GENETICS AND HEREDITY

1. Introduction

Epidermolysis bullosa (EB) is a disorder that is genetic, this means that the cause for this is found in the genes of a human. The processes in our genes are complicated and difficult to understand, there are still many unanswered questions. Of course, there are always many questions and misconceptions about inheritance in EB. In this section we'll summarize the complex processes, which play a role in the inheritance, and try to bring you closer to an understanding of the effects of the genetic changes that lead to EB.

Important points in a nutshell

- **Genes are the carriers of our heredity factors.**
- **The cause of EB lies in changes in individual genes.**
- **These altered genes can be inherited in different ways**
  Recessive:
  - **The disease usually occurs in this family as a complete surprise.**
  - **Usually both parents (healthy) are carriers of the gene.**

  Dominant:
  - **There usually is already one or more victims in a family.**
  - **A parent usually is affected by EB.**
- **There are a number of exceptions to this rule and cases, even in EB!**
- **A detailed genetic counseling is important for a better understanding of EB.**

2. General information

This section cannot explain all the relationships that play a role in heredity factors to you. These processes are very complex and not yet completely explored. However, it might interest you to know a few basics to better understand the background of a disease like EB.

Basics for understanding the processes involved in hereditary factors:

In biology, heredity is called the transmission of traits from parents to their children. This applies only to material properties (e.g. hair color, body size) but not for skills and knowledge that children learn from their parents.

Genes are the carriers of genetic information; they are like the "base unit" of heredity. They contain so to speak the "blueprint" for certain "building blocks" from which our bodies are built and are distributed on 23 pairs of chromosomes, which are located in the nucleus of every cell in the body. In all body cells, these 23 pairs of chromosomes in humans are included, so 23 x 2 = 46 chromosomes, except egg and sperm cells. These contain 23 chromosomes only once. In the fusion of egg and sperm a complete set of chromosomes with 23 pairs occurs again, with each pair one chromosome from the mother and the other inherited from the father.

The chromosomes 1 - 22 are known as "autosomes" and this denotes that they look the same in men and women. The 23 pairs of chromosomes are the sex chromosomes X and Y. They determine the sex of a person. The human chromosomes are therefore either 46, XX (= female) or 46, XY (= male). Chromosomes are (DNA = Deoxyribonucleic Acid) from the so-called deoxyribonucleic acid that builds the individual genes. A gene is a piece of DNA that is the blueprint for a single protein or protein molecule from which our bodies are built.

Recently, the entire DNA (genome) of humans was entirely decrypted; it is now estimated that there are approximately 30 000 genes on the human chromosomes. So far, the genes responsible for about 16 000 hereditary characteristics are known. They are responsible for the diversity and uniqueness of each person. Hair color, eye color, but also the blood group and many other features are passed on from generation to generation in various combinations. Each person inherits half its genes from their mother and the other half from their father. The genes are

constantly being reshuffled, only identical twins have exactly the same genetic information.

Changes in genes are referred to as mutations. They may be relatively unimportant and unnoticed, or can even lead to different diseases. They have currently found for 1300 diseases specific changes in the corresponding genes and in many other diseases gene alterations are also suspected.

The causes and the nature of the inheritance of genetic diseases are generally divided into:

Chromosomal Disease:

There is not only a change to one of or several genes, but a change in the total chromosome number or structure. The most famous example is Down's syndrome, in which there is too many of the same chromosome. Instead of a pair of chromosome No. 21 there are three chromosomes 21 in the cells, that is to say there is a total of 47 chromosomes in each cell instead of 46.

Polygenic Diseases:

These are caused by the interaction of many individual changes of undefined genes on the one hand, and often unknown environmental factors on the other. The occurrence and recurrence risk of polygenic or multifactorial genetic disease cannot be as easily determined as with the monogenic diseases with rules or read from the family tree, but it is known to occur more frequently in some families. These include allergies and diabetes.

Monogenic Disease:

There is a single altered gene responsible for a disease outbreak. This genetic alteration results in the loss or malformation of a particular enzyme or protein molecule. This is the cause in the different forms of EB, but also many other diseases. Seen statistically, about 1 child in 100 babies has a condition that is due to a change in a single gene. Some of these genetic disorders are expressed at birth, others only in the course of life. Thus, metabolic or muscular disorders are often seen already in infancy, while other diseases such as Huntington's chorea ("Saint Vitus' Dance") or even some family tumors don’t show up until adulthood.

Inheritance of Epidermolysis Bullosa:

Epidermolysis bullosa is one of the monogenic diseases, and this means, that the change in a single gene is responsible for the disease. There are now 16 different genes that are known to cause changes in EB, and it may be that more are discovered in the coming years. The genetic modification ensures that certain proteins that are produced are not formed or not changed, which are responsible for the anchoring of the epidermis and the dermis. The result is, that the anchoring of the epidermis does not work properly and it results in blister formation under mechanical stress. These changes are inherited in a legitimate manner, namely with autosomal recessive and autosomal dominant genes.

For the sake of completeness it should be mentioned that there is also other monogenic modes of inheritance, namely those that are tied to the sex chromosomes (X-linked recessive, X-linked dominant) and also those that are bound to the mitochondria (the "power plants cell "). These modes of inheritance are not relevant for EB, so we will not discuss it further.

Please see the chapter for which specific heredity type you or your child with EB is suffering from „EB-subtypes".

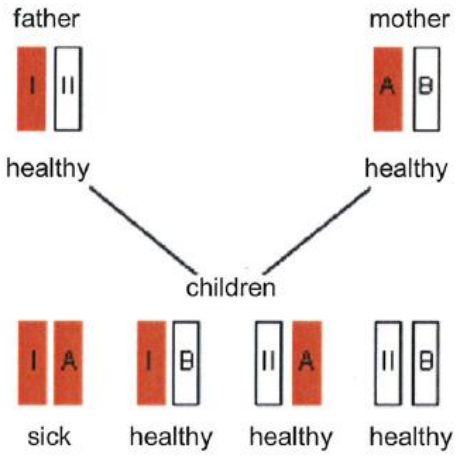
What does an Autosomal Recessive Inheritance mean?

Examples of autosomal recessive forms of EB are: recessive dystrophic EB, EB simplex with muscular dystrophy and all forms of junctional EB.
Recessive could be translated into "oppressed" or "retreating". This means that a change is present in a gene, but it is covered by the second, unmodified gene. The gene on the second chromosome is "healthy" and often able to produce intact functional building blocks. The disease did not break out, even though a gene mutation occurred.
This type of gene mutation that is a gene pair - one of a modified and one normal gene exists - is called heterozygous (roughly translated: "two different"). The carrier of such a gene is even healthy, they also are mostly not aware that they carry the affected gene of this disease with them. It has now been estimated that probably 6 - 8 of these gene mutations are carried by every person on earth, without knowing it and without becoming ill because of it.

How can there be a Disease in this Case EB?

If the parents of a child - by chance or by fate, or whatever you want to say – are both carriers of the same gene mutation, there is a risk of 25% for the child that it inherits two mutated genes and a disease (see figure 1). It may also be, that there are none or they only inherited one of the mutated genes and it is healthy (see figure 1).
Sometimes it is assumed that at a risk of 25% for 4 children therefore one is affected. This is not right, it just means that at every birth there is a 25% chance for that child that it is affected, and a 75% chance that it is not affected. It may be that in this mode of inheritance all children are affected, or even none are affected. The data are purely statistical data, but the genes are shuffled with each pregnancy! The disease is otherwise independent of the sex of the child, since the altered gene in the case of EB is not on the chromosomes that determine the sex.

Figure 1: Autosomal recessive inheritance:



Summary of Autosomal Recessive Inheritance:

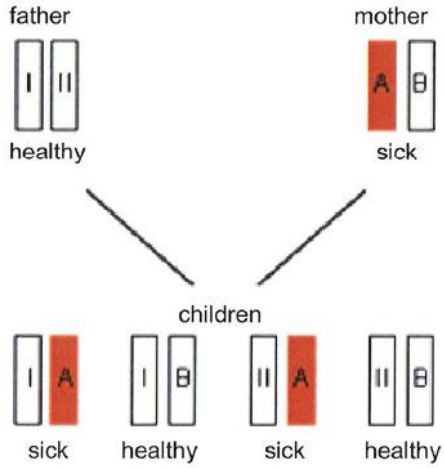
- The carrier of an altered gene will have only one healthy gene because the gene function is maintained by the second, non-altered gene.
- Only when two altered genes (one from mom, one from dad) come together in the child, this will result in a disease.
- Both sexes are equally affected.

What is an Autosomal Dominant Inheritance?

Examples of autosomal dominant forms of EB are: EBS localized, EBS generalized severe and the dominant dystrophy EB form.

Dominant means "prevalent". In these forms, a single gene mutation cannot be compensated by a healthy partner gene. The change is too strong and outweighs the normal gene. The gene on the second chromosome is no longer capable of compensating for the non-functioning of his "neighbor" gene. The carrier of this gene will definitely become ill (see figure 2). The disease forms as soon as a gene is changed. In contrast to the recessive inheritance the disease in the family was already known, there are often more people affected in different successive generations.
Because only one of the two genes (either modified or not-changed) is passed from the affected parent, the children of an affected parent have (in the picture the mother) a 50% chance of getting the altered gene and of developing it. Again, this is a statistic because it is reshuffled again with each pregnancy. It is possible that all children are affected, several or even none.

Figure 2: Autosomal dominant inheritance:



Summary of Autosomal Dominant Inheritance:

- An altered gene from the mother or father is sufficient enough for the disease outbreak.
- The disease-causing gene dominates over the "healthy".
- The disease usually occurs in successive generations.
- Both sexes may be equally affected.
- The attribute does not occur in the offspring of non-diseased persons.

Spontaneous Gene Mutations:

At this point it must be mentioned that there may also be spontaneous changes in a gene regardless of the inherited disease, by genes during fetus development. This can also lead to a disease. One speaks of a "spontaneous mutation" that occurs in a brand new family member, but it can then be passed on in future generations. In this instance parents are healthy, none of them carries the mutated gene, and yet their child may be born with EB. This mostly relates to the dominant forms and it occurs fairly often.

Investigation of the Gene:

Today it is possible to search for genetic disorders in an appropriate laboratory, exploring the underlying genetic mutation. This can help to confirm the diagnosis and in some cases this may find possibilities for the future. So sometimes a prenatal examination is desired, for instance in subsequent pregnancies from the same pair. If necessary, you can also determine if there are more carriers of the disease in the family. Research is making steady progress and if one day there is a possibility to influence genetic diseases directly within the genes and heal it, then it is necessary to allow the gene mutation to be closely examined.
Of course it cannot be said here, whether it is in your case important to know the exact genetic mutation or not. It should also be mentioned that the health insurance plans (which are getting more expensive!) do not cover all costs. So before you decide for or against genetic testing, it is necessary to discuss this in detail with a specialist. In many countries this is also required by law and this is also useful, as the correlations to diseases may be different in each case. As part of a comprehensive genetic counseling you can then sort out all the issues that are important to you and your family.