Incontinentia Pigmenti - Dr. H.B. Woffendin

I would like to start by thanking Diana Perry for inviting me to write this article about Incontinentia pigmenti (IP) for the ED support newsletter. I will begin with a brief introduction of IP, including a description of the clinical features associated with this condition. I will then give a simple explanation of what a genetic disease is and how IP is passed from one generation to the next. Finally, I will outline our recent scientific breakthrough and go on to explain what this means for IP families.

**WHAT IS INCONTINENTIA PIGMENTI?**

Incontinentia Pigmenti (IP) is a rare genetic disorder originally described by Garrod in 1906. A more complete description of this disorder was published by Bardach, Bloch, Siemens and Sulzberger in 1928, hence a common alternative name for IP is “Bloch-Sulzberger Syndrome”. The name “Incontinentia pigmenti” describes one of the most characteristic features of this condition, the appearance of brown streaks on the skin of the trunk and groin, which is caused by leakage of skin pigment (melanin) from cells in the epidermis of the skin. The most recent comprehensive account of IP was written by Landy and Donnai and is presented in the Journal of Medical Genetics volume 30, pages 53-59, 1993. Further information about IP is also available at the Online Mendelian Inheritance in Man website: http://www.ncbi.nlm.nih.gov/Omim/. The national Incontinentia Pigmenti Foundation (NIPF) website is also an excellent source of reliable information for all IP patients and their families and is presented in a very user friendly manner: http://imgen.bcm.tmc.edu/NIPF/NIPF.htm. NIPF is a voluntary, nonprofit making organisation founded in 1995 by Susanne Bross Emmerich and is guided by a Scientific Advisory Council, whose members are acknowledged experts in their fields.

**PHYSICAL SIGNS OF IP**

The following description of IP is largely drawn from the Landy and Donnai review mentioned above. Here, I will concentrate mainly on the most common features of IP, although other abnormalities may very rarely be associated with this disorder. It must be stressed that all these features of IP may vary in both severity and combination from person to person, even within the same family.

IP mainly affects females and is characterised by abnormalities of the skin, hair, teeth, eyes and nails and may be linked with neurological problems in some cases. IP is also associated with an increased risk of miscarriage of male babies, although affected boys do survive in a minority of families. In the past, some boys have been misdiagnosed with IP, when they actually have a different condition which just looks like IP. Details of male IP cases can be obtained from a very good review published by Angela Scheuerle in the American Journal of Medical Genetics volume 77, pages 201-218, 1998.

**Skin:**

The skin problems associated with IP are diagnostic of this condition, although their absence does not exclude the possibility of having IP. These skin problems are usually described in 4 distinct stages, however all stages are not always present in each person and several stages may overlap.

**Stage 1:** appearance of a **vesicular** (blistered) skin rash, usually present at birth or soon after birth in approximately 90% of patients, normally disappearing by the age of 4 months. This rash may occur anywhere on the body, but is most commonly seen on the limbs and scalp. Blistering may recur throughout childhood and into adulthood, but is much less severe than the initial bout of early blistering. It is common for these blisters to mistaken for chicken pox, herpes, scabies and impetigo, especially when there is no previous family history of IP. This can lead to unnecessary treatment until a firm diagnosis of IP has been made.

**Stage 2:** development of ** verrucous** (wart-like patches) on the lower limbs, usually occurs after the first stage, generally clearing up by 6 months of age.

**Stage 3:** development of **hyperpigmentation** (dark brown streaks), typically on the skin of the trunk and groin, usually between 6 and 12 months of age. However, in approximately 5-10% of cases hyperpigmentation is present at birth. The severity of this stage may range from being barely noticeable to extensive involvement of the skin. These brown streaks remain intense for a few years, fading during adolescence and generally disappearing by the age of 20.
Stage 4: development of pale, hairless patches of atrophic (scarred) skin on the backs of the lower leg, usually appearing before complete fading of the hyperpigmented brown streaks. These pale patches are usually very subtle and can only be seen when viewed under ultraviolet light.

Teeth:
80% of IP patients have abnormalities of their teeth, which can affect both baby and adult teeth. We often see delayed eruption of the teeth, with some missing altogether. Those teeth which do erupt can be misshapen, most often appearing pegged or cone shaped. Few individuals have serious dental problems, most of which can be improved by cosmetic dentistry.

Hair:
Approximately 50% of IP patients have very minor abnormalities of their hair, including alopecia (hair loss or lack of hair) at the crown of the head. However, it should be pointed out that, as with all people, sparse hair as a child does not necessary lead to sparse hair in adulthood. In some cases the hair may also appear coarse, wiry and dull.

Eyes:
Landy and Donnai report that up to 40% of IP patients may have eye abnormalities, although this figure could be inaccurate, as not every affected person is given a detailed eye examination. One of the most common eye problems seen in IP patients is an abnormality of the blood vessels in the lining of the back of the eye (retina), which is usually apparent before the age of 5 years. Abnormal retinal blood vessels may lead to retinal scarring, which can be associated with loss of vision. However, if detected early enough, laser treatment may be used to help minimise loss of vision. It is therefore essential that on diagnosis all IP patients should have their retinas examined in detail by an ophthalmologist.

Nails:
Up to 40% of IP patients may have problems with the nails on their fingers and toes. The nails may be pitted, ridged, thickened (onychogryposis), or completely disrupted. When present, these signs often affect most or all of the nails of the hands and feet and are usually mild and transient, although they can recur. Occasionally, benign growths develop under the nail bed, which can be painful and may be linked to bone deformities at the ends of the fingers.

Central Nervous System:
From a study of 100 individuals, Landy and Donnai estimate that mental or motor retardation occurs in less than 10% of patients, with severe mental retardation present in only 3% of family cases. Although the number of patients studied may not be sufficiently large to be statistically significant, these observations do suggest that a very small minority of IP patients suffer from neurological problems. Also, neurological signs usually appear quite early in life, therefore an adult with IP is unlikely to suddenly develop neurological problems.

INHERITANCE AND GENETICS OF IP
Everybody inherits all their genetic material from their parents, half from their mother and half from their father. Genetic material, called DNA, is contained in 46 chromosomes present within each cell of the body. These 46 chromosomes are arranged in 22 pairs of autosomal chromosomes and 2 chromosomes which determine our sex, the X and Y chromosomes. We all receive one sex chromosome and 22 autosomal chromosomes from each parent, which gives a total of 46 chromosomes in each cell. Females are XX, receiving one X chromosome from each parent and males are XY, receiving one X from their mother and a Y chromosome from their father.

Thousands of genes are contained within our chromosomes. Genes are pieces of DNA in which all our genetic information is contained. This genetic information controls development of our bodies by regulation of all our life processes, including control of physical characteristics such as hair colour and eye colour. Sometimes genes can change (mutate) which may prevent them from working properly. Such gene mutations can cause misregulation of our body processes, resulting in a genetic disease. Genetic diseases can be
passed on (inherited) in several ways, however, here I will only discuss the way in which IP is inherited.

IP is an X-linked dominant disease, which means it is caused by a mutation in a gene on the X chromosome. In families with X-linked dominant disorders, girls are affected and boys usually do not survive. IP affected females have two copies of the IP gene, a normal copy on one X chromosome and an abnormal copy on their other X chromosome. During each pregnancy IP women will pass on half of their genetic material to their baby. This means that for each pregnancy there is a 50% chance of passing on the X chromosome bearing the abnormal IP gene, regardless of the sex of the baby. On average, half of the daughters born to IP women will inherit the normal X chromosome and will not have IP and half will inherit the abnormal X chromosome and will have IP. Half of their sons will inherit the normal X and be free of IP and half will have IP, having inherited the abnormal X. Such IP affected males usually miscarry or are stillborn, although a small minority do survive.

IDENTIFICATION OF THE GENE RESPONSIBLE FOR IP
After many years of individual efforts towards determining the underlying cause of Incontinentia pigmenti (IP) an international consortium was brought together in December 1996, by Susanne Bross Emmerich the Executive Director of the National Incontinentia pigmenti foundation (NIPF). This consortium consists of 6 scientific groups from 5 countries, France, Italy, Germany, UK and USA, plus Susanne. Over the past 4 years we have worked together with the aim of finding the gene responsible for IP. Susanne has been and continues to be an extremely motivated driving force behind the consortium, providing financial support for our scientific research and personal support during our bi-annual meetings. We are extremely pleased to announce that we have now identified the gene responsible for IP and have published our findings in the scientific journal Nature in volume 405, pages 466 - 472, 25th May 2000.

During the course of our research, involving more than 250 IP families, we identified mutations in a gene called NEMO (NF-kappa B modulator), which lies on the X chromosome. We also found that approximately 80% of new cases of IP there is the same mutation in NEMO. The NEMO gene plays a crucial role in many immune and inflammatory processes and is essential for human survival. The physical signs associated with IP can also be explained by absence of a normal working copy of the NEMO gene. In this article, I think that is unnecessary to go into the biological details of how the NEMO gene works, so I will just discuss what I think is most relevant to IP families.

SIGNIFICANCE OF IDENTIFICATION OF THE IP GENE
Diagnosis:
Identification of the gene responsible for IP will have a major impact on the diagnosis of IP. Prior to our discovery of the IP gene, diagnosis of new cases was very difficult, as we had to rely on the presence of clinical signs. Diagnosis was usually straightforward in newborns with the distinctive blistering skin rash. However, in milder cases, skin biopsies were required, which were then analysed microscopically for leakage of pigment into the dermis of the skin. Diagnosis was even more difficult in cases where there was minimal skin involvement. In these cases, a woman suspected of having IP would be checked for additional clinical features, such as bald patches and tooth abnormalities, with presence of affected female relatives adding weight to her diagnosis.

Since characterising the NEMO gene, we have developed a simple, accurate diagnostic test which is capable of picking up the common mutation found in approximately 80% of new cases of IP. However, for the remaining 20% of new cases of IP, diagnosing IP by DNA testing is more complex but still possible in many cases. This test is also very useful from a family counselling point of view. For example, a mother of an IP baby can now be tested to determine whether she herself has IP, thus gaining information which can be invaluable when planning future pregnancies. Likewise, female relatives of IP patients can now determine whether they are affected.

Another benefit of identification of the IP gene is that we can now distinguish between IP and other diseases which are often mistaken for IP. This is particularly useful in the case of boys previously diagnosed with IP, who may be affected by a completely different disease. We
have found that surviving males with IP have more subtle, less damaging mutations in the NEMO gene, which accounts for their survival.

In the future, identification of the IP gene should allow development of a prenatal diagnostic test. This would allow expectant mothers to determine whether the child they are carrying has IP. Ultimately, it may be possible to use in vitro fertilisation/preimplantation techniques to select healthy embryos prior to implantation. To date neither of these tests are available, as further research is required. We hope that in the not too distant future these options will be available to IP families.

What the test involves and how to get tested
(1) Everyone requesting a test should already be under the care and guidance of a trained genetic counsellor. If this is not the case, then the patient should ask their General Practitioner (GP) to refer them to their local genetic counselling service.

(2) Prior to testing, all patients must complete one of our consent forms, which must then be signed in the presence of an independent witness. These forms can be obtained by contacting Dr. Sue Kenwrick, or myself Dr. Hayley Woffendin at the UK laboratory address given below. Usually all correspondence is conducted via your genetic counsellor or GP, although we will respond to patient requests.

(3) The patient should then contact their own GP or doctor at their genetics service and arrange for a small blood sample (10ml) to be taken. This blood sample should be collected in an EDTA tube (which must not contain heparin). The doctor should then send the blood sample to our laboratory (address given below). Whenever possible, we also need blood samples from both natural parents of the patient undertaking the test. Once we have received the blood samples, we will extract the genetic material (DNA) from it, then perform our test on the DNA. This test can be applied to blood from babies, children and adults. However, with small babies a 2ml blood sample should be sufficient.

(4) All test results will be sent via the diagnostic centre at Addenbrooke's Hospital to the referring doctor, who will then pass them on to the patient concerned. Providing the blood sample reaches us in good condition, we can obtain a definitive diagnosis in patients with the common NEMO mutation (i.e. 80% of new cases) within a few days of receiving it. However, this test cannot be applied to those patients lacking the common mutation (approximately 20% of new cases). In these patients the NEMO mutation can take many months to identify, hence we can not give them a rapid and definitive diagnosis.

Blood samples should be sent to:
Dr. H.B. Woffendin,
Laboratory 4.2,
Cambridge Institute for Medical Research,
The Wellcome Trust Centre for Molecular Mechanisms in Disease,
Wellcome Trust/MRC Building,
Addenbrooke's Hospital,
Hills Road,
Cambridge,
CB2 2XY,
UK

This is a non profit making academic research laboratory, funded by the charity "Action Research". Patients will be tested free of charge. To make arrangements for testing, please call Dr. Sue Kenwrick at (01223) 762616 or e-mail SJK12@mole.bio.cam.ac.uk.

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