





The science behind diagnosing types of EB

Types of EB

Epidermolysis Bullosa (EB) is a collection of conditions that have similar symptoms including skin that is vulnerable to damage and blistering. Different types of EB are caused when different proteins, important for skin strength, are missing or don't work properly. EB symptoms vary from rare types that are fatal in early infancy to types that improve with age and do not affect life expectancy. An accurate diagnosis of EB type can mean better information about how symptoms might change over time and what treatments are available. The type of EB a person has cannot change, although rarely a mistaken diagnosis may be corrected later with a different test.

EB has been split into different types and classified in different ways with doctors publishing updates every few years. This means that older diagnoses may use names that are not used currently and this can cause confusion. Current diagnoses split genetic EB into EB simplex (EBS), dystrophic EB (DEB), junctional EB (JEB) or Kindler EB (KEB).

Type of EB	Inheritance	Occurrence	Commonly affected protein	Skin layer
EB simplex (EBS)	Usually dominant	Most people with EB have EBS (7 in 10, 70%) 	Keratin-5 Keratin-14 Plectin Others	Epidermis (top layer)
Dystrophic EB (DEB)	Can be recessive (RDEB) or dominant (DDEB)	Around a quarter of people with EB have DEB (1 in 4, 25%) 	Collagen-7	Dermis (lower layer)
Junctional EB (JEB)	Usually recessive	Only 1 in 20, 5% of people with EB have JEB 	Laminin Integrin Collagen-17	Basement membrane (between epidermis and dermis)
Kindler EB (KEB)	Usually recessive	Fewer than 1 in 100 people with EB have KEB (less than 1%) 	Kindlin-1	All layers

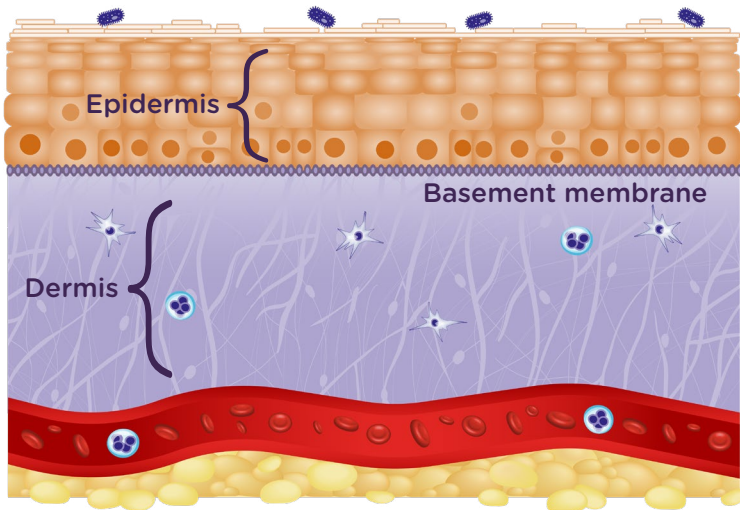
Diagnosing the type of EB by looking

EB can be suspected when wounds and blisters appear on a person's skin. At birth, a doctor specialising in childbirth and babies will likely ask a specialist skin doctor (dermatologist) to help make the diagnosis. This is often not reliable in the first years of life without further tests because different types can have similar symptoms. Later in life, symptoms of different types of EB can be more obvious, and it will likely be a person's GP who makes a referral to a dermatologist. It can be important for parents/carers to be able to explain to a healthcare professional or social worker that their child's wounds are because of EB. Having a diagnosis can make it easier to access support throughout a person's lifetime.

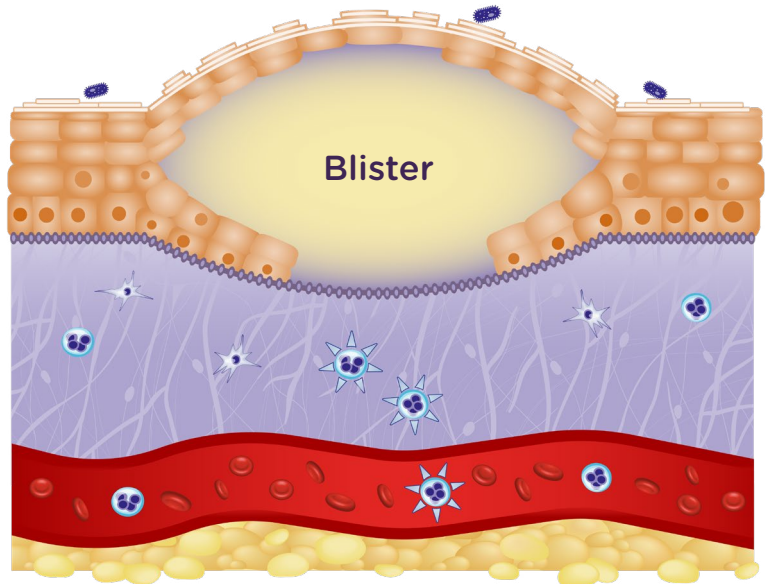
Doctors have described some types of EB as "severe" or "intermediate" depending on how much the symptoms affect a person's quality of life. The term "localised" is used when symptoms happen only to specific parts of the body, commonly the hands and feet, or "generalised", when symptoms happen across the body and inside it. Some types have been named after the doctor(s) who first published the specific pattern of symptoms they saw in a scientific journal.

Diagnosing the type of EB by looking under a microscope

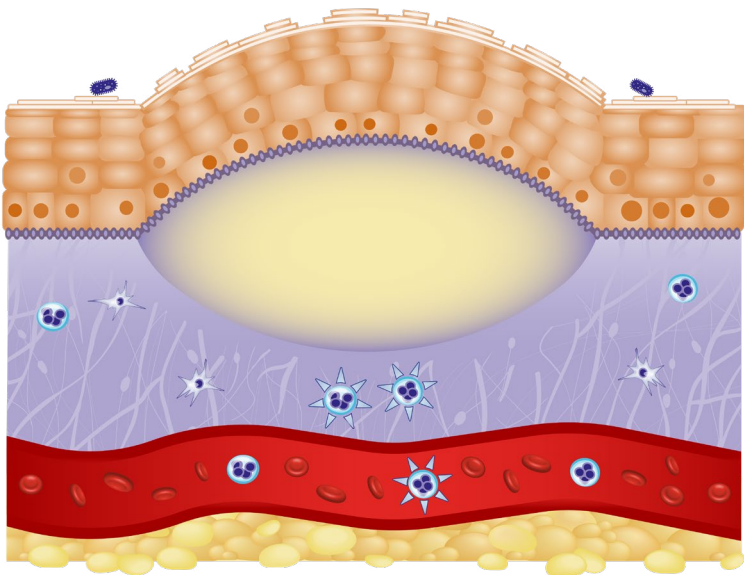
A very small piece of skin can be cut out (biopsy) and studied more closely under a microscope to identify which layers of the skin are damaged or which proteins are missing. This can often allow doctors to diagnose EBS, DEB, JEB, or KEB. Within these types, EB symptoms can vary and overlap, but knowing the type can be helpful to guide expectations.



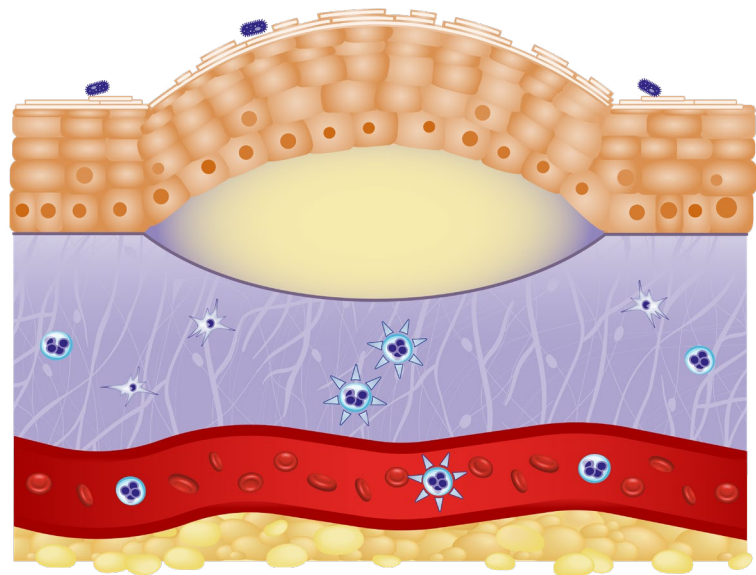
Healthy skin is made from two layers. The epidermis at the surface (orange) and the dermis (purple) are stuck together by a layer of proteins called the basement membrane.



In EBS, blisters form above the basement membrane in the epidermis.



In DEB, blisters form below the basement membrane in the dermis.



In JEB, blisters form at the junction of the two layers because the basement membrane itself is affected.

Family history of EB

While some cases of EB occur without any family history, many cases of EB are inherited and appear across multiple generations of the same families. The pattern of inheritance in a family can be used to say whether inheritance is dominant (from one parent with EB) or recessive (from two unaffected parents). Dominant types of EB may be milder than recessive types, but this is not always the case.

The pattern of inheritance can predict the likelihood of future children having EB. Future siblings of a child with dominant EB have a 50:50 chance of also inheriting EB. Future siblings of a child with recessive EB have a one in four chance of also inheriting EB. Knowing which gene is affected makes it possible to screen future pregnancies and brings greater certainty to family planning.

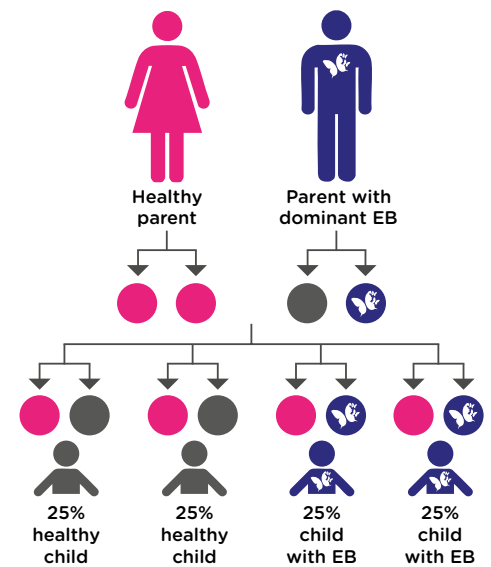
Genetic testing

Genetic testing involves taking a cheek swab or blood sample from someone and preparing a tiny amount of their DNA. Most human cells contain over 6 billion DNA 'letters' (A, C, G, or T), 3 billion from an egg cell that came from a person's mum and 3 billion from a sperm that came from their dad. These are copied into each new cell as a baby grows and spell out two recipes each for about 20,000 different proteins that human bodies are made from. (Impressive - but cabbages have more than twice as many!)

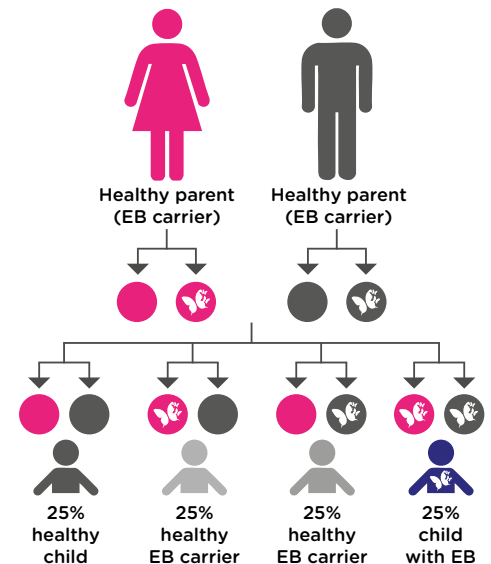
The order of the DNA 'letters' can be discovered by laboratory processes called 'sequencing', then compared to a reference sequence using computer programs. Rather than sequencing the whole lot, many genetic tests will first look specifically for changes in the genes that are the recipes for proteins known to be affected in EB. Changes in the genes for keratin-5 and keratin-14, among others, cause EBS, accounting for most cases of EB. Changes in a gene for collagen-7 cause DEB, and changes to genes for laminin, integrin and collagen-17 cause junctional EB. Kindler EB (KEB) is caused by changes to the gene for Kindlin-1 protein.

If these genes are checked and found to be unchanged, whole genome sequencing can look for changes in genes that are less commonly responsible for EB. However, every person will have many changes in their DNA that don't cause EB, and it can be difficult to show which change might be responsible for EB symptoms. One way of checking is to look at that bit of DNA in family members who have EB and those who don't have EB to confirm that it is only present when there are EB symptoms. Sometimes it is not possible to identify a genetic cause for EB and diagnosis relies only on the biopsy and family history which can be less certain than a genetic diagnosis.

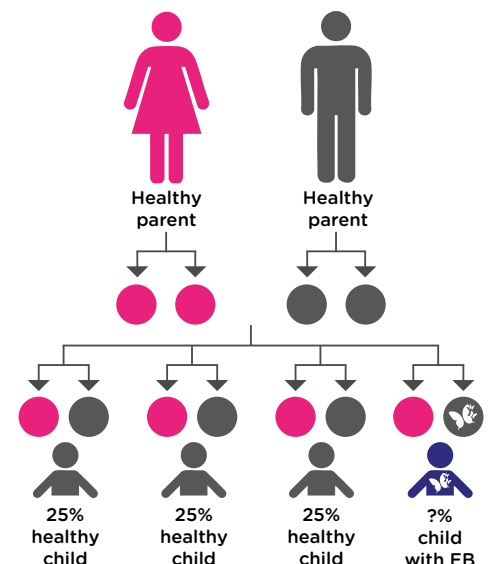
Autosomal Dominant Inheritance



Autosomal Recessive Inheritance



De Novo Inheritance



Genetic testing can provide detailed information

Different changes to a gene sequence can have different effects on the protein it is a recipe for. Some changes to the DNA don't alter the protein it makes at all: like substituting "two" for "2", the meaning stays the same and the recipe works as normal. Some changes make a difference to how well the protein works. This could be like a change in a cake recipe from "2 eggs" to "3 eggs", or from "2 eggs" to "20 eggs", or from "2 eggs" to "2 bananas". It is sometimes possible to predict from the genetic change, how badly damaged the protein will be and, therefore, how severe the EB symptoms might be. Some genetic changes just say "STOP!". This can happen right at the beginning of the recipe, and no protein will be made, or near the end so a protein will just be missing a small part and still be of some use in strengthening skin.

Because everyone has two copies of the recipe (gene) for each protein, one from each parent, having one altered version doesn't always cause symptoms. Recessive inheritance happens when both parents only have one working recipe for a skin protein. Their skin is fine because their body uses the working recipe and ignores the altered one. They can be called "carriers" because they 'carry' the altered gene without knowing about it. By chance, their child may inherit the altered recipe from both parents and be unable to make that skin protein at all. Sometimes having one altered recipe is enough to change how skin works. In dominant EB, symptoms happen even when there is one correct recipe.

Even when people have identical genetic changes, their EB symptoms may be quite different. This is because there will be lots of other slight changes in lots of other genetic recipes making lots of other proteins throughout the body and these can make symptoms worse or better.

EB that isn't inherited

A child can have a genetic change that neither of their parents have. This is called a *de novo* change. It is new and happened in mum's egg or dad's sperm or in the early embryo soon after the egg and sperm joined. If the *de novo* change happened in one cell, very early on, when there were only four cells, eight cells or sixteen cells, a person can have genetic 'mosaicism' where not all of the cells in their body have EB (maybe a quarter, an eighth or a sixteenth) leading to more complicated genetic testing results.

Sometimes there is no genetic change and EB symptoms start later in life when a person's immune system mistakenly attacks a skin protein (autoimmunity). Damage to collagen-7 by a person's own immune system causes a rare, non-genetic form of EB called EB acquisita (EBA). There are other similar conditions that may look like EB. A genetic test is the best way to determine the type of EB and allow clearer prediction of future symptoms and access to clinical trials and future treatments.

Diagnosis informs treatment options

Knowing which type of EB a person has will let them know whether they can participate in a clinical trial or benefit from a treatment. **Clinical trials** find evidence for treating specific types of EB. Without a diagnosis of that type, a **treatment** may not be prescribed. Gene therapy treatments can be very specific in correcting one genetic change and would have no benefit for people without that genetic change. To take part in clinical trials and to get the best treatment, a genetic diagnosis is essential.

