The gene for ichthyosis vulgaris is finally found

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Ichthyosis vulgaris is not only the most common form of ichthyosis but it is the most common disorder of the skin caused by a defect in a single gene and arguably, is one of the most common of all human genetic disorders. Although the condition is relatively mild compared to other rare forms of ichthyosis, it should not be trivialised by the public or medical profession, as it so often is. Ichthyosis vulgaris can cause great discomfort to those who have it and since it is so common, these number in the millions worldwide. Furthermore, as we will discuss below, the gene defect that causes ichthyosis vulgaris is also the root cause of eczema (atopic dermatitis), in particular, moderate to severe childhood eczema. This explains why many individuals with ichthyosis vulgaris also have eczema or have had it at some stage in their life, especially during childhood. Some but not all of these individuals go on to get asthma later in life. In the March 2006 issue of the top genetics journal Nature Genetics, we three, with our many lab staff and collaborators, reported the gene that unambiguously causes ichthyosis vulgaris. In the April issue of the same journal, which was published on the internet on 20th March, we reported very strong data linking this gene to eczema and a form of asthma associated with eczema. Here we will try to explain what this gene normally does and how it can lead to ichthyosis vulgaris, eczema and the seemingly unconnected disease, asthma.

The epidermis is the outer part of the skin – the part which does not bleed if you scratch or graze it. All the cells that make up the epidermis are packed full of a variety of proteins called keratins. In fact the proper name for these cells is "keratinocyte" which means "keratin cell". Keratins assemble into special filaments known as keratin filaments found within these skin cells. Thus, the epidermis is made of cells packed with keratins and other proteins related to keratins. When something goes wrong with one of the genes that produce any one of these important proteins, the person with that gene defect has what is known as a keratinizing disorder. Most of these disorders are associated with various degrees of skin thickening, scaling or flaking and sometimes skin blistering. Our research groups, in Dundee and Dublin, are leading international experts on the genetic causes of keratinizing disorders, having identified the faulty genes in more than 20 such diseases over the last 15 years or so and between us have published about 150 papers in the dermatology and genetics literature entirely focused on this area of medicine. Ichthyosis vulgaris is the latest keratinizing disorder we have taken on and figured out and it was our toughest job yet. The gene has been known about for a long time but it is one of the most difficult genes to analyze. One of us, Frances Smith, persevered on when other labs had given up, and finally cracked it.

The gene that causes ichthyosis vulgaris is called filaggrin (sometimes known as *FLG* for short) and its job in the skin is to manufacture large quantities of a protein known by the same name, filaggrin. The name is derived from "filament aggregating protein". This is what filaggrin does – it aggregates the keratin filaments found within the skin cells in the outermost layers of the epidermis. The epidermis is constantly worn away through physical abuse from the outside world but is continually replaced by dividing cells deeper down the skin that migrate up towards the surface where they die and get turned into flat, chemically modified, layers of dead cells, resembling plastic. Figure 1 (see below) shows cross sections through the skin of a normal

person, compared to someone with severe ichthyosis vulgaris. These slices of skin have been stained in special way that shows up the dark filaggrin granules in the outermost layers of the skin. In the person with severe ichthyosis vulgaris, these granules are completely missing.

Keratin filaments are responsible for maintaining the strength of skin cells allowing them to resist the physical trauma that the skin takes in everyday life. These filaments also help skin cells maintain their shape, which in the lower, innermost parts of the epidermis, is a bit like a cube. In the uppermost, or outer layers of the epidermis, the cells undergo a major change in shape and this is brought about by these keratin filaments being reorganised and pulled together or aggregated. This is what filaggrin does – it pulls these filaments together. In a very crude analogy, imagine that a skin cell is a shoe with laces. When putting the shoe on your foot, you pull the laces and the shoe tightens up onto your foot. Filaggrin does something similar in the upper layers of the skin – it pulls these filaments together and that has the effect of shrinking or tightening up the whole cell. In fact, the cell dies in the process and becomes a completely flat package of protein that will eventually be shed at the skin's surface under wear and tear.

Once filaggrin has tightened up these filaments and shrunken the cell, the next thing that happens is that all the proteins and other fatty molecules within these shrunken cells are chemically modified by a variety of enzymes. This turns the flattened cells in something not unlike plastic or cling film – sheets of a tough chemical material that stops moisture being lost from the skin. This is what we call the skin barrier. Not only does it stop water loss but it stops foreign substances such as bacteria, allergens and chemicals, from getting into the body. If this skin barrier is not formed properly, the skin dries out because the barrier is not intact and able to prevent water loss. This will sound very familiar to those of you with ichthyosis – dry skin is one of the problems associated with this genetic disorder. The other consequence of the skin barrier not being formed properly is that the dead, plastic-like skin cells at the surface of the skin do not have a normal structure and tend to flake off, especially when the skin dries out. This again, will be familiar to anyone with ichthyosis vulgaris.

So what we found was that about 10% of the population carries a mutation in the filaggrin gene. This mutation basically switches off the gene and stops it manufacturing filaggrin protein. You have two copies of each and every gene, one inherited from your father and one from the mother. In people with full-blown ichthyosis vulgaris, about 1 in 400 of the UK population, both copies of the gene are knocked out and so there is absolutely no filaggrin protein present in the skin. If you have one copy of the defective gene and one normal copy, you get very, very mild ichthyosis vulgaris, which most often will go unnoticed. These people may have dry skin that perhaps might have mild scaling periodically, or not at all. If someone has the severe form, then both of their parents have one copy of the gene and may have the mild form, if it is noticeable at all.

What we, and others before us, observed is that a large number of people with ichthyosis vulgaris also have eczema. In addition, a possible gene for eczema had been located in the region of the genome where the filaggrin gene is found. There was also some obscure reports in the literature that some people with eczema have less filaggrin protein in their skin. In view of all this circumstantial evidence, we set out to see if this gene is really involved. Very briefly, what we did was to look at families with ichthyosis vulgaris and proved that eczema is a second disorder caused by the same gene defect but at a lower rate. We then went on to look at a collection of Irish children with eczema and compared them to the normal Irish population. About 60% of the kids with eczema had either one or two copies of the filaggrin defect, whereas only 10% of the population carried filaggrin gene defects. We got a similar result in the Scottish population and the Danish population, adding further proof. We also proved that a smaller percentage of children with eczema go on to get asthma.

We now know that ichthyosis vulgaris is caused by filaggrin defects. One copy gives very subtle dry skin and two copies the full ichthyosis vulgaris presentation. We are now looking at larger numbers of patients to get better estimates, but we reckon that filaggrin defects may cause about half of all childhood eczema and a percentage of asthma, maybe 15-20%. Importantly, the gene is only involved in people with eczema and asthma, not in people with asthma alone. There are other genes still to find that are involved in the remaining 50% of eczema and the other 80% or so of asthma.

Filaggrin protein is not found in the lungs, only in the skin, so how then does this skin defect lead to asthma? This is not obvious to many people, including asthma specialists and we have had to explain this many times over. The lack of filaggrin in the skin weakens the skin barrier function that normally keeps foreign material out of the body. In people where the barrier is weaker, foreign material enters the skin and is seen by the immune system, whereas in normal people the barrier keeps it out and the immune system never sees it. This foreign material can be bacteria, dust and dirt, chemicals, basically anything from the outside environment. In some people with this "leaky" skin barrier, the immune system ignores it and they may have dry skin or ichthyosis vulgaris but no eczema or asthma. In others, their immune system does react and produces inflammation of the skin – eczema. In some of these people with eczema, when they later breathe in foreign material such as dust, to which they have already been sensitized through their leaky skin, they get inflammation of the airways – this is asthma.

So what happens now? This research has a number of very positive aspects for those of you with ichthyosis vulgaris, be it mild or severe. Firstly, we now know the underlying cause of the condition and can start now to develop new therapies to treat it. This will take years, possibly many years, but it will come now that the cause is known. Secondly, the very strong link to eczema, which affects 15-20% of kids in the UK, will attract a lot more attention to therapy development for this gene defect than ichthyosis vulgaris alone. Similarly, the link to at least one form of asthma will also attract a great deal more attention from researchers. Thus, we fully expect that our discovery will trigger a great deal of activity in this area of research by both the pharmaceutical industry and academia that will lead to improved treatments for ichthyosis vulgaris and its close relatives eczema, and eczema with asthma. How long will this take? We would estimate that this will take more than 10 years but we'll have to wait and see. At least the cause is now known and can be tackled whereas a few months ago, nobody knew with any certainty what caused any of these important and very common diseases.

We hope that this article helps those of you with ichthyosis vulgaris understand what the problem is with your skin, including the many of you who either have or have had eczema and/or asthma. We also hope that this gives you some hope, not only for you but for your children or grandchildren, that an effective treatment may come out of this in the future. We would like to take this opportunity to thank the many patients with all these conditions who sent us mail and email with best wishes following the recent media coverage. It means a lot to have your support and drives us on with our work. We have also had many kind offers of volunteers and we greatly appreciate your offers but since these conditions are so common, we already have as many as we need for now. We will seek out more patients through the Ichthyosis Support Group and other channels when we need bigger numbers.

W. H. Irwin McLean, Frances J. D. Smith and Alan D. Irvine, 25th 2006.

Figure 1

KEY FACTS

- ~1:10 people carry 1 filaggrin mutation
  - They have only 50% of the normal amount of filaggrin protein in their skin
  - They have very mild IV and a high risk of eczema, or eczema plus asthma

- ~1:400 people carry 2 filaggrin mutations
  - They have no filaggrin protein in their skin
  - They have severe IV and a very high risk of eczema, or eczema plus asthma