Ichthyosis Support Group

People who care about ichthyosis

Genetic testing

Patients with ichthyosis, or their parents, naturally want as much information about their condition as possible. A common request is for "genetic testing". But many people have a rather vague idea of what genetic testing means - not only patients, but also many doctors. This article will try to explain.

What is a gene?
Genes are the physical instructions, copied from one generation to the next, that programme us to be what we are. They consist of the chemical DNA. Identical sets are packed into the nucleus of every single cell in the body, arranged on chromosomes, like beads on a string. There is at least one gene, and sometimes hundreds, for every item of body structure and function. There are many genes responsible for the skin: these genes are present in all other organs as well as skin, but they are mostly "silent" in other organs, and only "expressed" in the skin. The "human gene map" has been published, so the names and locations of all human genes are now known. But scientists are still a long way from understanding what they all do, and research is going on all the time.

How do genes cause disease?
If there is a mistake (mutation) in the DNA of a gene, that gene may not work properly and can cause a genetic disease. For example, a mistake in the keratin 10 gene means that the structure of the epidermis is defective, causing epidermolytic ichthyosis, previously known as bullous ichthyosiform erythroderma (BIE). We have two copies of every gene, one from each parent. Some genetic diseases result from a mutation in only one copy of the gene ("dominant conditions" like BIE). Others only occur if there is a mutation in both copies ("recessive conditions" like congenital ichthyosiform erythroderma CIE). The parents of children with recessive conditions are usually "unaffected carriers" (mutation in just one copy).

What genes cause ichthyosis?
We know about several genes that can cause ichthyosis and the list gets steadily longer as more are discovered. For each gene, many different mutations have been recognised, perhaps explaining why the same condition can appear slightly different in different families.

What is genetic testing?
The term "genetic testing" covers all methods of investigating genes. It requires living cells, and the most convenient source of these is blood. Chromosomes are big enough to see under a microscope, using a technique called cytogenetics. But only very large mutations can be detected in this way. Most mutations can only be detected by chemical analysis of DNA which is usually extracted from blood cells. DNA can also be obtained from saliva but it is a bit less reliable - imagine if the smear picks up some germs, or a bit of meat from your dinner, it won't be your DNA that gets tested! Usually saliva samples are obtained after rinsing out the mouth and before lunch, rather than after.

Why does it take so long to get the results?
Mutation testing is difficult and laborious. Many genes are large and complex, so it can be like looking for a needle in a haystack. Even if the lab finds an abnormality, it might not actually be the cause of the disease, because of "normal variation" (so-called polymorphisms): for example my normal keratin10

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gene might not be exactly the same as someone else's, even though it does the same job. So there can be "false negative" and "false positive" results. For some genes there are known "hot-spots" or short-cuts for finding common mutations. But even then the results must be thoroughly checked. When you finally get the result you can be confident that it is correct, and if you are still waiting for a result after many months or years it is usually because the lab hasn't yet found a mutation.

Is genetic testing used to make a diagnosis?
No, usually it's the other way round – we need to know the diagnosis to decide what gene or genes to test! However, now technology is available called exome sequencing and it is possible to test all known ichthyosis and skin disease-related genes quickly from one individual. However, there is a huge amount of information and a lot of expertise is required to perform analysis. At the moment, it is mainly performed in research labs and takes about 3 to 6 months.

So how do doctors diagnose the type of ichthyosis?
Doctors have a standard way of making a diagnosis. First we "take a history" asking questions about the way the ichthyosis developed (eg collodion baby), other cases in the family, and any other medical problems like deafness, eye problems or delayed development. Then we examine the patient and look at the pattern, severity and type of scales, whether there are blisters, and whether there are other physical abnormalities. Thirdly, depending on what we think it might be, we may request some laboratory tests, like a blood count, steroid sulphatase measurement, hair analysis, or occasionally skin biopsy. We might also request an opinion from another specialist (eg a neurologist or ophthalmologist) if there is an associated problem that might be relevant. After all that we can usually make a diagnosis.

When is genetic testing carried out?
A diagnosis of ichthyosis can be made without genetic testing. In recent years genetic testing has been mainly carried out for the purpose of genetic counselling, particularly in recessive conditions. If the causative mutation can be identified in a person with a recessive type of ichthyosis, then relatives can be tested to see if they are carriers, and unborn babies can also be tested ("prenatal diagnosis"). However, recent European and UK rare disease legislation will probably result in an attempt to give any patient, certainly with a severe ichthyosis, a genetic diagnosis.

When is genetic testing not carried out?
If we have absolutely no idea of the diagnosis, genetic testing is unlikely to help, because we don't know which test to ask for. For example, genetic testing is not useful in a collodion baby initially because lots of genetic conditions can cause that appearance. With time the true diagnosis usually becomes apparent simply from observing the patient, and can be confirmed by genetic testing if necessary. For some conditions we don't know the gene yet (eg some types of erythrokeratoderma), or there may be several candidate genes (like CIE), and it would be expensive and unrewarding to do tests. But even if there is no test at the current time, more genes are being found every year, and the situation can be revisited when the child is older. Sometimes parents ask for their unaffected children to be tested to see if they are carriers, but carrier testing is not carried out on children when the result has no relevance to them and they are too young to understand the implications.

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Who can request it?
Genetic testing for ichthyosis is usually requested by a geneticist or dermatologist. In theory GP's can request it, but usually they would not have the expertise to know what test to request, or how to interpret the result. Patients can request some genetic tests ("direct to consumer genetic testing") but we would advise against this. Firstly, as with GPs, lay people do not have the breadth of knowledge required to request and interpret genetic tests. Secondly it costs hundreds and sometimes over a thousand pounds, which the NHS will pay for if it is requested by a health professional.

Who does genetic testing?
When a new gene is discovered, usually only the research lab that discovered it will test for it. While it is still new and interesting, labs will do the test for free (provided the request comes from a reliable dermatologist who is likely to have made the right diagnosis and requested the right test). Later they start to charge a commercial rate for the test, and subsequently big commercial labs will add that gene to their range on offer. Web sites offering genetic tests include www.ukgtn.org and www.genetests.org.

Who gets the result?
The result is sent to the person requesting the test. I usually send it on to the GP and the patient, with an explanatory letter, but very few doctors do that. I know that patients are unlikely to understand the report, but it seems to me to be a very important piece of information which rightly belongs to the patient. You can request a copy of the report from your doctor if you wish. DNA tests requested for medical purposes are confidential and never shown to anyone other than the family and their medical professionals without the patient's consent.

What are the benefits of genetic testing?
Having a genetic diagnosis is more precise than a clinical diagnosis, as you will know the exact mutation causing ichthyosis in your family. As explained above, a genetic diagnosis is necessary for prenatal diagnosis. Finally, it is likely that in the future (10-20 years) treatment may be based on the gene affected, so to be able to participate in trials of some new treatments, a genetic diagnosis may be needed.

Any more questions? If you have further questions after reading this, you can email them to the ISG and we will try to answer them.

Written by Professor Celia Moss, Consultant Dermatologist, Birmingham Children's Hospital (updated by Professor Edel O'Toole - 30.04.2014)

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Table: List of ichthyoses, giving the name of the gene probably responsible in most patients with that condition, and the symbol used in the genetic literature.

Disorder	Gene	Gene symbol
Epidermolytic ichthyosis	***Keratins 1 and 10***	**KRT1, KRT10**
Chondrodysplasia punctata (Autosomal Recessive Rhizomelic form[1] and X-linked recessive form[2])	Peroxisome biogenesis factor 7[1]	*PEX7*
	Aryl sulphatase E[2]	*ARSE*
Conradi-Hunermann-Happle syndrome	Emopamil binding protein	*EBP*
Erythrokeratoderma variabilis	Gap junction proteins beta 3/4 (=connexins 31/30.3	*GJB3/4 (=CX31/30.3)*
Harlequin ichthyosis	ATP-binding cassette subfamilyA member 12	*ABCA12*
Superficial epidermolytic ichthyosis (Ichthyosis bullosa of Siemens)	Keratin 2	*KRT2*
Ichthyosis vulgaris	Filaggrin	*FLG*
KID syndrome	Gap junction protein beta 2 (=connexin 26)	*GJB2*
Lamellar ichthyosis	Transglutaminase 1 Cytochrome P450, Family 4, Subfamily F, Polypeptide 22 Lipase N	*TGM1* *CYP4F22* *LIPN*
Multiple sulphatase deficiency	Sulphatase modifying factor 1	*SUMF-1*
Netherton syndrome	***Serine protease inhibitor Kazal-type 5***	**SPINK5**
Neutral lipid storage disease (Chanarin Dorfman syndrome)	Abhydrolase domain-containing 5 (comparative gene identification 58)	*ABHD5 (previously CGI-58)*
Non-bullous ichthyosiform erythroderma (also known as ARCI)	Transglutaminase 1	*TGM1*
	Arachidonate lipoxygenase 3/12B	*ALOXE3/12B*
	ATP-binding cassette subfamilyA member 12	*ABCA12*
	Ichthyin	*ICHYN*
	Ceramide synthase 3	*CERS3*
	Patatin-like phospholipase domain-containing protein	*PNPLA1*
Progressive symmetric erythrokeratoderma	***?Loricrin***	**LOR**
Refsum's disease	Phytanoyl-CoA hydroxylase	*PHYH*
	Peroxisome biogenesis factor 7	*PEX7*
Sjogren-Larsson syndrome	***Fatty aldehyde dehydrogenase***	**FALDH (=ALDH3A2)**
Trichothiodystrophy	Excision repair cross-complementing	*ERCC2, ERCC3*
Vohwinkel syndrome with ichthyosis	Loricrin	*LOR*
X-linked ichthyosis	Steroid sulphatase	*STS*