

DISEASE

(hypertension) and gradually kidney failure develops. The involvement of the blood vessels of the heart and brain may lead to heart disease (myocardial infarcts [heart attacks], heart failure and disorders of the function of the heart valves) and brain disorders (strokes, seizures, brain haemorrhage, and personality changes). Other features include arthralgia (painful joints), diarrhoea, weight loss and disturbed temperature sensation. Intelligence is normal.

The advancing kidney disease is the main cause of death. If untreated, the average age of death in males is 41 years. Both the quality and duration of life have been improved by advances in dialysis and transplantation to treat the kidney disease; improved pain management using drugs such as phenytoin and carbamazepine; and general improvements in the management of cardiac and nervous system disease.

Females who carry the gene usually have either no symptoms or much milder symptoms than the males. The most common finding in females is a whorl-like pattern in the lens of the eye. A special instrument called a slit-lamp is required to detect it.

In males the diagnosis is made by the measurement of the enzyme, α -galactosidase, in blood cells or cultured skin cells. In females the enzyme activity may be reduced but this test is not reliable. A more reliable test in females is direct testing of the change in the gene if it has been identified in affected males in the family. If gene testing is not available for the family then it may be necessary to measure the enzyme activity in hair roots. In carrier females some of the hair roots have very low α -galactosidase activity and some normal. (See Diagnosis of affected males and carrier females).

X-linked Recessive Inheritance

All of our characteristics are controlled by genes, which are packaged on structures called chromosomes and exist in every cell of the body. Humans usually have 46 chromosomes, and two of these, the X and the Y, determine our sex. Females have an XX pattern and males an XY pattern. The gene for Fabry disease is located on the X chromosome. Males have only one X chromosome, and if there is a mistake in any gene on the X chromosome, disease results. If a female has the gene for Fabry disease on one of her two X chromosomes this usually causes her no major problems as the back-up copy of the gene on the other X chromosome usually compensates. Such a female is said to be a carrier for the Fabry gene.

When a carrier female (Diagram 1) has children, she can pass on either the X chromosome with the Fabry gene (shown as X^F) or the partner X chromosome. Her children therefore have a 1 in 2 or 50/50 chance of inheriting the gene from her. If the child is a girl she will have a 1 in 2 chance of being a carrier. If the child is a boy, he will have a 1 in 2 chance of being affected. Overall, there is a 1 in 4 (or 25%)

chance for an affected boy with each pregnancy, regardless of the outcome of previous pregnancies.



Typical skin rash seen in patients affected by Fabry disease. Fabry disease is an 'X-linked disorder', which means that females 'carry' the genes, but males are affected. However, symptomatic female carriers are not uncommon.

Photos reproduced courtesy of Dr. Eric Haan, Director, South Australian Clinical Genetics Service, Women's and Children's Hospital.

When a male with Fabry disease has children (Diagram 2), he will pass on his X^F chromosome containing the Fabry gene to all of his daughters who will all therefore be carriers. He will pass on his Y chromosome to his sons who will therefore be unaffected.

Diagnosis of affected males and carrier females

In males, the diagnosis of Fabry disease is made by measuring the level of α -galactosidase activity in blood or cultured skin cells. Affected males have very low enzyme activity and the test is diagnostic of the condition.

However, this test is not reliable for the identification of carrier females.

The gene for Fabry disease was discovered in 1986. If a particular change ('mutation') in the Fabry gene has been identified in an affected male, his female relatives can be tested for their carrier status by specific gene analysis to determine the presence or otherwise of the mutation. This method offers a definitive result for the individual.

Before the Fabry gene was isolated and mutations responsible for the disorder were found, it was often necessary to measure the enzyme activity in up to 100 individual hair roots to determine carrier status for females. This is a time-consuming and resource-intensive process, as enzyme activity in each hair root required measurement individually. With the identification of the gene, the method of choice for identifying carriers for Fabry disease is analysis of the mutation(s) identified in a Fabry-affected male within the family.

Treatment

Clinical trials to determine the effectiveness of enzyme replacement therapy as a treatment for Fabry disease are currently underway in Australia and elsewhere. This form of therapy, where commercially manufactured α -galactosidase is infused into patients every two weeks, is being

developed separately by two US companies, Transkaryotic Therapies Inc. and Genzyme Corporation. Results of clinical trials held to date were made public at the recent American Society for Human Genetics meeting held in Philadelphia, and suggest that these therapies have positive effects in patients.

Authors:

Dr. Jim McGill,
Metabolic Physician,
Herston Hospitals Complex, Queensland

Ms. Mardi Versteegen,
Fabry Support Society, Victoria

Ms. Margaret Sahhar,
Social Worker,
Victorian Clinical Genetics Service, Victoria

X-linked Recessive Inheritance

Diagram 1

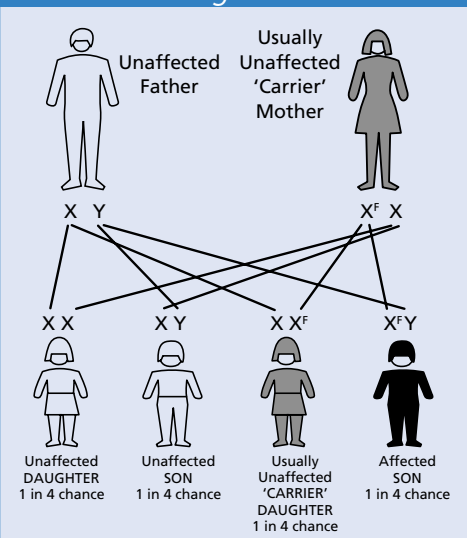
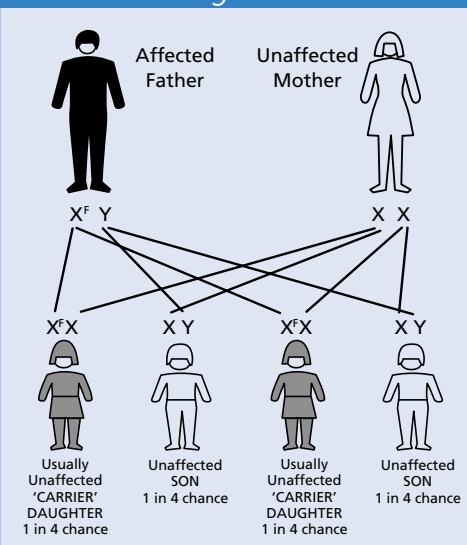


Diagram 2



Reproduced courtesy of the NSW Genetic Education Programme. X^F denotes affected chromosome.