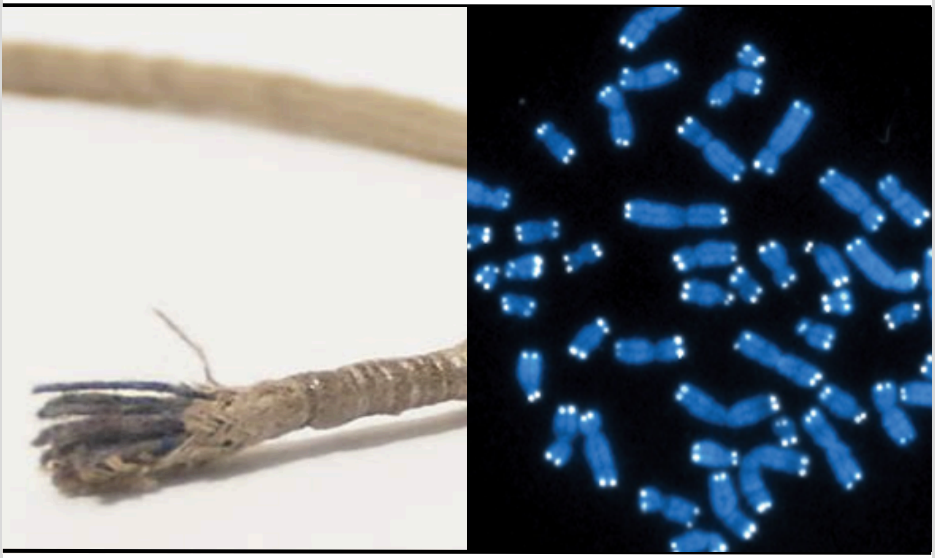
TELOMERE BIOLOGY DISORDERS



A GUIDE

Prepared by DC Action

WITH KING'S COLLEGE HOSPITAL HAEMATOLOGY DEPARTMENT AND THE INTERSTITIAL LUNG DISEASE SERVICE ROYAL DEVON AND EXETER HOSPITAL

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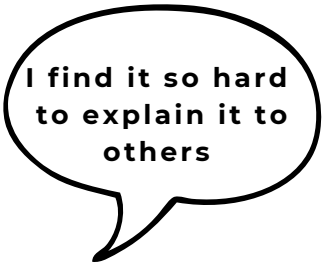
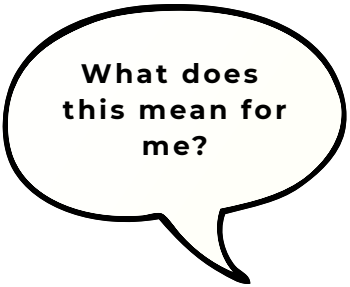
DC ACTION

YOU ARE NOT ALONE!

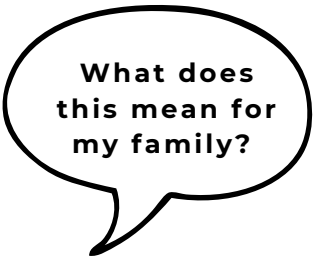
Having tests for or being diagnosed with a rare disease can be frightening and leave you feeling isolated and alone.



For many people who have lived with unexplained symptoms for a long time it can be a relief to finally understand why you have been unwell. For others it may come as a shock. Some people will feel a combination of these emotions and this is normal and expected.



We want you to know that you are not alone and that your specialist team is here to help and support you and your family, friends or carers, while you navigate through what may be a difficult time.



Before we go on.....

Understanding rare diseases can be difficult and we appreciate that often people are asked to learn a 'new language' both to understand their condition and to communicate effectively with their medical team.

Much of what can be found on the internet is in the form of published scientific papers which can be difficult to understand. It's also difficult to know what is directly relevant to you. There is also a great deal of confusing information from commercial sources related to the subject of telomeres and their effect on aging.

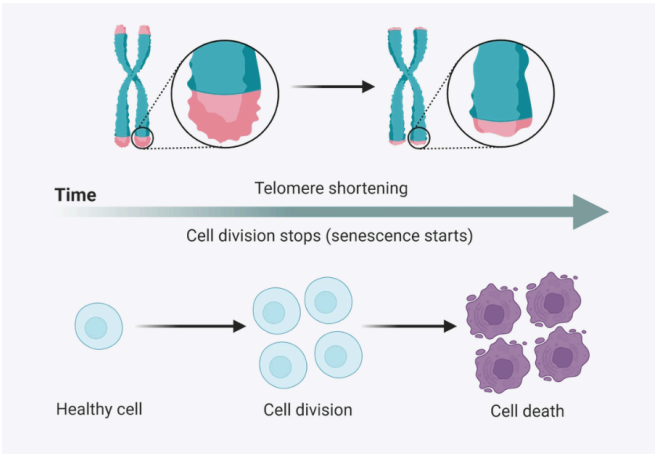
This leaflet looks at how Telomere Biology Disorders can affect the blood and other organs.

Doctors and scientists are learning all the time, but their knowledge is not exhaustive and there is much we still do not know.
If you need more information or further explanation please do not hesitate to ask.

So what are Telomeres?

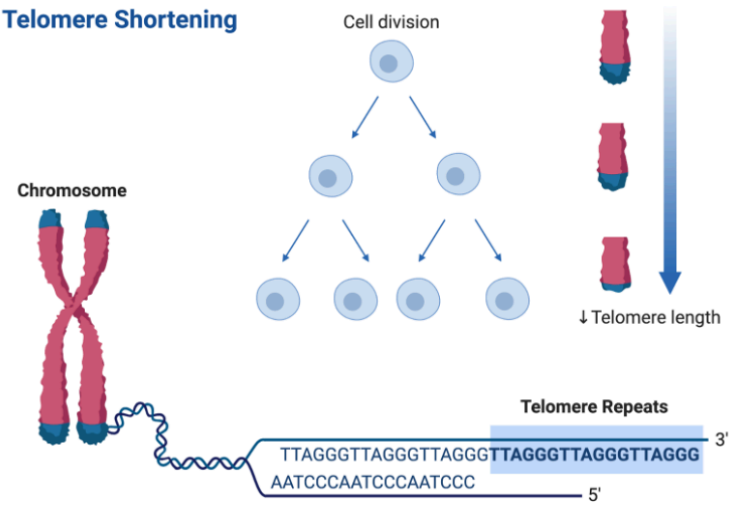
Our bodies are made up of trillions of cells all of which contain the genetic information we need to grow from a single cell at conception, into adult human beings. All the information needed to make this happen is encoded in the DNA of our genes which are organised into 46 different chromosomes - 23 pairs.

The end of each chromosome is protected by the telomere, a 'shoelace cap' made of repeated DNA sequences together with a number of proteins. Our cells are constantly being replaced by a process called cell replication. Every time a cell divides to produce a copy of itself the telomere gets shorter and shorter. When telomeres shorten to a certain length this sends a signal to the cell to stop dividing and the cell eventually dies. This process, including cell death, is a normal part of the biological aging process.



What are Telomere Biology Disorders?

Alterations in genes involved in telomere maintenance can make telomeres become too short too quickly and cells stop working or die earlier than they should. This can affect many different parts of the body, especially 'high turnover' cells that need frequent cell renewal, like those in bone marrow (which makes blood cells), lung, liver, skin, nails, and the lining of the mouth. The effects in the body can vary, depending on which gene is altered and the type of gene alteration. We can measure the length of telomeres in the laboratory. This, along with other tests, gives a diagnostic clue.



Collectively, the conditions that result from telomere gene alterations are known as Telomere Biology Disorders (TBDs), Short Telomere Syndromes or Telomeropathies.
The archetypal TBD, Dyskeratosis congenita (DC), was first described in 1906. Several other genes have now been linked with TBDs.
These conditions are often described as 'Dyskeratosis congenita and related Telomere Biology Disorders'.

How do Telomere Biology Disorders affect the body?

TBDs can affect many different parts of the body because telomeres are important in all cells. However, the most common effects are in:

Bone Marrow: This can lead to low blood cell counts (anaemia, low white blood cells, low platelets)

Skin, Nails, and Mouth: Causing the classic triad of symptoms (skin pigmentation changes, nail dystrophy, and oral leukoplakia or white patches in the mouth, premature greying of hair)

Lungs: Sometimes causing pulmonary fibrosis (scarring of the lung tissue)

Liver: Potentially leading to liver problems (inflammation or scarring/ cirrhosis)

Immune System: Increased risk of infections

Eyes: Some gene variants can affect vision

How seriously and at what stage in life people are affected can vary enormously and may depend on the specific gene alteration. Siblings with the same gene alteration can have very different health outcomes. Some never know they have a TBD and others with very short telomeres can appear unaffected.
It seems that the combination of a gene alteration plus possible additional genetic and environmental factors (e.g. smoking, diet, exercise) all play a role.

Tests for Telomere Biology Disorders

Family History is very Important

Be sure to tell your specialist team if any other members of your family have had health issues especially blood, lung or liver problems.

Telomere Length Testing

This specialised test measures the length of telomeres in your blood cells. It's one of the most important tests for diagnosing TBDs. The most accurate methods are called "flow-FISH" (flow cytometry with fluorescence in situ hybridization) or STELA (Single Telomere Length Analysis)

Genetic Testing

Genetic tests look for alterations in TBD genes by comparing your DNA from a blood sample to a panel of known TBD genes. A test may identify which specific gene is responsible but often, no genetic variant is found even when a TBD is strongly suspected based on symptoms and telomere length

Other Tests

Complete blood count (CBC) to check levels of different blood cells

Bone marrow biopsy

To examine how well new blood cells are being produced

Lung function “blowing” tests to check lung capacity

Liver function tests

Imaging studies such as chest X-rays, CT scans, ultrasound or fibroscan of the liver

How do Telomere Biology Disorders affect your blood?

TBDs can cause the bone marrow to produce fewer or less functional blood cells

- Insufficient red blood cells cause anaemia. As mild anaemia is very common, especially in young women, your doctor will ensure that any additional causes of anaemia are corrected. Anaemia can cause fatigue, or if severe, shortness of breath, paleness of skin, and faintness.
- There are several different types of white blood cell which work together to prevent infection. Severe reductions in white blood cells are associated with infections, which can sometimes be severe.
- Platelets are essential for blood clotting. Very low platelet numbers are associated with bruising, pinpoint rash which doesn't disappear when pressed (purpura) or bleeding.

Medications such as hormones may be prescribed to help normalise the blood count but a stem cell transplant or allogeneic bone marrow transplant (cells from another person) may be necessary. It is important to check that a potential related donor does not have any telomere genetic variant even if they have no symptoms.

Special low intensity conditioning regimens are commonly used prior to stem cell / bone marrow transplant to avoid unnecessary damage to telomeric DNA. Your haematologist or specialist nurse will explain this to you.

How might a Telomere Biology Disorder affect your lungs?

TBDs can increase the risk of developing interstitial lung diseases (ILDs) which involve scarring or inflammation of lung tissue, leading to reduced lung function which can worsen over time.

This may manifest as increased breathlessness, cough and the need for oxygen therapy in advanced disease.

Early diagnosis and treatment can keep you healthy for longer. You may be referred to a specialist centre for ILD diagnosis and treatment.

A high-resolution chest CT scan may be requested to diagnose ILD early and pulmonary/lung function (breathing) tests may be done regularly to monitor your lungs.

Regular ILD consultations are helpful to track progression and to discuss ILD-specific treatment options, such as antifibrotic medications. Certain invasive procedures (e.g. lung biopsy) and immunosuppression may be avoided if you have a TBD.

ILD can worsen faster in people with TBDs, therefore earlier referral for lung transplantation may be considered if it is required.

Relatives may also require screening for ILD and for consideration of telomere genetic tests.

How might a Telomere Biology Disorder affect your liver?

Liver involvement in dyskeratosis congenita (DC) and related Telomere Biology Disorders (TBDs) is common and may vary from mildly abnormal liver tests results to more serious disease.

The cause of liver disease development is not clear but it is thought that shorter telomeres and inflammation resulting from Telomere Biology Disorder gene alterations makes liver cell regeneration less efficient and the liver more prone to disease.

The time of onset of liver involvement can vary depending on the specific gene alteration, the length of telomeres in liver cells and other genetic and environmental factors such as drinking too much alcohol and obesity.

Your doctor should arrange for you to be screened by a specialist liver doctor when you are diagnosed followed up by monitoring every year.

If there is concern, you may need further tests, for example elastography (fibroscan), ultrasound, CT or MRI scans. These may need to be more frequent, for example every 6 months.

In some cases , if liver disease is more serious or has led to cirrhosis (severe liver scarring) or hepatopulmonary syndrome (where liver problems are associated with tiny abnormal blood vessels which cause severe breathing problems), a liver transplant may need to be considered.

Genetics and Telomere Biology Disorders

You may be offered a genetic test because:

- **your doctor thinks you might have a health condition caused by a change to one or more of your genes**
- **someone in your family has a health condition that's caused by changes to genes**

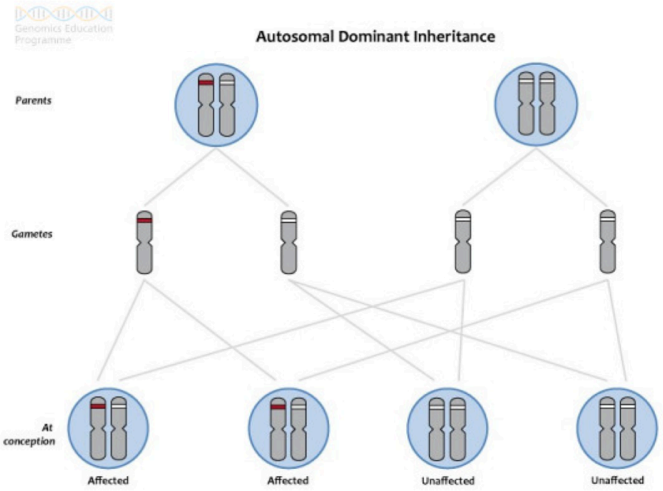
You can find out more here: https://www.nhs.uk/tests-and-treatments/genetic-and-genomic-testing/

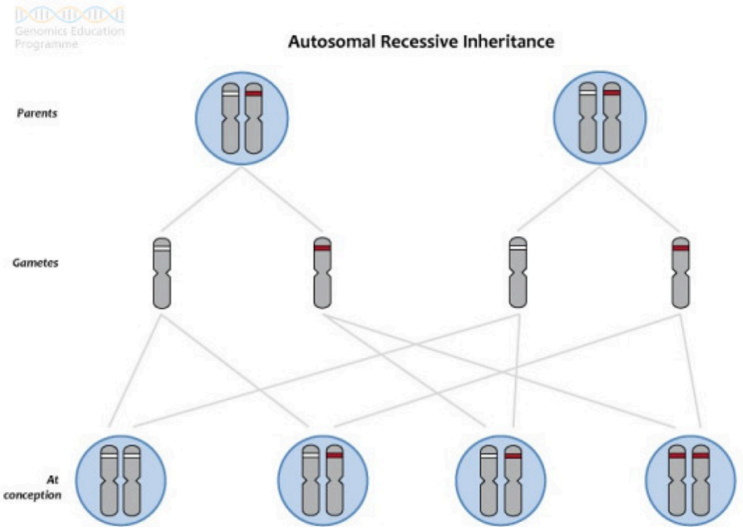
Telomere Biology Disorders can be caused by alterations in many different genes
If your doctor suspects a TBD, a blood sample will be sent for a gene screen or for whole genome sequencing (WGS) to identify the possible gene variant. It's best to discuss with your specialist doctor or nurse and the genetics team what the implications of your individual case may be.

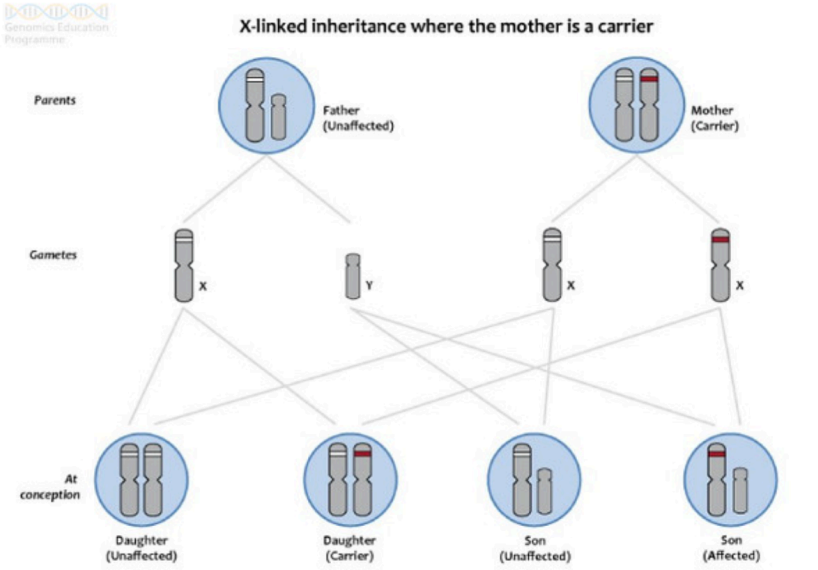
Inheritance patterns or how the affected gene may be passed on in your family, will depend on which gene is identified.
You can see the possible different inheritance patterns in the diagrams below but ask your geneticist or genetic counsellor to explain what this means for you and your family.

It is important to consider genetic screening for family members and to discuss family planning.

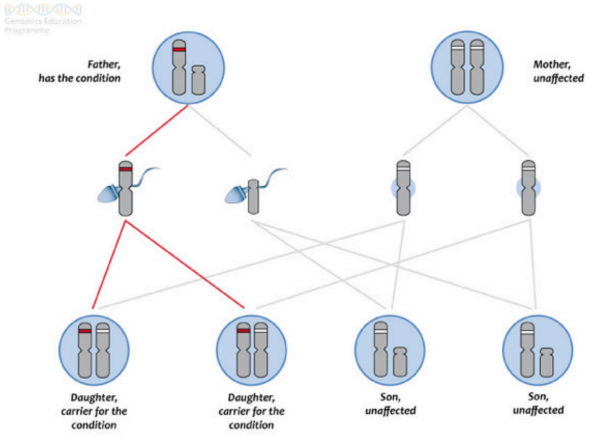
50%
of children
are affected
50% unaffected
(their children
are also
unaffected)







X linked inheritance when the father has the condition



daughters will be carriers (50% chance of sons affected, 50% of daughters are carriers), sons will be unaffected (their children will also be unaffected)

Images from Health Education England's Genomics Education Programme (GEP)

https://www.genomicseducation.hee.nhs.uk/

What can be done to minimise problems?

Recognising the signs of a Telomere Biology Disorder early is important

- allows for proper monitoring and preventive care
- some complications can be prevented or minimised with appropriate treatment
- helps families connect with specialists who understand these rare conditions
- allows for genetic counselling and testing of family members when appropriate

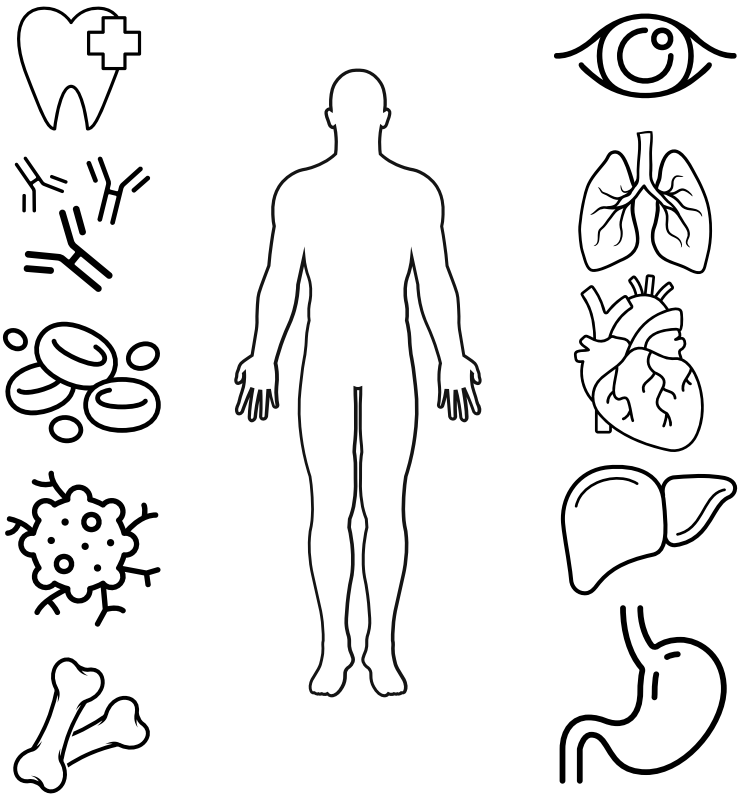
Because TBDs can affect the whole body, it is important that your general health is monitored on a regular basis.

Be sure to keep your GP, dentist and optician informed about your condition so that they can spot any problems early.

This form of monitoring is often called a 'watch and wait' approach although it is appreciated that 'watch and worry' may better describe the patient experience.

If you have any concerns about any aspect of your health, be sure to speak to your specialist nurse or doctor straight away. We ask you to be open about your emotions and anxieties.

It’s possible but by no means certain, that you will need to see other specialists at some point. These might include liver doctors, immunology, orthopaedic, respiratory, gut, vascular or cancer specialists



Your specialist team will make sure that you are properly monitored, will advise you on self care and which other specialists you need to see and when.

You can download a monitoring checklist to share with your doctors here
https://dcaction.org/wp-content/uploads/2025/02/Surveillance-Poster-.pdf

Caring for Yourself

If you are diagnosed with a TBD, even if you don't have any symptoms, it's important to take care of yourself and minimise future problems.

It is wise

- not to drink alcohol
- not to smoke or vape
- to follow a sensible healthy diet
- to keep the weight down
- take regular exercise
- to always use sunscreen
- to avoid X-ray radiation if possible
- to keep up to date with vaccinations

If you are being treated for other conditions

Let your doctor know that prescription of corticosteroids, methotrexate, nitrofurantoin and alkylating agents is not advisable.

Patient Passport

You may find it useful to carry a Patient Passport to give to doctors or healthcare professionals explaining your condition and to draw their attention to medications you are taking and procedures and medications that are best avoided or minimised.
You can register for a Patient Passport here:
https://www.camraredisease.org/patient-passport/
Click on DC Action as the charity

If you need help to complete the Patient Passport don't hesitate to contact info@dcaction.org

Treatments for Telomere Biology Disorders

Treatment focuses on managing symptoms, preventing complications, and supporting your overall health and quality of life. Since TBDs can affect multiple body systems, treatment can depend on which area of the body is affected but typically involves a team of specialists working together.

Androgen Therapy

Androgens are hormones that can stimulate blood cell production in many people with TBDs. Medications like danazol or oxymetholone may be prescribed.
These treatments can improve blood counts and reduce the need for transfusions.
Regular monitoring is needed as these medications can have side effects, including liver problems and masculinising effects (like deepening voice or increased body hair)

Transplant

Stem cell transplant or allogeneic bone marrow transplant. Lung or liver transplant may also be necessary.

Antifibrotic Medications

Nintedanib or pirfenidone may be prescribed to treat interstitial lung disease or pulmonary fibrosis by slowing the development of fibrosis or scarring in the lungs.

There is still a lot to learn about Telomere Biology Disorders

New genes are regularly being discovered and studies are helping us to understand how telomeres work and how TBDs affect different organs and cells.

Current Studies include
Telomeres and the Role of Sex Hormones in Pulmonary Fibrosis
How TBDs affect the bones
Improved transplant methods
The most efficient dosing of androgen medication

Areas of research include
Telomere maintenance:
How gene alterations contribute to cancer, aging, and other conditions
Telomerase Activators:
Compounds that might help maintain or increase telomere length
Gene Therapy:
Approaches that could potentially correct the underlying genetic causes
Targeted Therapies:
Medications that address specific complications of TBDs
Regenerative Medicine:
Using stem cells to repair damaged tissues

For information and support

DCAction UK Support Organisation
Email info@dcaction.org
https://dcaction.org/

Team Telomere US Support Organisation
https://teamtelomere.org/

Action for Pulmonary Fibrosis
https://www.actionpf.org/

British Liver Trust
https://britishlivertrust.org.uk/

Genetic Alliance
https://geneticalliance.org.uk/

Human Fertilisation and Embryology Authority
https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/

The TeloNet network brings together patients and familes living with TBDs, clinicians and scientists to share expertise and research
Contact us info@dcaction.org