each gene has to make sense. When something goes wrong and the sequence is altered, then the gene does not work properly and this can cause a genetic condition such as one of the MPS or related disorders. Gene alterations are also known as mutations. We all have two copies of each gene. One copy is inherited from each of our parents. When we have children, we pass on only one copy of each of our genes.

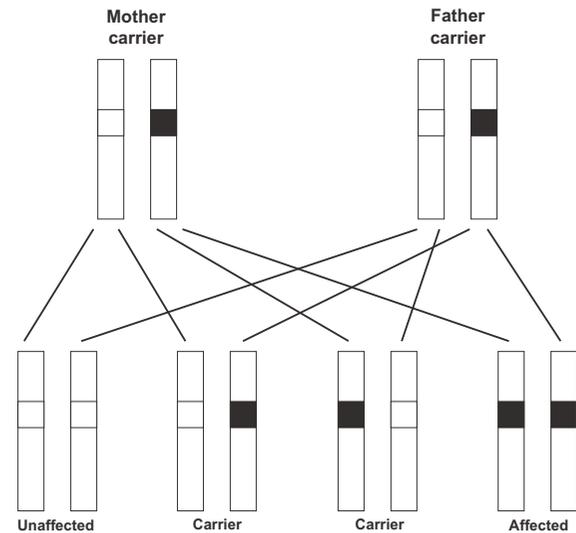
With the exception of Hunter Disease and Fabry Disease the MPS and related diseases are inherited in an autosomal recessive form of inheritance.

## What is autosomal recessive inheritance?

Autosomal recessive describes the pattern of inheritance of a disease that requires the presence of two copies of a mutation in the same gene in order for the condition to manifest itself. A child who is affected by one of these MPS or related diseases will have two altered copies of that particular gene in each cell of their bodies. This means that the parents will each have one copy of the gene that works normally and one copy that is altered. Parents of children with an MPS or related disease caused through an autosomal recessive inheritance pattern are called 'carriers', and because they have one normally working gene they are unaffected by the disease. This type of inheritance applies to all MPS and related diseases covered by the MPS Society except Hunter Disease and Fabry Disease.

The top illustration on this page shows the pattern of inheritance when both mother and father are carriers. The bottom illustration on this page shows the pattern of inheritance when one parent is affected with the disease and the other parent is neither affected nor a carrier.

### Autosomal Recessive Inheritance

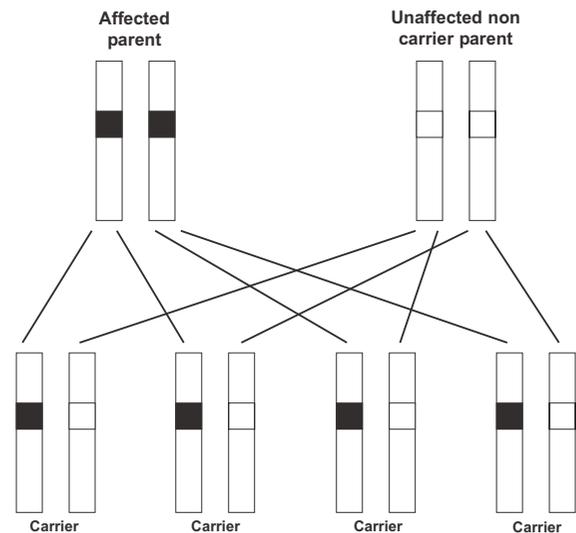


1 in 4 chance that the child would be affected by MPS

2 in 4 chance that the child would be a carrier

1 in 4 chance that the child would not inherit either altered gene and would not be a carrier

### Autosomal Recessive Inheritance



All children will be carriers irrespective of sex



If one parent is affected with the disease and the other parent is a carrier for this disease there is a 2 in 4 chance of the child having the disease and a 2 in 4 chance the child would be a carrier.

## Having children

If both healthy parents carry the same altered recessive gene, then each child they have has:

- A 25% (1 in 4) chance of inheriting the altered gene from both parents and therefore being affected. For each child regardless of their sex, the chance is the same.
- A 50% (1 in 2) chance of inheriting one copy of the altered gene from one of their parents. These children would then be healthy carriers like their parents.
- A 25% (1 in 4) chance of inheriting two normal copies of the gene. These children will be completely healthy.

If only one parent is a carrier of the altered gene, then each of their children has a 50% chance of being a healthy carrier, but will not be affected.

Parents who are closely related to each other, such as first cousins are more likely to have children with recessive conditions.

## What are the chances of being a carrier for an autosomal recessive disease?

MPS and related diseases are rare and estimates of their occurrence in a population vary. The possibility of two carriers coming together by chance is an unlikely event. This is the case for all MPS and related diseases that are autosomal recessively inherited.

## What is X-linked recessive inheritance?

X-linked recessive inheritance usually causes the disease to be expressed in males. Female carriers are usually non symptomatic carriers in Hunter Disease.

Genes are carried on structures called chromosomes. It is usual to have 23 pairs of chromosomes that are numbered in

pairs from pair number 1 to pair number 22 with one pair of sex chromosomes, XX for a female and XY for a male. A child will inherit one set of chromosomes from the mother in the egg and one set from the father in the sperm.

The altered gene responsible for Hunter Disease is found on the x- chromosome. If a woman has an altered gene on one of her x- chromosomes then she will be a carrier. Carriers of x-linked diseases are usually healthy because they have a second normal copy of the gene on their other x- chromosome that compensates for the gene that is not working.

## Hunter disease (MPS II)

This disease is passed on in families in what is known as x-linked recessive inheritance. The top illustration on this page shows where a mother is a carrier of Hunter Disease. The bottom illustration shows the inheritance pattern where the father is affected by Hunter Disease and the mother is not a carrier.

## Having children

If a woman carrier has a boy there is a 1 in 2 (50%) chance that the boy will be affected by the altered gene that she carries.

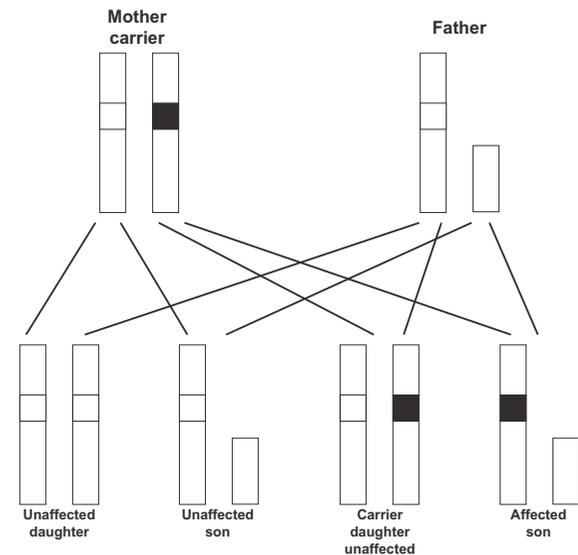
If a woman carrier has a girl, there is a 1 in 2 (50%) chance that the girl will inherit the altered gene and be a carrier like her mother.

When men who are affected by an x-linked condition have children, all the daughters will inherit the altered gene on their x- chromosome. These daughters will be carriers. Men do not pass on the x- chromosome to their sons. Therefore all sons of men with x-linked conditions are completely normal.

Sometimes the gene alteration occurs for the first time in an affected boy and the mother is not a carrier. Apart from the small chance that more than one of her eggs may carry the gene alteration, her chance of having a further affected child will be low.

Males are mainly affected by Hunter Disease. There are rare exceptions when females can have the disease and this is usually caused by a chromosome abnormality.

## X-linked Recessive Inheritance

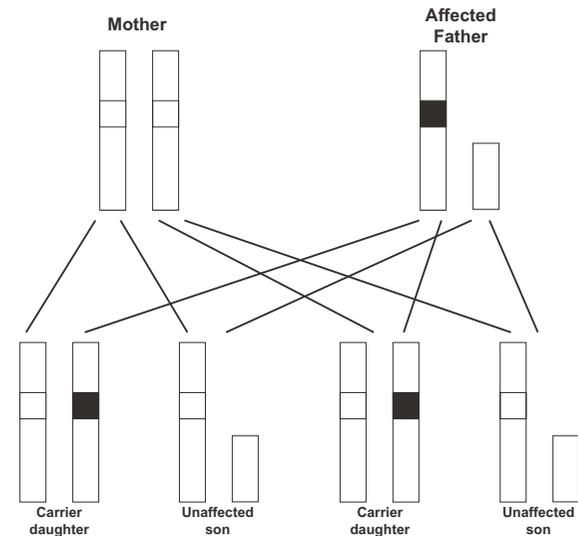


1 in 4 chance that a child would be affected e.g. Hunter's

All sons would have a 1 in 2 chance of being affected

All daughters would have a 1 in 2 chance of being a carrier

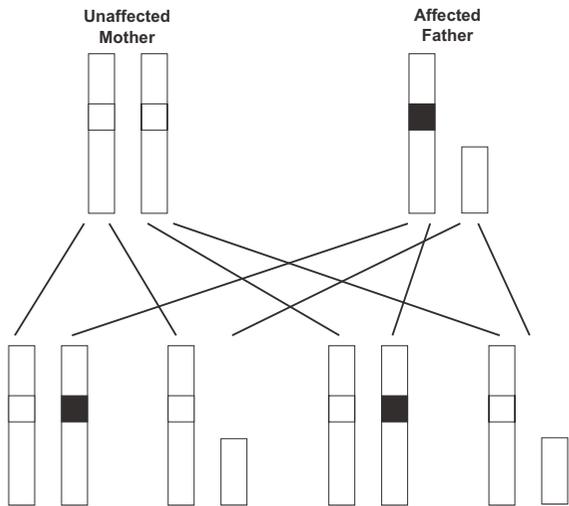
## X-linked Recessive Inheritance



All daughters are carriers.

All sons are neither affected nor carriers.

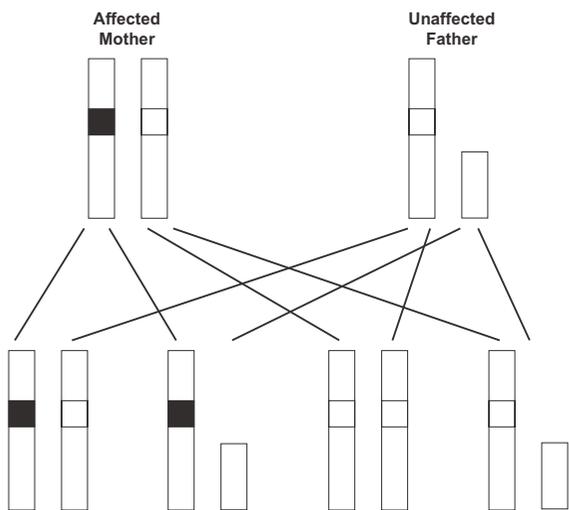
## X-linked Inheritance Father affected by Fabry Disease



All daughters will be affected by Fabry Disease

All sons will not be affected by Fabry Disease

## X-linked Inheritance Mother affected by Fabry Disease



All children have a 50% chance of being affected by Fabry

It can also be caused by the inactivation of the healthy x- chromosome therefore leaving the x- chromosome with the mutated gene to be expressed.

## Fabry disease

Fabry disease also follows an x-linked pattern of inheritance but differs in that both males and females can be affected. The inheritance pattern is called x-linked semi-dominant inheritance.

Women may have less severe disease manifestation than men but this is not always the case. The reason for this is that females have two x- chromosomes, one of which will be active and one inactive. It is a matter of chance which chromosome is active in a particular cell. If the pattern of inactivation is skewed in favour of the x- chromosome with the gene alteration, then a female is likely to have more severe symptoms.

## Carrier testing for MPS & related diseases

Once the disease-causing gene alteration has been identified in an affected individual child or adult, carrier testing can be offered to family members. Any family member can ask their General Practitioner for a referral to their local Medical Genetic Service to discuss carrier testing.

## Genetic counselling

Specialist NHS Medical Genetic Services are based in Regional Genetic Centres throughout the UK. Alternatively, there are a number of specialist centres where you can go to be tested and see a genetic counsellor. Following the diagnosis of a child or adult with an MPS or related disease, genetic counselling may be sought.

Genetic counselling aims to help people gain sufficient understanding of their situation so that they can make informed decisions about what they wish to do.

Genetic counsellors can give people information about these diseases; how they are inherited and the chances of either inheriting or passing on these diseases.

Individuals, parents and other family members may wish to find out about carrier testing and tests that are available in pregnancy and discuss the options open to them.

## About the MPS Society

The Society for Mucopolysaccharide Diseases is a registered charity, founded in 1982, which represents from throughout the UK children and adults suffering from MPS and Related Diseases, their families, carers and professionals.

The Society's advocacy team provides a unique, needs-led, individual advocacy service to individuals suffering from MPS and Related Diseases, their families and carers.

The Society publishes a range of materials related to each of the MPS and related diseases. These explain in greater detail the presentation and clinical management of these diseases. They are an invaluable resource for individuals affected by MPS and related diseases, parents, carers and professionals working in this field.



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