**Important points**

- A number of genetic conditions are more common amongst descendants of Central and Eastern European (Ashkenazi) Jews than in people from other population groups. These conditions include Tay-Sachs disease, Canavan disease, Fanconi anaemia, familial dysautonomia and cystic fibrosis (CF).
- All of these are genetic conditions due to inheriting two faulty copies of a gene.
- Tay-Sachs disease (TSD) is a degenerative condition of the nervous system where apparently healthy babies at about 6 months of age lose already acquired skills, gradually become blind, paralysed and unaware of his/her surroundings and die before about 5 years of age. All have a ‘cherry-red spot’ on the retina at the back of the eye even before symptoms appear and both boys and girls are affected.
- TSD is due to inheriting two faulty copies of a gene called the HEX A gene that contains the information for the production of an important protein in the brain and nervous system.
- People who have one working copy of the HEX A gene and one that is faulty are called ‘carriers’ of the change that makes the gene faulty i.e. genetic carriers for TSD.
- Genetic carriers for TSD do not have Tay-Sachs disease because they can still produce enough HEX A protein.
- About 1 in 25 Ashkenazi Jewish Australians are genetic carriers for TSD.
- People with TSD have both copies of their HEX A gene faulty: they cannot produce the important HEX A protein.
- The pattern of inheritance in families of the faulty gene causing TSD is described as autosomal recessive inheritance.
- When both parents are carriers of the faulty gene, they have 1 chance in 4 (or 25% chance) in every pregnancy of having a child with TSD.
- If only one parent is a carrier of the faulty gene, they will not have a child with TSD.
- The information above applies similarly to the inheritance pattern of Canavan disease, Fanconi anaemia, familial dysautonomia and CF.

**Genetic testing** to determine if a person is a carrier of the faulty gene(s) involved in these conditions can be discussed with a doctor or a genetic counsellor. Testing may be available pre-pregnancy and in pregnancy and is appropriate when there is a family history or a blood relative is a genetic carrier for these conditions.

- Where both parents are genetic carriers of the same genetic condition, they can find out information about the condition and their chance of having an affected child and discuss their reproductive options with a genetic counsellor (see Genetics Fact Sheet 3).
- **Genetic carrier screening** may also be available for these conditions based on Ashkenazi Jewish ancestry, even if there is no family history of the condition. The screening conducted pre-pregnancy, including with senior high school students as part of a community genetics screening program and in pregnancy will only pick up those who are carriers of one of the more common changes in the gene(s) involved (see Genetics Fact Sheet 21).

A number of genetic conditions are more common amongst descendants of Central and Eastern European (Ashkenazi) Jews than in people from other population groups. These conditions include:

- Tay-Sachs disease
- Canavan disease
- Fanconi anaemia
- Familial dysautonomia
- Cystic fibrosis (CF)

This Fact Sheet discusses Tay-Sachs disease (TSD) as an example of these conditions that all follow the same pattern of autosomal recessive inheritance in families and for which community screening programs have been established worldwide. Brief information is also provided on the other conditions.

**What are the characteristic features of Tay-Sachs disease?**

Tay-Sachs disease (TSD) is a severe genetic condition of the nervous system and is named after two doctors - a physician, Dr Bernard Sachs and an ophthalmologist, Dr Warren Tay - who first described the condition in 1887. They noted that a number of children of Central and Eastern European (Ashkenazi) Jewish ancestry:

- At birth had no apparent problems
- By about 6 months, stopped smiling, crawling or turning over, lost their ability to grasp or reach out, and gradually became blind, paralysed and unaware of their surroundings despite seeming otherwise happy and healthy from birth
- All had a ‘cherry-red spot’ on the retina at the back of the eye even before symptoms appeared (see Figure 35.1)
- Both boys and girls were affected and death occurred before the age of 5

**What causes TSD?**

An enzyme is a protein that is essential for normal body function. Everyone has a particular enzyme called hexosaminidase A or HEX A that breaks down a fatty substance found in the brain called GN12 ganglioside. Small amounts of this substance are essential for proper brain function.

Babies born with TSD do not produce the HEX A enzyme and so the fatty substance accumulates in their brain cells, irreversibly damaging the cells.

**Why do babies with TSD lack this important brain function enzyme?**

The cells of the body contain information, in the form of genes, for the body to make all the necessary structural components and chemicals to ensure normal function (see Genetics Fact Sheet 1).

If a gene contains a variation in the information so that it does not work properly, it is described as faulty. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

The information for our cells to make the HEX A enzyme is contained in a gene, called the HEX A gene, located on chromosome number 15.
TAY-SACHS DISEASE and other conditions more common in the Ashkenazi Jewish community

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We all have two copies of chromosome number 15 in all our body cells and therefore two copies of the gene that codes for the HEX A enzyme.

- Everyone therefore has two copies of the HEX A gene in their body cells.

As there are two copies of each gene, if a person has a variation in the information in one copy of their HEX A gene that makes it faulty, and the other copy is working, they will still produce sufficient amounts of the HEX A enzyme for normal body function.

- People who have one working copy of the HEX A gene and one that is faulty are called 'carriers' of the change that makes the gene faulty or genetic carriers for TSD. Genetic carriers for TSD do not have Tay-Sachs disease and are not affected in any way because they can still produce enough HEX A enzyme.

People with TSD have both copies of their HEX A gene faulty: they cannot produce the important HEX A enzyme.

Who is affected with TSD?

TSD is most common amongst descendants of Central and Eastern European (Ashkenazi) Jews, although the disease occurs rarely in people from other population groups.

- Worldwide, the frequency of genetic carriers for TSD among Ashkenazi Jews is about 1 in 30.
- In Australia, it is about 1 in 25.
- In Sephardic Jews and non-Jewish people, the frequency of genetic carriers for TSD is about 1 in 280.

What does it mean to be a genetic carrier of TSD?

Genetic carriers of TSD are:

- Individuals who are genetic carriers for TSD have one working copy of their HEX A gene and one copy that is faulty in every cell.
- Being a genetic carrier for TSD is not like being a carrier of an infectious virus like hepatitis where the hepatitis virus is carried in the body.
- Genetic carriers for TSD do not carry TSD in their bodies and cannot pass it on to others like a virus. They can, however, pass the faulty gene on to their children as described below.

There are several theories as to why the frequency of the condition, and the number of genetic carriers for TSD, is high in the Ashkenazi Jewish population.

- Once a mutation occurs in a gene of an egg or sperm cell, it is passed down through the generations of a family.
- The preference for marrying other Jews would have kept the faulty HEX A gene within the Jewish population. There would be a higher chance of an Ashkenazi Jewish couple having a child with TSD as they would both have an increased chance of being genetic carriers for TSD.
- Another theory is that it is thought that being a genetic carrier for TSD would have had a better chance of surviving tuberculosis and have children.

How does a person inherit TSD?

TSD is a genetic condition (see Genetics Fact Sheet 2). Therefore it is passed from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty HEX A gene causing TSD in families.

1. The HEX A gene is located on chromosome 15, an autosome (one of the numbered chromosomes).
2. The effect of the change in the gene is ‘recessive’ or hidden by the presence of the working copy of the gene (see Genetics Fact Sheets 1, 4 & 5).

The pattern of inheritance in families of the faulty gene causing TSD is therefore described as autosomal recessive inheritance (see Genetics Fact Sheet 8).

In Figures 35.2 and 35.3 which illustrate the pattern of inheritance, the faulty HEX A gene is represented by ‘r’; the working copy by ‘R’. There are four possibilities, in every pregnancy, for the combinations of genes passed from the parents.

As shown in Figure 35.2, if a couple are both carriers of the faulty HEX A gene, in every pregnancy there is a

- 1 in 4 chance, or 25%, 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 TSD.
- 1 in 4 chance, or 25%, that their child will inherit both copies of the working gene and will be unaffected by TSD and cannot pass the faulty gene on to their children.
- 1 in 2 chance (2 in 4 chances), or 50%, that their child will inherit one faulty copy of the gene and one working copy of the gene from each parent and he/she will be an unaffected genetic carrier for TSD, just like the parents.

Figure 35.1: The ‘cherry red spot’ seen on the retina at the back of the eye is diagnostic for Tay-Sachs disease even before other symptoms are evident. (Photo William F Hoyt)
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**Figure 35.2:** Autosomal recessive inheritance where both parents are carriers of the faulty HEX A gene. The faulty HEX A gene copy is represented by 'r'; the working copy by 'R'.

**Figure 35.3:** Autosomal recessive inheritance where only one parent is a carrier of the faulty HEX A gene. The faulty HEX A gene copy is represented by 'r'; the working copy by 'R'.

If only one parent is a carrier of the faulty HEX A gene (Figure 35.3), in every pregnancy there is:
- No chance that the couple will have a baby affected with TSD
- 1 chance in 2 (2 chances in 4) or 50% that the baby will be an unaffected genetic carrier for TSD, just like his/her parents

Other conditions that are more common in the Ashkenazi Jewish community

Canavan disease (CD) is another condition affecting the central nervous system. At two to four months, an apparently healthy baby loses their ability to hold their head up and starts having fits (seizures). They gradually lose other abilities such as grasping or reaching out and responding to their surroundings and their head becomes larger than normal. The babies usually die before the age of two years.

Fanconi anaemia (FA) is a condition with a wide range of symptoms including severe anaemia, immune system failure, problems in the growth and development of the arms and legs, darkening of the skin, short stature and kidney problems. In addition affected individuals have a high susceptibility to develop several types of cancer. Diagnosis usually occurs in children between the ages of three and twelve years. Such early diagnosis means that checking for symptoms can lead to the prevention of many of the problems.

Familial dysautonomia (FD) is a condition that also affects the central nervous system. Most common symptoms include an inappropriate perception of heat and pain, skin blotching, greatly fluctuating blood pressures and problems with digestion. Only a third of patients survive to the age of 20 years. Effective and early treatment is essential for the individual to allow them to survive and to be able to live independently.

Cystic fibrosis (CF) is a condition that affects mainly the lungs, pancreas and sweat glands. People who have CF produce mucus that is thick and sticky and clogs the small air passages in the lungs encouraging bacteria.

Incomplete digestion, due to blockage of the ducts that connect the pancreas to the intestine, results in weight loss in spite of a hearty appetite. As a result of early diagnosis and treatment, 50% of people with CF now live into their late 30s but the condition can severely affect their quality of life. CF is due to inheriting two faulty copies of an important salt-transport gene. While CF is common in all people of European ancestry, certain changes (faulty genes) in the salt-transport gene are found more often in people of Ashkenazi Jewish ancestry. See Genetics Fact Sheet 33 for more information about CF.

How can people find out if they are genetic carriers for TSD and other conditions more common in the Ashkenazi Jewish community?

There is an increased chance that someone is a carrier of a faulty gene involved in these conditions if they have a family history of the condition or a blood relative who is known to be a genetic carrier for the condition.

Genetic testing to determine whether an individual is a carrier of the faulty gene running in the family may be available and can be discussed with their doctor or a genetic counsellor (see Genetics Fact Sheet 3).

Genetic carrier screening may also be available for those people with a high chance of being a genetic carrier for these conditions based on their Ashkenazi Jewish ancestry, even if there is no family history of the condition. The screening test looks at the in the gene(s) in a individual’s DNA obtained from a sample of their cheek cells using a swab and will only pick up those who are carriers of one of the more common changes in the gene(s) (see Genetics Fact Sheet 21).

The genetic carrier screening may be available as part of pre-pregnancy planning and may also be available for senior high school students as part of a community genetics screening program.
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How can knowing about having the faulty gene(s) help?

If both partners in a couple are genetic carriers for these conditions, they can find out information about the condition and their chance of having an affected child and discuss their reproductive options with a genetic counsellor (see Genetics Fact Sheet 3)

Prenatal testing for these conditions in pregnancy and in association with assisted reproductive technologies (ART) such as in vitro fertilisation (IVF) may be possible (see Genetics Fact Sheets 17C & 18)

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 8, 17C, 18, 21, 33

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