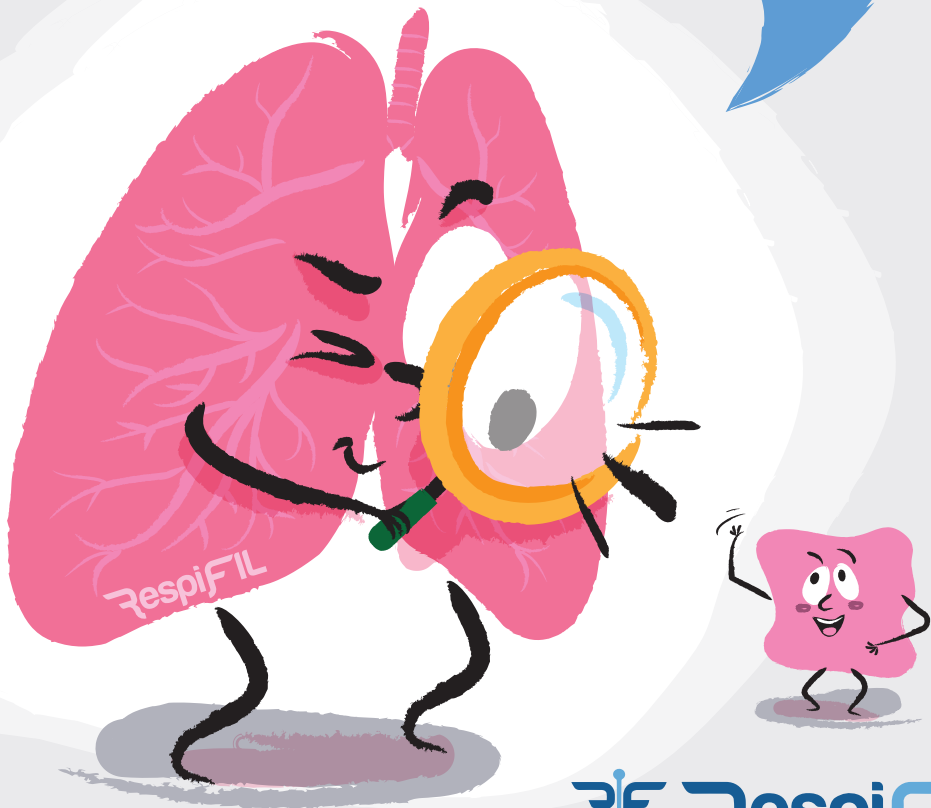


Surfactant disorders and inheritance



How can this information booklet help you?

This booklet was given to you during a surfactant disorder consultation.

It has been conceived as a guide, a "landmark" to support you after the consultation.

It is also a tool that will help you to explain and discuss the disease, its consequences and genetic aspects with your family and relatives.

This booklet is organised in two parts:

- The first part provides information on surfactant disorders: their mechanisms, symptoms and treatments.
- The second part focuses on their genetic basis and inheritance pattern.

This booklet has been produced with the support of RespiFIL, the French reference network for rare respiratory diseases.

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How do we breathe?

To help you better understand surfactant disorders, it is important to understand the breathing mechanism.

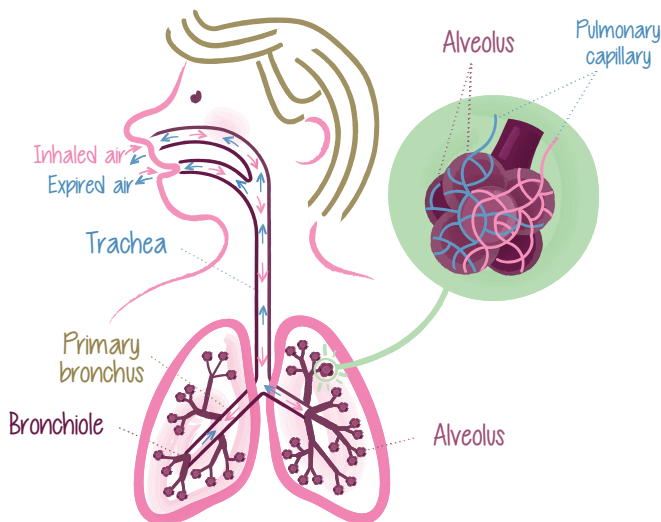
Breathing is aimed at collecting oxygen (O_2) from inhaled air in order to supply the body's organs and remove their carbon dioxide (CO_2) in the air breathed out.

The respiratory system

The inhaled air enters the trachea through the nose and mouth and then reaches the primary bronchi (left and right).

The bronchi branch many times to form the bronchioles and, at their extremities, terminate into the pulmonary alveoli (comparable to bunches of grapes). It is at this level that the O_2 and CO_2 gas exchange between the air and the blood takes place.

The respiratory system



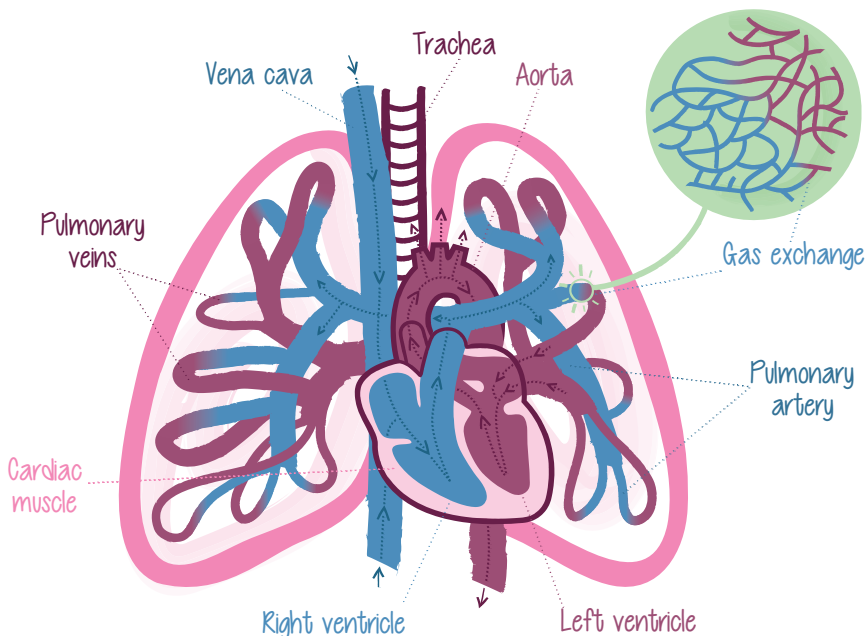
Heart and lungs: breathing partners

The respiratory and cardiac systems work together. The heart is a pump that enables blood circulation in the body. It is made up of four chambers: the left atrium and ventricle form the left heart; the right atrium and ventricle form the right heart.

Gas exchange takes place between the alveoli and the vessels surrounding them, the pulmonary capillaries, where the blood is enriched in O_2 and depleted of CO_2 .

The left heart (in red in the diagram) ensures blood circulation from the lungs to the organs: arterial blood (in red) recharged with O_2 is thus carried throughout the body. Blood rich in CO_2 and poor in O_2 (blue), coming from the organs, returns to the right heart (blue), which in turn sends it to the lungs via the pulmonary artery (blue).

Pulmonary circulation



Pulmonary alveoli: centre of gas exchange between air and blood

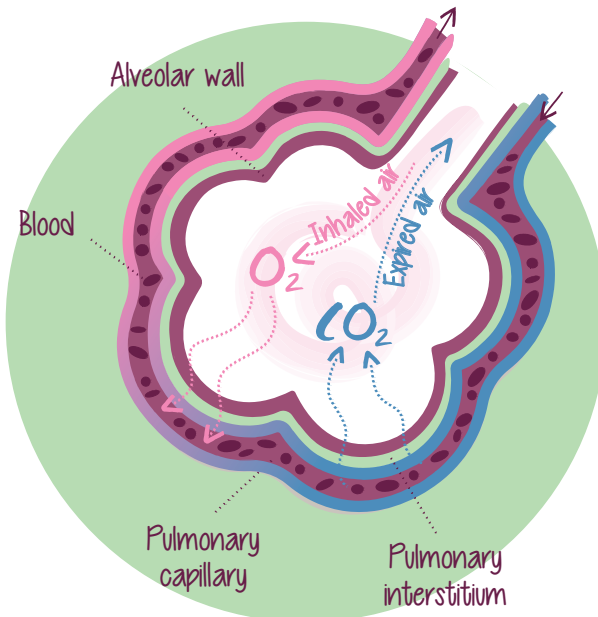
A child is born with about 100 million alveoli and has about 300 million alveoli by the age of 3-4 years. After the age of 4, the alveoli grow but no longer increase in number.

As tiny bags, the alveoli inflate with air upon inhalation and are partially emptied upon exhalation. They are coated by a supporting tissue, the pulmonary interstitium. The pulmonary capillaries surround this interstitium.

To facilitate the O_2 and CO_2 gas transfer, three conditions are crucial:

- A thin alveolar wall of a few micrometres in thickness
- A thin interstitium
- A large alveolar surface

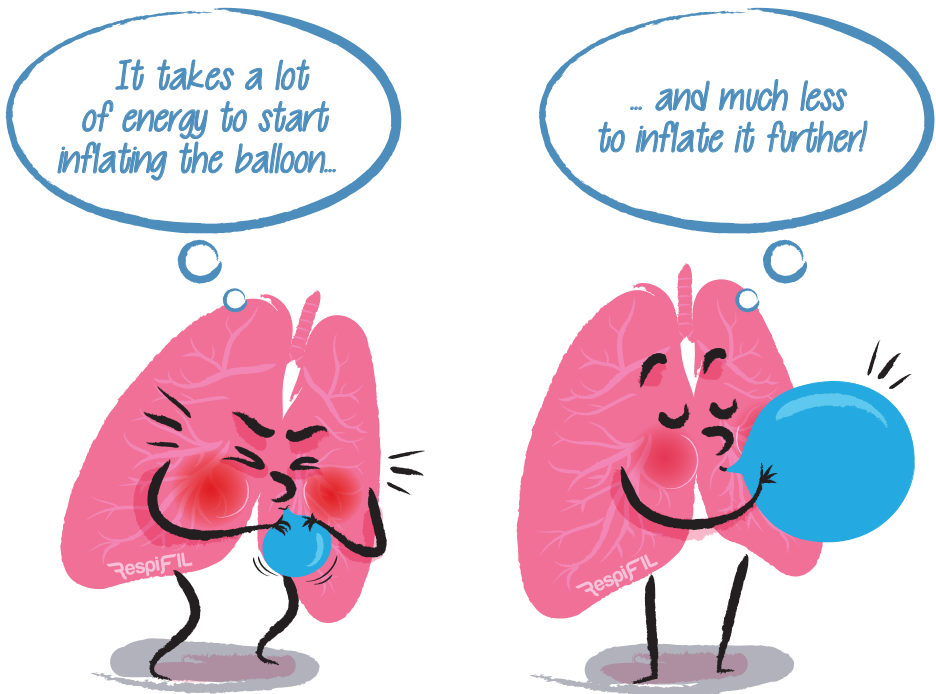
Pulmonary alveolus and gas exchange



What is alveolar surfactant?

Mechanical role of the surfactant

Let's take the example of a balloon (comparable to an alveolus): you need to blow it up very strongly at the beginning to start inflating it. This requires a lot of energy. On the other hand, to continue inflating the same balloon midway, it requires much less effort.



In the case of pulmonary alveoli, the situation is identical. If the alveoli were entirely empty, the respiratory muscles would be exhausted trying to open them with each breath. The surfactant is a "tensioactive" agent that coats the inside of the alveoli: it helps to keep the alveoli open. This prevents the respiratory muscles from expending more energy and becoming exhausted.

Thus, the pulmonary surfactant is indispensable for normal effortless breathing.

The pulmonary surfactant: a complex mixture

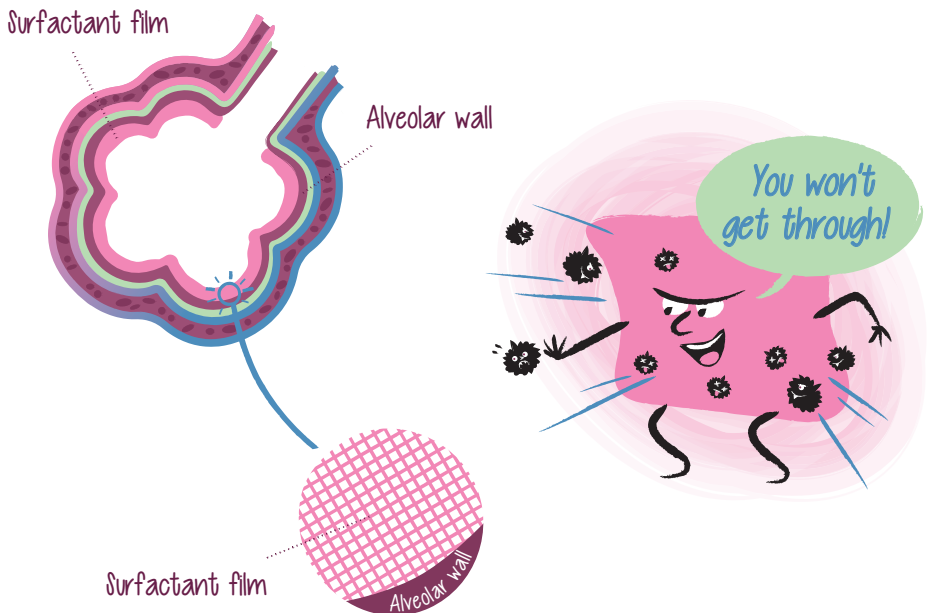
The pulmonary surfactant is made up of 90% lipids (fatty substances) and 10% proteins. The main surfactant proteins, called SP, are: SP-A1, SP-A2, SP-B, SP-C and SP-D.

Two other significant proteins are involved in the surfactant system: ABCA3, which carries the SP-B and SP-C into the cells, and NKX2-1 (also called TTF-1), which stimulates SP-B and SP-C production.

This complex mixture of proteins and lipids is organised in the form of a fishing net mesh which coats the inside of the alveolus.

The surfactant therefore also plays a role in protecting the alveoli, by preventing the penetration of small particles brought in by the air, such as dust or micro-organisms (bacteria, viruses, etc.).

"Protective" role of the surfactant



Alveolar surfactant disorders

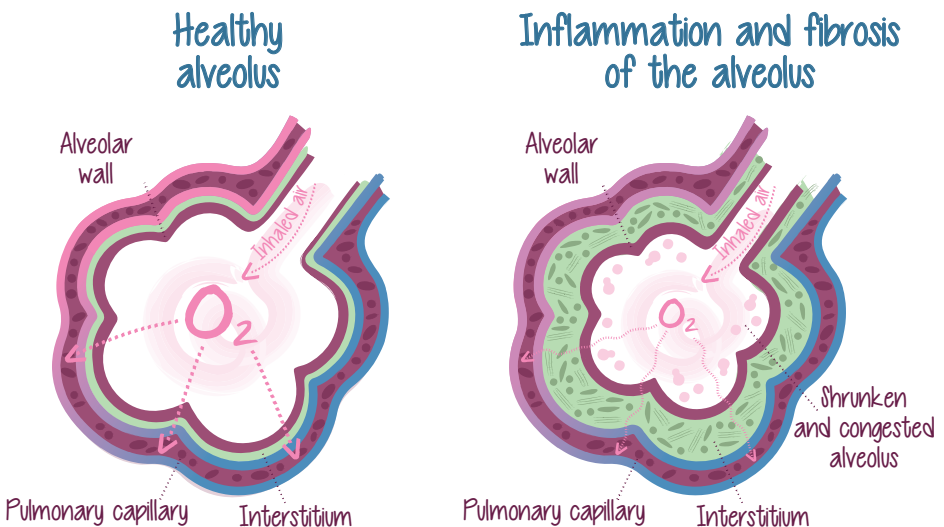
Surfactant disorders are part of interstitial lung diseases (ILDs). They are more common among children than adults.

ILDs are very rare disorders, and their prevalence is probably underestimated due to the difficulty in making the diagnosis.

They encompass a wide variety of diseases that all have in common an alteration in gas exchange. This can be related to:

- A thickening of the interstitium (the gap between the alveolar wall and the capillaries), due to:
 - chronic inflammation of the alveoli;
 - or poor repair of the alveoli following pulmonary aggression (microorganisms, inhalation of pollutants, etc.).
- An abnormal accumulation of dead cell remains or material such as blood, abnormal surfactant, etc... inside the pulmonary alveoli.

At an advanced stage of ILDs, the persistence of thickened interstitium can lead to pulmonary fibrosis (scarring around the alveoli).



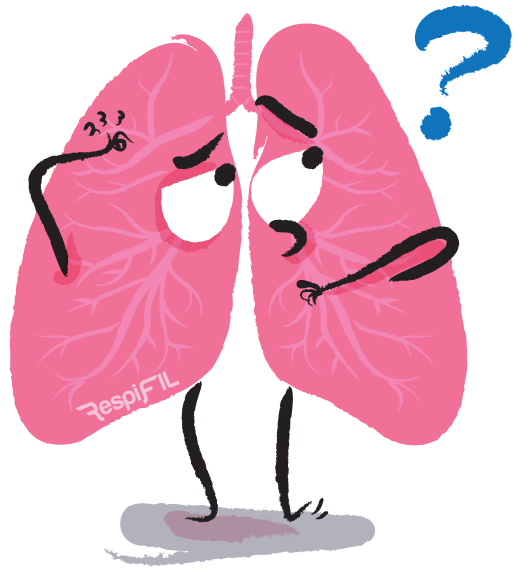
What are the symptoms?

In some cases, the disease can appear as early as at birth, but most often its onset is progressive in early childhood, youth, adolescence or even adulthood.

The first symptoms are a dry cough and shortness of breath (dyspnea), first during exercise (or while bottle-feeding for infants/babies/toddlers), and then sometimes at rest.

Other symptoms may appear:

- an increase in respiratory rate (tachypnea),
- signs of retractions when breathing,
- an enlarged appearance of the fingertips with domed and enlarged nails (digital clubbing),
- feeding difficulties and poor weight gain in infants and young children,
- cyanosis (bluish lips and sometimes fingertips) caused by poor oxygenation of the blood.



In diseases related to abnormalities of the NKX2-1 gene, non-pulmonary symptoms may also exist such as:

- thyroid disorder (hypothyroidism),
- reduced muscle strength (hypotonia) or abnormal movement disorder (chorea).

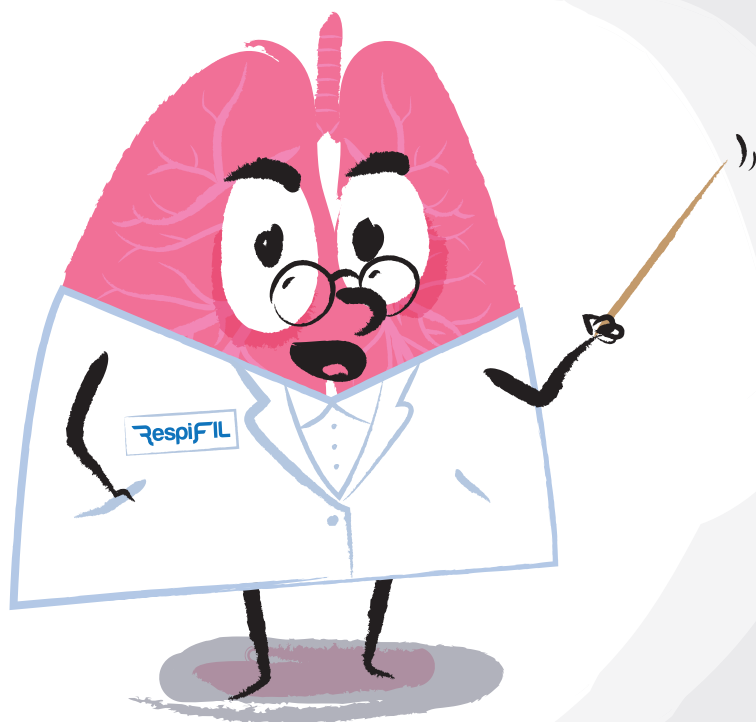
What treatments are available?

Depending on each patient's situation, various treatments can be offered to relieve symptoms, to improve exertion capacity and to improve the quality of life.

- Corticosteroids are the main treatment for ILDs in children. This anti-inflammatory medication is targeted against the inflammation of the alveoli. They can be taken orally or by intravenous infusion.
- Other oral medications may be used such as hydroxychloroquine (antimalarial) and azithromycin (antibiotic). Anti-fibrotic drugs may also be used for adults.
- Oxygen supplementation (oxygen therapy) at home is often prescribed (at night and sometimes during the day or when exercising).
- In addition, ILDs, like all chronic lung diseases, involve significant levels of physical energy expenditure. For this reason, oral nutritional supplements or nasogastric tube feeding may be necessary to maintain adequate weight and growth.
- There is always a need for general measures such as adapted physical activity*, a balanced diet and quitting smoking.
- In addition to the usual vaccination schedule, supplementary vaccinations may be prescribed.
- If the disease evolves despite maximum treatment, a transplant of one or both lungs may be considered.

*Always talk to your doctor before starting an exercise program or changing your level of physical activity.

Let's talk about the genetics
of these diseases. To fully understand it,
we must start from the cell.



Let's talk genetics!

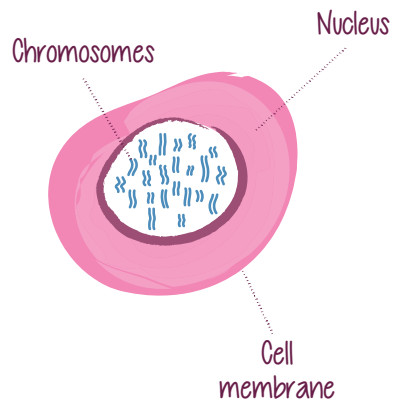
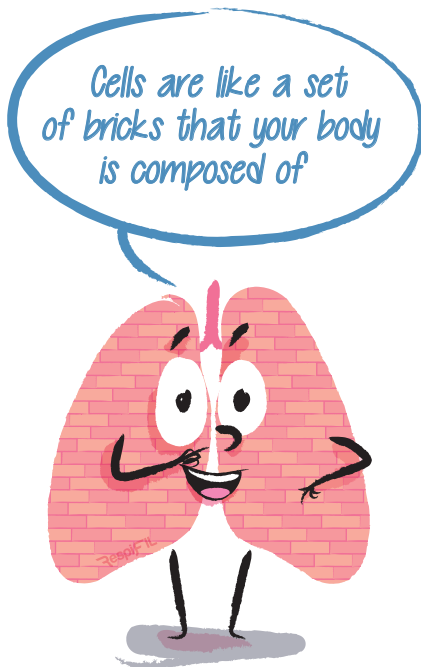
Pulmonary surfactant disorders are genetic diseases. Like any genetic disease, they can affect not only an individual but also his or her family.

From cells to chromosomes

Each individual is made up of several billion cells, each having a nucleus. Each nucleus has 46 chromosomes (23 pairs), which are identical from one cell to another. Each pair consists of one chromosome inherited from the father and one from the mother.

Among the 23 pairs, 22 pairs are common to both sexes and are called "autosomes". The 23rd pair is formed by two sex chromosomes: XX for women and XY for men.

The cell

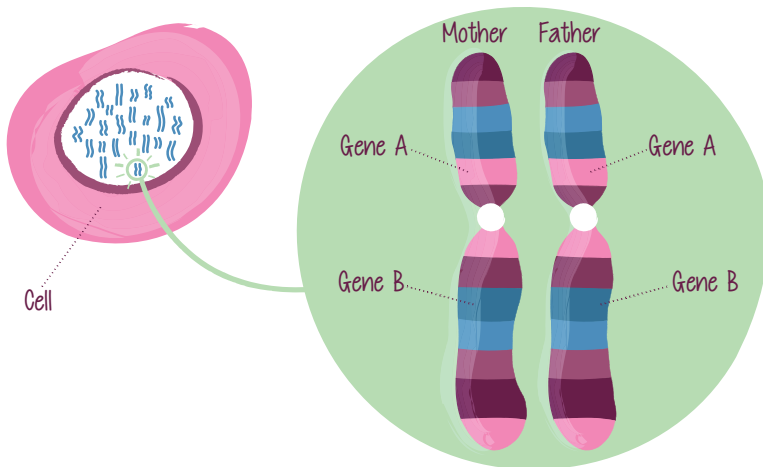


From chromosomes to genes

Each chromosome consists of a succession of genes. The human being has almost 30,000 different genes that contain the information determining our physical and behavioural traits, such as the colour of our eyes, hair, skin, height, etc.

The creation and functioning of an organ require the action of numerous genes.

Chromosomes



From genes to proteins

A gene consists of a sequence of ordered letters forming a genetic code that allows the production of proteins. This sequence can be compared to a sentence in a book. In order for the protein created to be functional, the sentence must be correct.

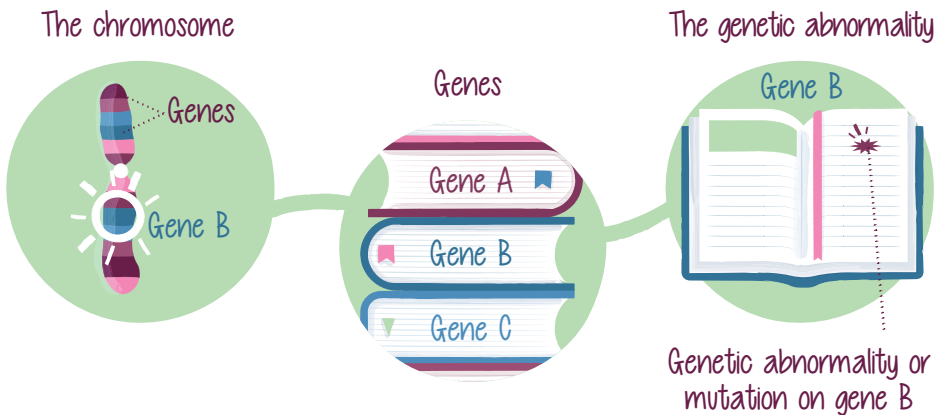
Each protein has a specific function in the cell (for example: haemoglobin is responsible for carrying oxygen in the blood).

Errors can occur in the genes

Just like in a book, a spelling mistake can possibly occur in the form of a “mutation” in the sequence of a gene.

This results in incorrect information and the protein produced will then be abnormal or absent. This mutation will therefore lead to a dysfunction of the cell, tissues and organs involved.

From the chromosome to the genetic abnormality



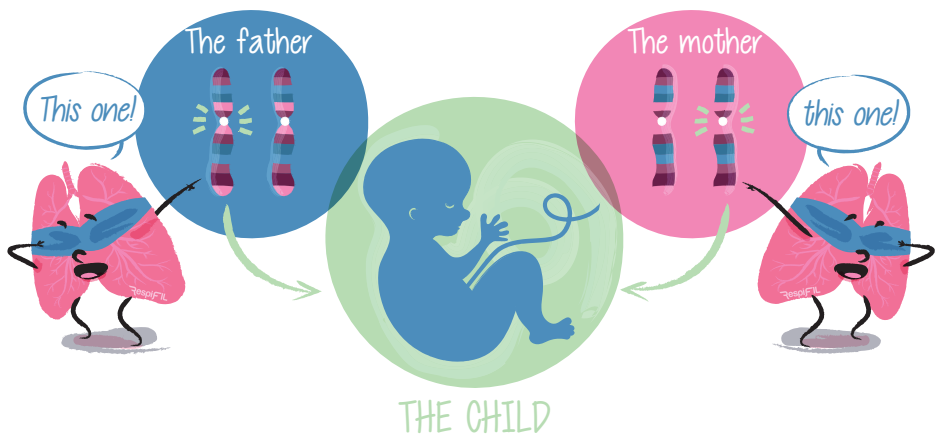
Inheritance

As we have seen previously, the nucleus of each cell has 46 chromosomes organised into 23 pairs. Therefore, the genes, located on these chromosomes, are present in double copies in each of our cells.

During fertilisation, for each pair of chromosomes, one of the 2 chromosomes of the father (at random) and one of the 2 chromosomes of the mother (at random) are combined to form the 23 new pairs of chromosomes of the child.

The child will therefore have inherited half of the genetic material from both parents.

The genetic mixture



Thus, when a parent is a carrier of a genetic mutation, each child may in turn be a carrier of the mutated gene at random.

Specific case

Genetic abnormalities may appear for the first time in the sick patient. This is called *de novo* mutation. In this particular case, the patient's parents do not carry the genetic abnormality.

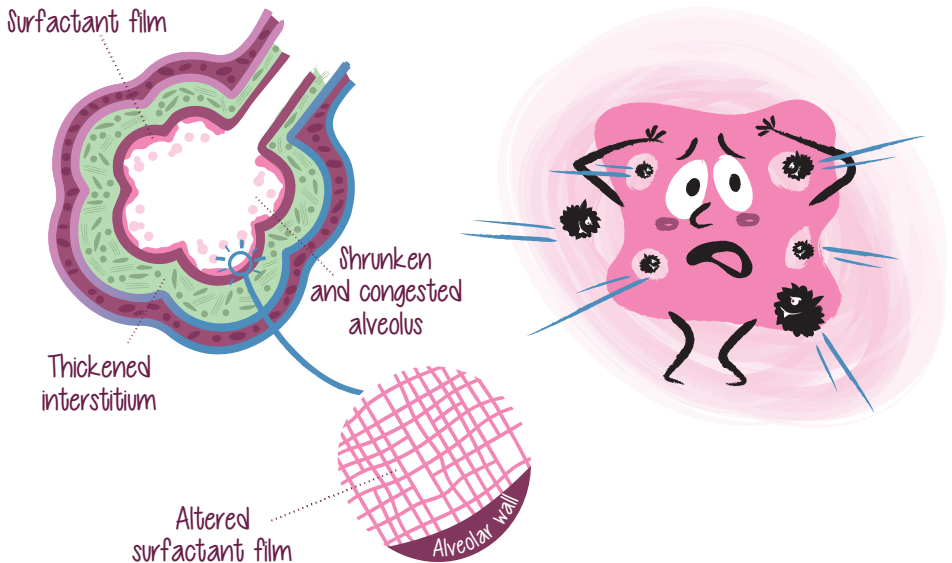
Which genes are involved in surfactant disorders?

Of the 30,000 genes that constitute the genetic heritage of each individual, a number of them, when altered, play an important role in the development of surfactant disorders.

Several genes have been identified: *SFTPA1* (involved in the production of the SP-A1 protein), *SFTPA2* (for the production of SP-A2), *SFTPB* (for the production of SP-B), *SFTPC* (for the production of SP-C), *ABCA3* or *NKX2-1*.

Mutations in these genes cause an abnormality in the making of the alveolar surfactant which becomes more loose and less functional. This affects the movement of the alveolus (inflating/deflating) and sometimes the protection against external particles. This increases the susceptibility to chronic inflammation and suffering of the cells in the alveolar wall.

Altered surfactant film



How are these genes inherited?

The genes involved in surfactant disorders are located on the non-sex chromosomes (autosomes). This implies that the inheritance of these disorders is not linked to the sex of the child. They affect girls and boys equally.

Surfactant disorders can be either autosomal dominant or autosomal recessive. We will describe these two inheritance patterns and, depending on the gene, you will be informed which inheritance pattern concerns your family.

Autosomal dominant inheritance

Autosomal dominant inheritance involves mutations in the *SFTPA1*, *SFTPA2*, *SFTPC* and *NKX2-1* genes.

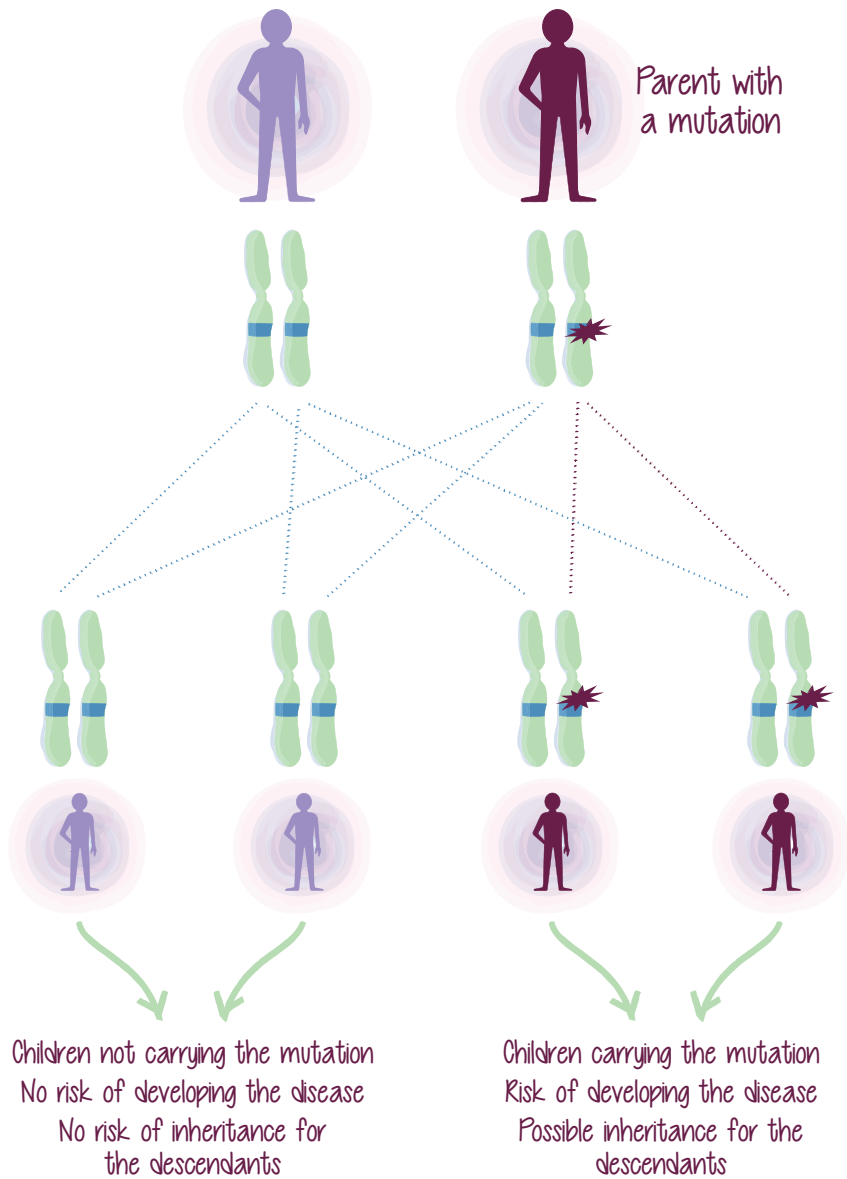
- **Autosomal:** means that the disease affects both girls and boys.
- **Dominant:** means that a mutation in only one of the 2 copies of the gene is sufficient for the disease to develop. Most often (except in the case of *de novo* mutations), one of the parents (father or mother) of the patient is also a carrier of the mutation on one of his chromosomes.

These mutations are said to have **incomplete penetrance**: this means that a person can carry the genetic abnormality but never develop the disease. However, he or she can pass on the mutation to his or her descendants.

When a parent carries a mutation, there is, at each birth:

- 50% probability that the child to be born is a carrier of the genetic abnormality and has a risk of developing the disease.
- 50% probability that the child to be born has received the chromosome carrying the normal gene. He will therefore not be affected.

Dominant inheritance of a genetic abnormality



■ Normal gene

■ Mutated gene

Autosomal recessive inheritance

Autosomal recessive inheritance involves mutations in the *SFTPB* and *ABCA3* genes.

- **Autosomal:** means that the disease affects girls and boys equally.
- **Recessive:** means that both copies of the gene must be mutated for the individual to be at risk of developing the disease.

These abnormalities are said to have **incomplete penetrance**: this means that a person can carry the 2 genetic abnormalities but never develop the disease.

Most often (except in the case of *de novo* mutations), both parents of the patient are carriers of a single mutation. Having only one mutation is not enough to develop the disease, thus, the parents are not ill.

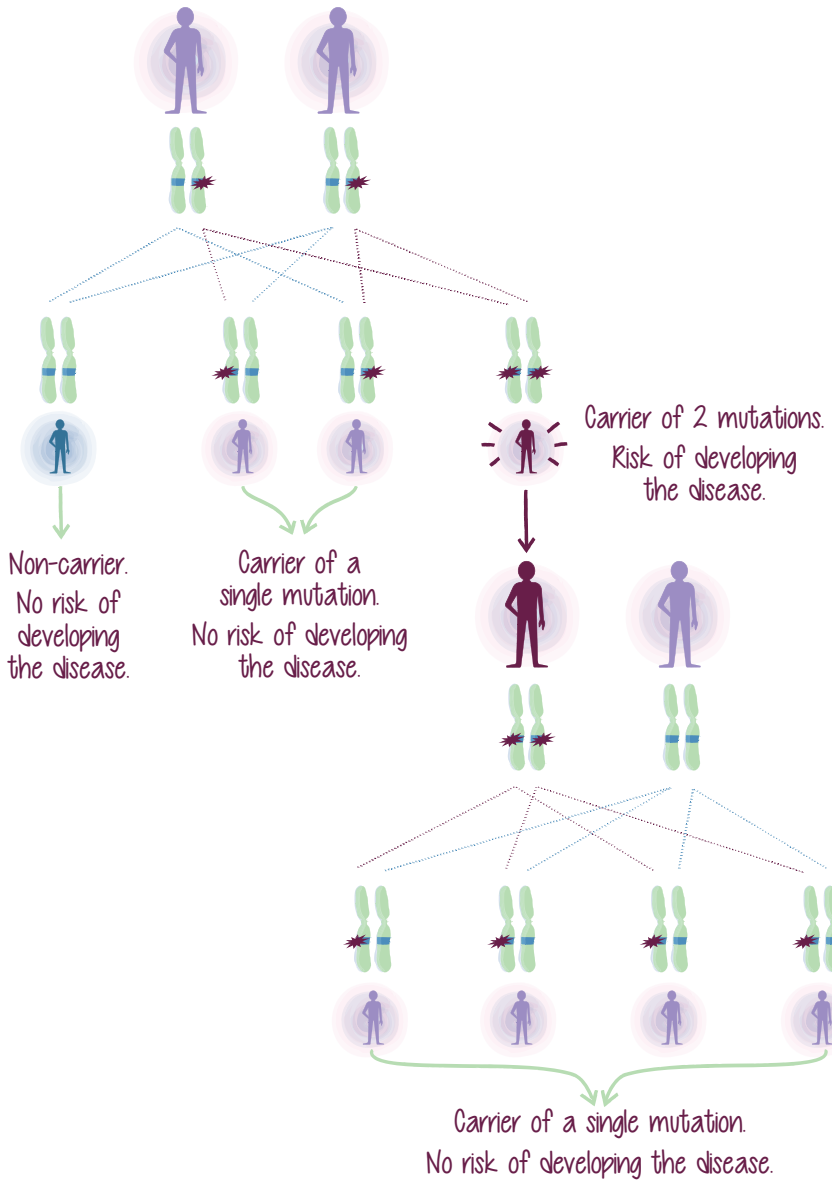
When the future parents are both carriers of a single mutation on the same gene, they will have for each birth:

- 25% probability that the child to be born does not carry any of the mutations. The child will have inherited the two normal chromosomes from his/her parents. There is no risk of developing the disease.
- 50% probability that the child is a carrier of a single mutation. He will have inherited a single chromosome carrying the mutation that he/she will be able to transmit in turn. There is no risk of developing the disease.
- 25% probability that the child to be born will carry both mutations. The child will have inherited the two chromosomes carrying the two mutated genes. The child will therefore be at risk of developing the disease.

For the descendants of ill individuals, it all depends on the genetic status of the other parent:

- If the other parent does not have any mutations in this gene - which is the most common case as these mutations are very rare - all the children will be carriers of a single mutation. They will not be at risk of developing the disease.
- In rare cases, if the other parent is also a carrier of a mutation, the risk that the unborn child will be ill is 1 in 2 (50%), the risk that he or she will be a carrier of a single mutation is also 1 in 2 (50%). This situation is possible, for example, if both parents come from the same family (siblings, etc.).

Recessive inheritance



Unmutated gene



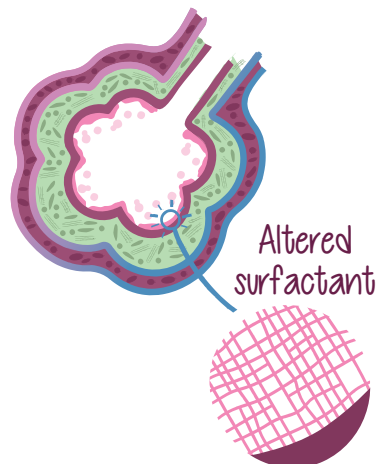
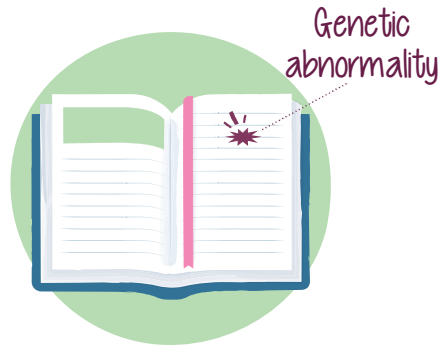
Mutated gene

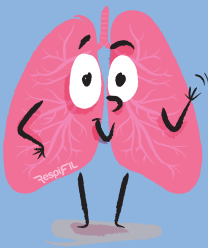
To sum up...

No genetic
abnormality



Presence of a
genetic abnormality





We hope that this booklet has given you a better understanding of the consequences of a mutation in a surfactant gene on the proper functioning of breathing, as well as the different modes of inheritance of these disorders.

Do not hesitate to contact us if you or someone in your family would like more information.

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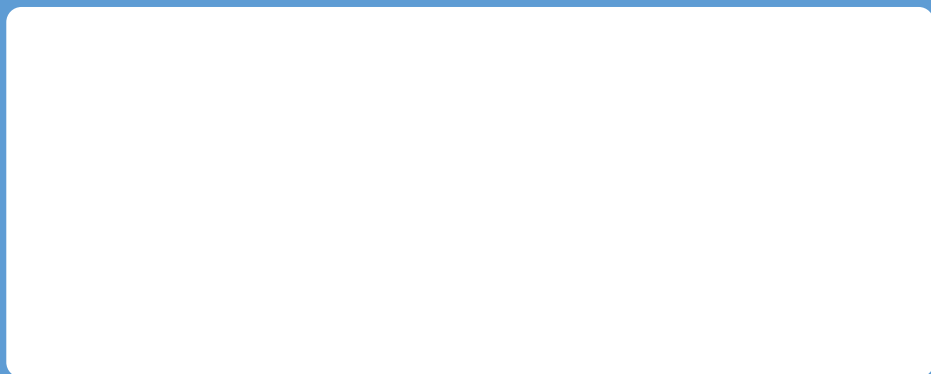
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