Inherited disease-causing variants in the *TP53* gene and Li-Fraumeni syndrome

Information for patients and family members

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US English translation. This document is a translation of the Swedish brochure. Medical advice and surveillance should always be individualized by your healthcare team.

What does it mean to have an inherited *TP53* variant, and what is Li-Fraumeni syndrome?

In 1969, two physicians, Dr. Li and Dr. Fraumeni, described several families in which individuals had developed unusual types of cancer and cancer at an early age. They proposed that this was due to an increased inherited risk of cancer. They described the features the families had in common, which became the criteria used to define Li-Fraumeni syndrome (LFS). Just over 20 years later, other researchers, including Dr. Malkin, showed that the inherited cause of LFS is a germline alteration in the *TP53* gene. There are many different types of alterations in the *TP53* gene, and they appear to be associated with different levels of cancer risk and with cancer in different organs. In Europe, the condition is therefore often called *TP53*-related cancer predisposition syndrome, while in North America it is more commonly called Li-Fraumeni syndrome. These are two terms for the same condition.

A gene is a part of our DNA (our genetic code), and each gene controls a specific function in our cells. A change in the genetic code is called a mutation or a genetic variant.

In LFS, the affected gene is called *TP53*. The *TP53* gene provides instructions for making a protein that is also called TP53 (formerly known as p53). TP53 is an important protein that helps protect our cells from becoming cancer cells. It does this by protecting the cells' DNA from damage. The TP53 protein is therefore often called the "guardian of the genome."

Having an inherited variant in *TP53* means that the cells are not as well protected from damage. This damage may lead to abnormal cell growth, which increases the risk of developing cancer. The condition is hereditary and follows an autosomal dominant inheritance pattern. This means that if one parent has the variant, each child has a 50% chance of inheriting the variant and the associated cancer risk.

Can I have genetic testing?

If you think you may be at risk of carrying an inherited cancer-predisposition gene variant, talk with your primary care physician or oncologist (cancer specialist). They will review your personal and family history of cancer. If they also believe that an inherited cancer-predisposition gene may be involved, they can refer you for evaluation at a clinical genetics or hereditary cancer clinic. These services are available at all university hospitals in Sweden: Umeå, Uppsala, Stockholm, Linköping, Örebro, Gothenburg, and Lund.

At the clinic, you may meet with a genetic counselor or physician to discuss whether further evaluation is appropriate and whether a variant in a cancer-predisposition gene could help explain your or your family's history of cancer. Genetic testing is usually performed using a blood sample.

How does having a *TP53* variant affect your health?

Being a *TP53* carrier does not automatically mean that you will develop cancer, but it does mean that your cancer risk is increased. Different *TP53* variants appear to be associated with different levels of risk. In some families, cancers occur during childhood and several different types of tumors are seen. In other families, only breast cancer and prostate cancer are more common, and these occur in adulthood.

The most common tumor types among *TP53* carriers are breast cancer, brain tumors, sarcomas (cancers of connective tissue), and adrenocortical cancer. Other types of cancer may also occur. *TP53* carriers often develop cancer at a younger age than people in the general population.

I am a *TP53* carrier - what happens now?

As a *TP53* carrier, you will be offered a surveillance program aimed at detecting cancer early. Surveillance is tailored to your specific gene variant and individual cancer risk. To find out exactly what applies to you, talk with your physician. You should have received specific information about this when you were informed that you carry a *TP53* variant.

For children, surveillance may include clinical examinations during medical visits, urine tests, and ultrasound examinations. Magnetic resonance imaging (MRI) may also be used in some cases.

For adults, surveillance includes annual clinical examinations and usually whole-body MRI, tailored to the individual's cancer risk. Women are also examined with breast MRI and breast ultrasound if they still have their breasts. Many choose to have risk-reducing breast surgery to lower the risk of breast cancer. Men are offered prostate-specific antigen (PSA) testing.

For some families in which only breast cancer and prostate cancer occur in adults, whole-body MRI may not be needed. Depending on the cancers that occur in the family, examination of the stomach or colon with a camera may also be appropriate. These examinations are called gastroscopy and colonoscopy. If you would like to discuss your surveillance, talk with a physician at the clinic where you had your genetic evaluation or where you receive your clinical follow-up.

What can I do myself?

There are steps you can take to reduce your overall risk of cancer, and these also apply if you have a *TP53* variant. Many of these steps are also good for your general health. In brief: do not use tobacco and avoid high alcohol intake. Avoid sunburn, and protect yourself with clothing and sunscreen. A healthy diet (including plenty of whole grains, fruits, and vegetables, and less red meat and sugar), physical activity, and avoiding excess weight are beneficial for your health. The usual dietary guidance from the Swedish National Food Agency applies.

As a *TP53* carrier, it is important to avoid unnecessary ionizing radiation. Ionizing radiation is used in conventional X-rays. For this reason, ultrasound or MRI is chosen whenever possible. If an X-ray or CT scan has been ordered, talk with your physician and ask whether the examination truly needs to use conventional X-rays or CT. Sometimes an examination using ionizing radiation is the only way to obtain the information that is needed. In that situation, the examination should be performed. The aim is to avoid examinations that are unnecessary.

Pay a little extra attention to your body. Pain that does not go away within about two weeks and gradually becomes worse should be discussed with a physician. Blood in the stool or urine should be evaluated. Moles that change (grow, itch, or bleed), sores that do not heal, new lumps, and weight loss when you are not trying to lose weight are also symptoms that should be evaluated further. If you are worried about anything, contact your physician to discuss it. There are many causes of these symptoms other than cancer, but it is important to investigate changes in your body that are unfamiliar to you.

I am a *TP53* carrier. Does my family also need testing?

If you are a *TP53* carrier, it may be appropriate for your close relatives - siblings, parents, and children - to discuss genetic testing to determine whether they also carry the variant. If you have very young children, the question of testing may be complex. Talk with the healthcare professionals at the clinic evaluating you.

In some cases, when there is no childhood cancer in the family, the recommendation may be to wait until the child is older (18 years of age), so that the child can decide whether to undergo testing.

Family planning and *TP53* carrier status

If you want to avoid the risk of passing the *TP53* variant on to future children, help is available. In vitro fertilization (IVF) may be offered, with testing used to select embryos that do not carry the gene variant. Only embryos without the variant are transferred. This can prevent the child from inheriting the gene variant and the associated cancer risk. If you would like to discuss this option, contact the clinical genetics clinic where you were evaluated or the hereditary cancer clinic.

Support and assistance

Learning that you carry a cancer-predisposition gene can cause worry. You are not alone, and support is available. Your healthcare team can provide supportive counseling. There is also a Facebook support and information group for *TP53* carriers (see below). Support is also available through international organizations and through a recently established patient network in Sweden.

Help, support, and more information

Clinical genetics clinics are available in Umeå, Uppsala, Stockholm, Linköping, Örebro, Gothenburg, and Lund. You can contact these clinics by referral for more information and testing. If you have further questions about an earlier evaluation, contact the clinic where the evaluation was performed.

LFSA Sweden. A recently established patient network in Sweden. It can help connect you with other *TP53* carriers in Sweden and internationally through LFSA's international branch.
Website: https://www.lfsassociation.org/sweden/

LFSA International. An international organization founded in the United States. It supports individuals with LFS and their families, raises funds for research, organizes family camps and family gatherings, and holds youth camps.
Website: https://www.lfsassociation.org/

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