How I came to specialise in the genetics of IP

Dr. Helen Stewart

While I was working as a registrar (trainee in genetics) in 1996, Professor Dian Donnai CBE, who I worked for at the time, asked me to continue the research that she and Dr Sarah Landy had been conducting. They had studied as many families as they could in the UK, looking at the range of features seen in IP and the frequency of these features. They built up a list of families with IP and my job was to contact these families and ask for blood samples. In some cases, I visited families in their homes, took medical histories, examined people and obtained a blood sample. In doing this I built up my experience of the condition.

The blood samples were sent to Dr Sue Kenwrick in Cambridge, where the genetic testing was done. We kept in touch with ladies who were expecting babies, in case an affected boy was born. This is a very rare event and we thought that testing the DNA of an affected boy might lead to a breakthrough in our understanding of IP.

Staff at the laboratory in Cambridge were looking at the end of the long arm of the X chromosome as they knew the IP gene was located there. There are lots of genes in this region, so a number of laboratories around the world worked together to analyse all the genes until they found the one that causes IP. The NEMO gene that causes IP was discovered in 2000.

Current research

Since the discovery of the NEMO gene, lots of research has been done and continues to be done worldwide. Initially, some other conditions were also found to be caused by changes in the NEMO gene. These have also tended to cause skin problems sometimes with other medical complications. Examples include 1) hypohidrotic ectodermal dysplasia with immune deficiency and 2) anhidrotic ectodermal dysplasia with immune deficiency, osteopetrosis and lymphedema.

So far in 2006, 20 papers on IP have been published. Some of these are case reports, in which one or a few people with IP are described in detail, to raise awareness of the condition and emphasise a particular new or important feature. Other papers are studies of groups of people with IP. One example is a study looking to see whether affected people have particular features on MRI scans of their brains. Researchers looked at MRI scans in 12 people with IP, seven had skin changes only and 5 had a neurological problem. The 5 with neurological problems all had changes on their MRI scans, present from the newborn period which did not change over time. In contrast, none of the people without neurological problems had MRI changes. This probably means that people with IP who do not have neurological problems do not need to have MRI scans.
Yet more papers have been written broadening our understanding of the IP gene, how it works, which other genes it interacts with and so on. NEMO is important in activating a gene called NF-kappaB, which in turn regulates or controls the expression of other genes. Greater understanding of this process will hopefully lead to better care for patients with IP.

There seems to be a common change in the NEMO gene in many families with IP, but individuals in different families or even the same family have very variable effects from IP. This seems to be because affected girls and women have one normal IP gene and one with a genetic change. In the body, some cells will use the normal gene and switch off the altered one. In other cells this is the other way round, with the normal gene switched off and the altered one in use. Depending on the proportion of cells using the altered or normal gene, people can have more or fewer features of IP.

A very small number of males with features of IP have been born. A paper published this year detailed their clinical features. Males have just one X chromosome and one Y chromosome (which has no NEMO gene). An alteration in the NEMO gene cannot be tolerated by males, if the alteration is present in every cell of the body. A pregnancy with an affected male usually miscarries early on. It is thought that the males who are born with IP

have a change in the NEMO gene that arose in some cells while the baby was an embryo. This results in some cells having a normal copy of the NEMO gene and some cells having the altered NEMO gene. The effect of the altered NEMO gene is therefore greatly reduced. Boys born with IP seem to have it just affecting a portion of their body, reflecting this balance between the cells with the altered and regular NEMO gene.

Research ideas / funding

A lot of the research is done by scientists. I am not currently researching IP, however, I run a combined eye/genetic clinic and a combined skin/genetic clinic in Oxford and see patients with IP from this region. I would welcome your ideas about future research: are there particular questions you would like answered?

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