

# Ichthyosis

*The Genetics of its Inheritance*



**FIRST**

Foundation for Ichthyosis & Related Skin Types™  
Educate • Inspire • Connect

*Third Edition:*  
Reviewed by  
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Probably the question most commonly asked of people with Ichthyosis is: "Is it contagious?" The answer is, of course, "NO!" None of the ichthyoses or the related disorders in the family of skin conditions that are included in the umbrella of the FIRST<sup>1</sup> is contagious. These are all genetic disorders and can be "caught" only through heredity. Although not all members of the FIRST family of disorders are an "ichthyosis" per se, for ease of discussion, we will use that term to denote any of these conditions.

Probably the most common question asked by people who have ichthyosis, or by parents of a child with ichthyosis is: "How is it passed on? I have one child, and that child has ichthyosis. Will all my children have it?" Or, "I have ichthyosis. If I have children, will I pass it on to them?"

The answers to these questions will depend on the specific type of ichthyosis present in the family. Although the ichthyoses are all inherited or genetic disorders, the pattern or mode of inheritance varies considerably among the FIRST family of disorders. Therefore, the very first step in genetic counseling is a firm and accurate diagnosis.<sup>2</sup>

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<sup>1</sup> Members of the FIRST family of disorders are described in greater detail the Overview Booklet. <sup>2</sup> Diagnosis of the ichthyoses and its related disorders is usually achieved by consideration of the appearance of the skin in combination with the family history and sometimes other findings, such as skin histopathology or other laboratory testing. These diagnoses are based upon **phenotype**, i.e., on how the disorder manifests itself. Sometimes more than one gene (**genotype**) can cause a given phenotype. In other words, one's genetic makeup is his/her **genotype**. How he/she appears, i.e., how the genes are **expressed**, is his/her **phenotype**. This is important because a given appearance (phenotype) can be caused by more than one genotype. For example, one of more than 6 genes can underlie the Lamellar Ichthyosis/ Non-Bullous Congenital Ichthyosiform Erythroderma phenotypes. Phenotypes are very complex because the result of a given genotype may be modified by other factors, such as other, **modifying genes**, and environmental factors. As an example of the former, co-existence of the gene for Ichthyosis Vulgaris, which is very common in the population, with the less common gene for X-Linked Ichthyosis, may result in more severe skin disease. Darier disease is an example of a genetic condition that can be modified by environmental factors, e.g., ultraviolet light exposure. Because phenotypes are complex and sometimes confusing, the most accurate diagnosis for genetic counseling is one that is based upon determination of the causative gene (i.e., the genotype) in that family.

# AN INTRODUCTION TO BASIC GENETICS

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**G**enes are the basic units of heredity. Genes encode the information needed to make all the other parts of the cells that make up the human body. **Chromosomes** are the structures that carry the genes, like beads on a chain. Each person has 46 chromosomes, 44 autosomes and 2 of the sex chromosomes, the X and Y chromosomes. Females have 44 autosomes and 2 X chromosomes, while males also have 44 autosomes with one X and one Y chromosome. Twenty three of these chromosomes came from their mothers (i.e., 22 autosomes and one X chromosome) and 23 from their fathers (i.e., 22 autosomes and one that is either an X or a Y chromosome). Thus genes and the chromosomes that carry them occur in pairs – 22 autosome pairs and the 2 sex chromosomes.

An overview - and admittedly an oversimplified view - of basic genetics starts with the fact that all people have two genes for nearly every hereditary trait in their bodies. They receive one gene for each trait from each parent for a total of two genes.<sup>3</sup> One gene<sup>4</sup> on a chromosome they got from their mother and the other gene for that trait on the chromosome of that pair that they got from their father. Their parents, of course, also have two genes for each trait residing on a pair of chromosomes, but when they create a sperm or an egg, the chromosomes bearing those genes separate, such that there is only one chromosome of the pair, and hence, only one gene for each trait per each sperm or egg. At conception, the sperm from the father combines with the egg

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<sup>3</sup> The two members of each gene pair are called **alleles**. <sup>4</sup> allele

from the mother, and the fetus acquires his/her own pair of chromosomes with their attached genes.

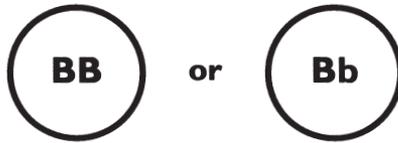
Genes are generally either **dominant** or **recessive**. The dominant gene is exactly that - dominant. You can think of it as the bully on the grammar school playground; when he's around he prevails. As the genes pair up, whichever gene is dominant will determine what traits will prevail (i.e., be **expressed**) in the new human being. The gene for the recessive "version" of a particular trait may be there, but it is not allowed to **express** itself if a gene for the dominant version is also there to overpower it.



## HOW GENES ARE PASSED AND TRACED

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The traits of the dominant gene are the easiest to trace through a family, since their effects are manifested in the offspring. An individual exhibiting a dominant trait can have one of two genetic make-ups<sup>5</sup>:



The capital letter is used to designate the dominant gene, the lower case letter the recessive gene for the same trait. A commonly used example is eye color, although it is important to point out that it is, in fact, an oversimplification because the inheritance of eye color depends upon more than one genetic factor.<sup>6</sup> With this in mind, however, we will use eye color here as an example of patterns of inheritance because it is something that everyone is familiar with, easy to conceptualize, and not terribly "clinical."

We'll say capital "B" is the gene for brown eyes and lower case "b" is the gene for blue eyes. The capital "B" indicates that brown eyes are dominant over blue eyes. A brown-eyed person could have two "B" genes (i.e., "BB") or he could have a "B" gene and a "b"

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<sup>5</sup> genotypes   <sup>6</sup> This type of inheritance is termed **multigenetic inheritance**. Many common traits, like eye color or skin or hair color, as well as many common diseases, such as diabetes or psoriasis, are caused by the action of several genes, i.e., are multigenetic traits. In contrast, members of the FIRST family of disorders are all single gene ("Mendelian") traits.

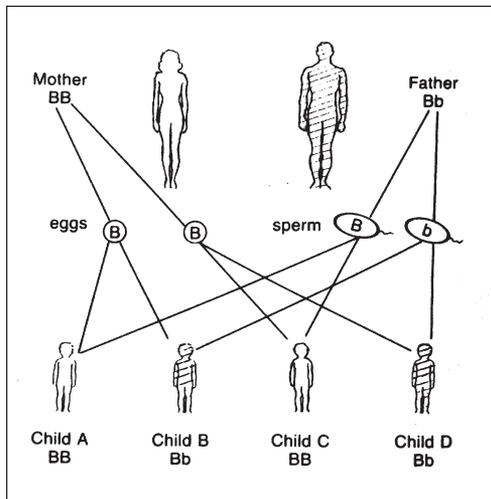
gene ("Bb"); either way he would have brown eyes because the "B" (brown) gene dominates the "b" (blue) gene, giving the person the trait represented by the "B" - in this case, brown eyes.

"BB" people pass on only "B" genes - it's all they have to give. "Bb" people, however, can pass on either a "B" or a "b" gene to each of the sperm or eggs they produce; that is, some eggs or spermatozoa will receive chromosome bearing "B" genes and others will get ones with "b" genes.

Thus, if two "BB" people marry and have children, there's no doubt what genes they will pass on or what color eyes their children will have. And all their children will also have a "BB" genetic makeup for their brown eyes.

### Example 1

If one parent is "BB" and one is "Bb", both parents will have brown eyes and all of their children will also have only brown eyes, as shown here:



No matter which gene the child receives from the father, it will always be paired with a gene from the mother. Since any gene from the mother will be a dominant "B" gene for brown eyes, any child from this pairing will have brown eyes, despite the father's

one recessive gene for blue eyes. This father would be called a carrier for blue eyes because he "carries" a recessive "b" gene for blue eyes, even though that gene cannot express itself in his eye color. It can, however, be passed to his offspring.

### Example 2

What if two brown-eyed parents have the genetic makeup of the father in the above example, however? If both parents are "Bb" they both will have brown eyes, but they will each pass on either "B" or "b" genes. The child who gets the "bb" gene combination will have blue eyes, not brown, because he has no "B" gene to bully his "b" gene. Thus the "weaker," or recessive trait is able to manifest itself - blue eyes.

In a later section (Autosomal Dominant Inheritance) we will further describe how the dominant inheritance pattern operates in these disorders. We will now describe the major patterns of inheritance. For simplicity of discussion we will use one type of ichthyosis as the example or paradigm. But the choice is arbitrary and the reader should bear in mind that the same genetics apply to all the other disorders that follow the same mode of inheritance.



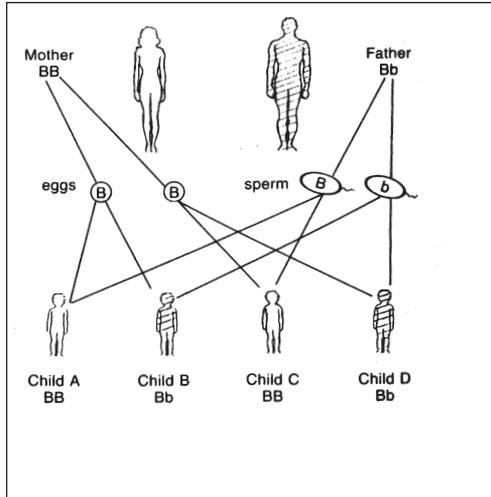
## AUTOSOMAL RECESSIVE INHERITANCE

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In the first FIRST family of disorders, Lamellar Ichthyosis, Congenital Ichthyosiform Erythroderma (CIE), Netherton Syndrome and Harlequin Ichthyosis (among others) are caused by recessive genes – like the blue eyes example above. They are caused by recessive genes which ordinarily are dominated by genes for normal skin. Only when a person receives two recessive genes for Lamellar Ichthyosis or two for Congenital Ichthyosiform Erythroderma or two for Harlequin Ichthyosis (etc.) will he manifest one of these disorders. In this section, we will use Lamellar Ichthyosis as our example of the autosomal recessive mode of inheritance.

In autosomal recessive inheritance, both parents of the affected individual are carriers. Since they do not have ichthyosis, they usually discover they are carriers only when they have a child with the disorder. The reason their skin is normal is due to the influence of their dominant “B” gene over the recessive “b” gene. In this case “B” stands for the gene for normal skin, which is dominant over the “b” gene for Lamellar Ichthyosis. Any children of this couple who inherit a “B” gene will also have normal skin, but the child who gets a “b” from both of his/her parents will have no normal “B” gene to counteract the genes that cause Lamellar

Ichthyosis.<sup>7</sup> This child, "Child D," will display the disorder in the same way that the child in the previous example displays blue eyes.



The parents of this child now know that they are both carriers; they each have a genetic makeup of "Bb" for Lamellar Ichthyosis. That means their chances of having a child with Lamellar Ichthyosis are one-in-four (25%) for every pregnancy. The chance that a child will be a carrier (as both parents are) is 50%, and the chance that a child will inherit only normal skin genes from both parents is 25%. However, since **each pregnancy is a new and independent event**, it is important to remember that the parents with one child with Lamellar Ichthyosis cannot assume that their next three children will have normal skin on the grounds that they have "satisfied the odds." Each pregnancy for this couple will carry the exact same one-in-four (25%) risk to produce a

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7. Recessive genes typically produce disease through **deficiency or loss of a function**. In Lamellar Ichthyosis, for example, the causative gene encodes an enzyme called Epidermal Transglutaminase 1. Mutations in this gene can result in decreased to absent function of this enzyme. But if only one gene of the pair (i.e., only one **allele**) is mutated this way, the other gene (allele) can produce enough enzyme to preserve this cellular function such that no skin disorder is manifested, hence the normal gene is dominant and the disorder is recessive. Only when both alleles are mutated is the loss of function sufficient to result in the skin disorder. The severity of the disease can also related (at least in part) to the specific mutation; i.e., mutations that result in complete loss of enzyme function may have a more severe phenotype than those resulting in only partial loss of function.

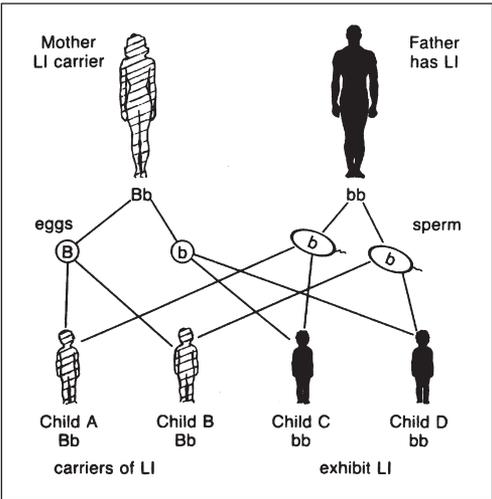
child with lamellar ichthyosis - somewhat in the same way that a couple has a 50-50 chance of having a son in each pregnancy, even though they may already have one, two, three or even twenty-three daughters!

The individual who has Lamellar Ichthyosis actually has a far smaller chance of producing a child with Lamellar Ichthyosis than his parents do. He has only “bb” recessive Lamellar Ichthyosis genes to pass on, that's true. But like any other parent, he will contribute only one half of his children's genes, and his child would need two “b” genes to display the disorder. That child could get another “b” gene only if his other parent were a carrier for that same disorder. Since Lamellar Ichthyosis is a very rare disorder, the odds of someone with the disorder meeting and marrying a carrier of the same disorder are just as unlikely as the odds that a carrier would meet and marry another carrier. It's possible, but very unlikely. Marrying a relative, however, would increase the possibility of marrying a carrier of “b” very significantly.<sup>8</sup> The only way a person with Lamellar Ichthyosis could be certain his/her children would exhibit the disorder would be to marry another person who had the same type of ichthyosis. Then the genetic makeup of both parents would be “bb” for this disorder and the child could inherit only recessive Lamellar Ichthyosis genes.

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8. It is important to bear in mind that everybody carries recessive disease causing genes, perhaps 5 or more per person. Recessive genes for rare disorders like Lamellar Ichthyosis may be passed on for many generations before a family member happens to mate with someone who carries the same recessive gene and an affected child is born. In families, the closer the degree of relationship (e.g., sibling vs. first cousin vs. 2nd cousin, etc.), the greater the likelihood for shared genes, including recessive, disease-causing genes. In geographically isolated populations, the chance that partners may be distantly related is increased and this can lead to increased frequency of otherwise rare genetic disorders (e.g., the increased prevalence of Sjögren-Larsson syndrome in Northern Sweden). In these instances both carriers will harbor the exact same mutation (i.e., they are homozygous for the mutation), traceable back to a common ancestor (founder effect). But more commonly in pluralistic, larger societies, the precise nature of the genetic mutation differs between the two carriers; (i.e., the specific genetic change in the gene inherited from mother is different from the one inherited from the father). The affected individuals bearing different mutations in the two alleles of the same gene are called compound heterozygotes. As discussed previously, these differences in the precise nature of the mutations can underlie some of the variability in disease manifestations and severity (phenotype).

If the person with Lamellar Ichthyosis planned to have children with a person of normal skin, the genetic counselor would want to take a hard look at the “normal “ partner's background to determine if there has been any cases of anything resembling Lamellar Ichthyosis in his or her family. The counselor is trying to determine if there is an increased chance that the normal spouse is a carrier, because if the spouse is a carrier, the couple would have a 50-50 chance of passing along this recessive disorder. However, the only definitive way to be certain that the normal spouse is NOT a carrier is to do a genetic test on the spouse.<sup>9</sup> Again, the odds of marrying a carrier greatly increase if the affected person marries a relative. In fact, the person who displays Lamellar Ichthyosis can presume that some of his relatives, on both sides of the family, are carriers.



9. The genes causing most of the FIRST family of disorders have been identified and can be tested for. Testing is expensive, particularly if multiple genes (genotypes) can cause the same condition (phenotype) and several genes therefore must be examined until a causative mutation is found. In the example here, Transglutaminase 1 would be the most likely gene. The affected partner would first be studied to make sure that this was the gene in question. Then the unaffected partner would be examined looking for potential disease causing mutations in this gene.



## AUTOSOMAL DOMINANT INHERITANCE

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It would be lovely to say that healthy genes are always dominant over unhealthy ones, but unfortunately that is not the case. In several of the FIRST family of disorders, genes for the skin disorder are dominant and overshadow the genes for healthy skin. Epidermolytic Hyperkeratosis will be used as the example in this section, but the genetics also apply to all other autosomal dominant traits. Among the FIRST family of disorders, Epidermolytic Hyperkeratosis, Keratitis-Ichthyosis-Deafness (KID) Syndrome, Pachyonychia Congenita and Darier Disease are some examples of dominant disorders following this inheritance pattern

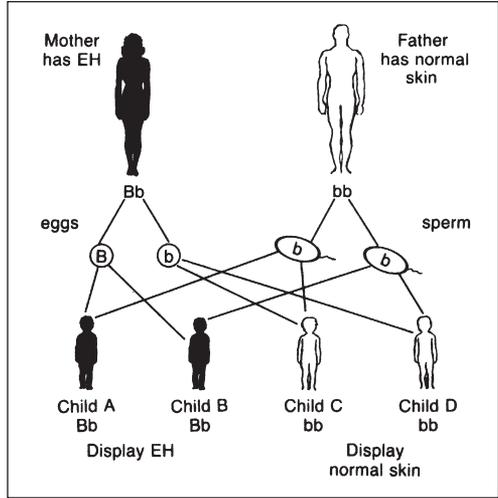
"Recessive" and "dominant" are not absolute terms in many instances. Genes for normal skin are dominant ("B") when compared to genes for Lamellar Ichthyosis or Congenital Ichthyosiform Erythroderma. The normal skin genes are not so dominant, however, when they come up against a gene for a disorder like Epidermolytic Hyperkeratosis.<sup>10</sup> Think of that grammar school playground bully again; he's not so tough when somebody from the high school comes to push him around. When comparing normal skin genes and those for Epidermolytic

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**10.** Dominant disease-causing genes can have their effect in one of two ways. First, the mutated gene may encode a protein that interferes with the function of the protein coming from the normal allele – this is termed a **dominant negative effect**. This is the mechanism operating in Epidermolytic Hyperkeratosis and Pachyonychia Congenita, for example. Conversely, having only one normal allele may result in critical deficiency of the gene product, i.e., in the protein encoded by the gene – this mechanism is termed **haplo-insufficiency**. Remember, in recessive traits, having one normal allele is sufficient. In dominant disorders attributed to haplo-insufficiency, a single normal allele is not enough. This appears to be the problem in Darier disease and in Hailey-Hailey disease.

Hyperkeratosis, the normal skin gene must now be represented by “b” and the genes for the disorder must be represented by “B”.

Since the gene for Epidermolytic Hyperkeratosis is dominant, in the usual situation there are no “invisible” carriers for it as there are in recessive disorders like Lamellar Ichthyosis.<sup>11</sup> A carrier of Epidermolytic Hyperkeratosis is expected to show Epidermolytic Hyperkeratosis. These individuals would probably have a genetic makeup of “Bb”. Let's say they marry a person with normal skin and a genetic makeup of “bb”. (You can safely assume a genetic makeup of “bb” for this mate since the gene for normal skin is recessive to the gene for Epidermolytic Hyperkeratosis and you need two recessive genes for the recessive trait, in this case normal skin, to show up.)



11. An “unusual” situation deserves mention here: **genetic mosaicism**. Genetic mutations can occur in cells at any point in their lives. If they occur in the DNA of eggs or sperm, all the cells of the developing person will contain the mutant gene. If, on the other hand, the mutation occurs during early fetal development, sometime after fusion of the egg and sperm and after the fertilized egg has begun to divide into more cells, only the daughter cells of the cell that mutated will carry the disease-causing genetic mutation. This person is a genetic mosaic – meaning that he/she has a mixture of cells, some that contain the new mutation (“Bb”) and some that do not (“bb”). When someone is a genetic mosaic for a mutation in one of the EHK-causing genes, the result can be an **epidermal nevus**. This is an ichthyosis-like condition where the scaling is limited to just part of the body, typically forming swirling lines or streaks. These streaks represent regions of skin that derived from a single embryonic mother cell. If that mother cell also gave rise to daughter cells destined to form some of the germ plasma (i.e., the cells that give rise to eggs or sperm), then the genetic mutation (“B”) could be passed onto future generations. But in that case, all of the offspring’s cells would carry the mutation (i.e., all would be “Bb”), and the child would have full-blown EHK. Rare cases have been documented in which a parent who had an epidermal nevus of the EHK type (not all epidermal nevi are caused by mutation in the EHK genes) had a child with full-blown EHK. Moreover, it is possible to have silent germline mosaicism – i.e., mosaicism in sperm or eggs without skin changes such as an epidermal nevus. Although rare, this is why the risk for recurrence of a dominant trait in parents who show no signs of the disease is still slightly greater than that of the general population, and underscores the importance of formal genetic counseling that includes examination of parents at risk.

Thus, the chances of this person passing on the disorder are 50-50. The “Bb's” will have the disorder; the “bb's” will not. It is important to emphasize again, that the odds are the same for each pregnancy. This couple, for instance, if they have a child with Epidermolytic Hyperkeratosis, cannot assume that they can safely have a second child without the disease because they have “satisfied the odds.” Each pregnancy for this couple carries the same 50-50 odds. Again, think about the odds of having a boy or a girl; they're exactly the same.

What about “BB”? Isn't it possible with Epidermolytic Hyperkeratosis just as it was with our original set of brown-eyed parents, that the person with the disorder could have two dominant genes, BB? Yes, it is possible, but extremely unlikely with a rare dominant disorder like Epidermolytic Hyperkeratosis. To get a “BB” configuration, a person would have to have two parents with the genetic makeup of “Bb”; i.e., have two parents with Epidermolytic Hyperkeratosis. As Epidermolytic Hyperkeratosis is both rare and severe, there would be few, if any, instances of two “Bb” Epidermolytic Hyperkeratosis people marrying and producing children. If they did, however, the risk with each pregnancy would be 75% that the child will have the disorder, and one-third of the affected children would be expected to have the genetic makeup “BB”.

These genetics are relevant, however, for one of the dominant disorders in the FIRST family, Ichthyosis Vulgaris. Mutations in the gene causing Ichthyosis Vulgaris<sup>12</sup> are extremely common in some populations. For example, in European populations, 10% or more carry a disease-causing mutation in the Ichthyosis Vulgaris gene. If they have one mutated gene (“Bb”), they may have a milder disease, sometimes with fine scaling, more like dry skin than ichthyosis – or they may show no obvious signs of carrying the gene, while individuals with the “BB” genetic makeup exhibit Ichthyosis Vulgaris and other features of the

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12. The affected gene FLG codes for the protein filaggrin.

disorder.<sup>13</sup> This form of inheritance is called **semi-dominant**. Using the playground analogy, one can imagine that the “B’s” are the kind of bully where if you meet one of them alone it may not go too badly for you, but when they are there together it is no fun.

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13. With 10% of the population carrying the mutated FLG gene, a random person would have a 1 in 10 chance being “Bb” (e.g. having one mutated FLG gene, and having, at most, somewhat dry skin). The chance of meeting and marrying another person who is Bb is also 1 in 10. (So the chance of two Bb people meeting is  $1/10 \times 1/10 = 1/100$ ). If those two people had children, the chance that a child would be “BB” is 1 in 4, and that child would have Ichthyosis Vulgaris. This gives the expected frequency of Ichthyosis Vulgaris in the population as 1 in 400. What we think of as the Ichthyosis Vulgaris phenotype may not be quite so common as 1 in 10 (clinical estimates have ranged from 1 in 250 to 1 in one or two thousand), but other features of the condition such as dry skin and eczema (**atopic dermatitis**) certainly are!



## WHERE DO DOMINANT GENES START?

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If a disorder like Epidermolytic Hyperkeratosis is fully dominant and always shows up if the gene is present, where did that first instance come from? How can it happen that the disorder appears in a family that had no previous history of it?

That first case in a family probably came about from a **spontaneous mutation** of a gene. In this age of movies and television, we tend to think of a mutation as something very dramatic, and usually negative. A mutation, however, is simply any new genetic change. Mutations can arise from a multitude of causes, some known, some as yet unknown. Although it may sound like a contradiction in terms, mutations are natural events. In fact, they are the very basis of evolution. Genes mutate at random: some of the changes are bad - they produce a defect or disorder which makes life more difficult for the organism; or they can be good - making the organism stronger and more efficient in its environment.<sup>14</sup> If Mr. and Mrs. Normal Skin have a child with Epidermolytic Hyperkeratosis, the disorder was probably caused by a spontaneous mutation in one of the genes causing this condition.

What's important for the person with Epidermolytic Hyperkeratosis to remember is that the causative gene is

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14. Mutations can also be neutral and have no apparent effect on the organism's survival. These mutations, termed genetic polymorphisms, are very common in the genome and are passed on through families, fanning out into the general population. Genetic polymorphisms, therefore, are useful markers of relatedness.

dominant. It doesn't matter where it came from - inherited from a parent who has Epidermolytic Hyperkeratosis or arising as a result of a spontaneous mutation- once it occurs, it persists and behaves like any other dominant gene. It will dominate the gene for normal skin in any subsequent generation. A dominant gene, just because it appeared spontaneously, will not disappear spontaneously. Anyone who has Epidermolytic Hyperkeratosis has a dominant gene for that disorder and a 50-50 chance, with each pregnancy, of passing it on to his/her child.

It is important to recognize that the preceding discussion has been simplified. Furthermore, there is often a certain amount of variability within each disorder. For instance, it is very slightly possible for a person to inherit a dominant disorder yet fail to express it at all. He would, nonetheless, pass it on as the dominant gene that it is, and his offspring could display it in full force, thus giving the appearance of "skipped generations." This phenomenon, called **non-penetrance**, is not common, and is more likely to occur in some dominant disorders than in others.<sup>15</sup>

In other instances, two people within one family inherit a disorder, but one gets a mild case and the other gets a severe case, though both have the same disorder, caused by the same genetic mutation. This phenomenon is termed **variable expressivity** and, again, it is more likely to occur in some genetic disorders than others. This can be the case, for example in some Pachyonia Congenita families.

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15. The Ichthyosis Vulgaris gene can be thought of as incompletely penetrant – where it is possible for someone to carry the gene but not show clinical signs of it.



## RECESSIVE X-LINKED INHERITANCE

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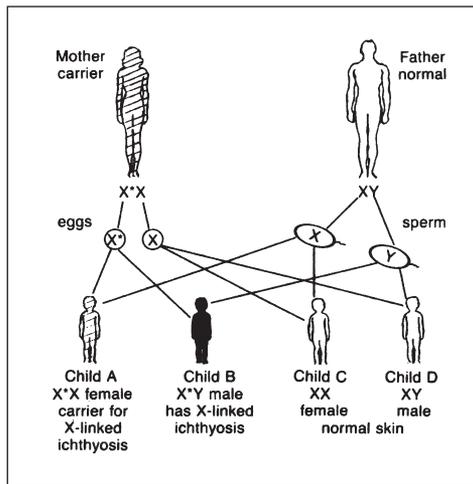
The last major type of inheritance is X-linked recessive. Our example here, **X-Linked Recessive Ichthyosis**, gives by its name a clear description of its genetic pattern: it is recessive and it is linked to the X chromosome.

As we discussed in the Introduction, chromosomes work in pairs, and the pair that is responsible for a person's sex is the XX (female) or XY (male) pairing. Females have two X chromosomes; males have one X and one Y. We also mentioned earlier that genes are attached to chromosomes; you can think of them as hitchhikers or riders who will take only one particular bus or subway train. Specific genes appear only on certain chromosomes, and X-linked genes appear only on X chromosomes. And finally, we have already discussed recessive genes - they can be bullied by another, more dominant gene for the same trait.

With X-Linked Ichthyosis, the gene responsible for the disorder can be bullied by a gene that overrides it, a gene that would also be attached to an X chromosome. Since women have two X chromosomes, they have two genes relating to the trait of X-Linked Ichthyosis. If one of these genes is abnormal and causes the disorder, the other gene, which overrides it, is present on the other X chromosome and dominates. The woman, therefore, has normal skin. All women have two X chromosomes and therefore have at least one gene that overrides the gene for this disorder. Since the gene for this disorder is recessive, women do not have X-Linked Ichthyosis.<sup>16</sup>

Men, however, are XY. If they receive an X-Linked Ichthyosis gene on their one X chromosome, they have no other, "normal" gene to override it because there was no other X "car" for that gene to ride in. He has just one recessive gene, but there is no other gene to keep it in line so it displays its trait. The result for him is X-Linked Ichthyosis.

In this schematic, X represents the X chromosome and the asterisk represents the gene for X-Linked Ichthyosis. A plain X represents the X chromosome that carries the normal gene for the disorder.



16. The gene for X-linked Ichthyosis is an interesting exception to the usual pattern of skin conditions that exhibit X-linked inheritance. Most of the genes on the X-chromosome undergo **lyonization** during early embryonic life. This is a process of **X-inactivation** where one X chromosome in each female cell is rendered inactive (non-operative) as a mechanism to equalize the genetic input of male and female cells, since the Y chromosome is very small and contains few genes. (In some instances too much genetic input is as bad as too little). Because of this, many of the X-linked conditions causing skin diseases show up in women only on part of their body, in lines and streaks, like the pattern in epidermal nevi due to somatic mosaicism discussed in an earlier footnote. Thus the condition manifests in skin cells where the X-chromosome carrying the mutant allele is the active X-chromosome. Where the skin is normal, the X-chromosome carrying the normal allele is the active one. In the FIRST family, Conradi-Hunerman-Happle syndrome and CHILD syndrome are examples of this pattern; these are considered X-linked "dominant" conditions, because the disorder is expressed with only one mutated allele (i.e., "X\* X"). In contrast, the part of the X chromosome that carries the X-Linked Ichthyosis gene does not undergo X-inactivation; i.e., the genes in this small region remain active on both X chromosomes. Thus female carriers of the X-linked recessive gene have one normal allele operative in all their cells and because the trait is recessive, do not exhibit skin disease.

For the female carriers of the disorder (the only ones who can transmit it directly to their children) the result is a risk identical to that of any other recessive disorder – i.e., one in four (25%). But in this mode of inheritance, the affected person will always be male, and the carriers will always be female.<sup>17</sup> The man who has X-Linked Ichthyosis will have only unaffected sons (they would get their X chromosome from their normal mother); and these sons will not be carriers, either. But the daughters of our X-Linked Ichthyosis man would all be carriers of the trait, although none would show the skin disease. Thus this couple can be reassured that their own children will not show the disorder, but they could still worry about their male grandchildren.<sup>18</sup>

Because of the "invisible", female carriers, X-linked recessive disorders frequently appear to skip a generation or two. In diagnosing a particular type of ichthyosis, or in trying to determine if the spouse with normal skin is a carrier, a doctor or genetic counselor will ask about family history, often going back several generations. Knowing that ichthyosis has appeared in a family before, but only in males, would be a clue that the condition in the family may be X-Linked Ichthyosis.

Although it is said that women "do not get" X-Linked Ichthyosis, it is not impossible for a woman to get it. If a carrier (woman) married a man who had the disorder, it would be possible for a daughter of this union to receive two X\*X\* chromosomes—two recessive genes for the disorder. It is not impossible, just unlikely.<sup>19</sup> And yet again, the likelihood of it actually happening is vastly increased by marrying a relative.

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17. Males born to the woman carrying the X-linked Ichthyosis gene have a 50:50 chance of inheriting the X-linked Ichthyosis gene. Females born to her likewise have a 50:50 chance of being carriers. 18. i.e., their daughter's male children 19. The likelihood depends upon the frequency of the condition in the population. Although X-linked Ichthyosis is uncommon in the general population, it is fairly common for a genetic disease, occurring in 1:2000 to 1:6000 males. The chance of a male with X-linked ichthyosis marrying a woman carrying the gene mutation would be somewhat greater than this – because more carriers are generated than affected males.



## SUMMARY

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Proper diagnosis and a detailed investigation into family backgrounds can help a particular couple, working with a skilled doctor or genetic counselor, to determine their genetic odds. Even knowing the odds, a couple still plays a bit of genetic roulette, but there's a huge difference between the odds of one in two, one in four, or one in thousands. Proper genetic counseling, and subsequent genetic testing, can enable a couple to determine those odds accurately. Whether or not they decide to "play the odds" is, of course, a very personal decision.

We have attempted in this brochure to answer the questions commonly asked about the genetics of members of the FIRST family of diseases. Many other questions will undoubtedly occur to you as you read. They can be answered by your doctor, genetic counselor, or by writing to the Foundation for Ichthyosis & Related Skin Types.

The information in this brochure is designed to be generally informative and is derived from sources believed reliable. The genetic concepts involved are extremely technical in many cases and have been simplified for clarity. The information presented is not, nor is it intended to be, sufficient for readers to make any decision about their personal genetic situations. Readers should always consult a professional geneticist or physician for individualized genetic counseling before making any decisions in their individual cases.



# FIRST

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