

First Newsletter of the Atypical Mole and Familial Melanoma Research Group

You kindly helped us in the past with our research into moles or moles and melanoma.

We thank you greatly for this help, as we are dependent upon your gift of time and information in order to make progress in understanding.

This is a newsletter, which is meant to give you the opportunity to find out what has happened with our research since you helped us.

HISTORY OF THE RESEARCH

In the period 1989 to 1995, the group was based at the Royal London Hospital and the Imperial Cancer Research Fund in London. Since 1995, we have been based primarily at the Imperial Cancer Research Fund's (ICRF) Laboratories at St James's University Hospital in Leeds. The ICRF has now become Cancer Research UK. Throughout this period we have collected information from patients for a number of different reasons such as:-

- They have a great number of moles and have had a melanoma of the eye or the skin, especially if other members of the family have also had a melanoma
- They come from a family with several cases of melanoma in that family

PURPOSE OF THE RESEARCH

- To understand why people get a lot of moles and what it means for them
- To find out the reason why melanoma sometimes runs in families

We, and others around the world, have made some progress in answering both of these questions in the last 10 years or so.

WHY DO PEOPLE HAVE A LARGE NUMBER OF MOLES?

Almost everyone has moles, but there is considerable variation in the number of those moles. We have found that around 1 in 50 of the population have more than 100 moles, and that these people often have more moles on areas of skin which are normally covered by clothes, such as the buttocks, than other people. They may also have larger moles, which may be slightly **irregular in shape and colour**, these are sometimes called **atypical** or **dysplastic moles**. When people have lots of moles and atypical moles we say that they have the '**Atypical Mole Syndrome**' (AMS).

We counted moles in Australian people and showed that it is more common to have the Atypical Mole Syndrome if you live in Australia than if you live in the UK. It is therefore likely that **sun exposure is important** i.e. that exposing the skin to the sun 'excessively' may result in the development of more moles.

We have counted the moles in entire families, and also in 250 pairs of twins, and it is clear that moles **do run in families**. That is, that our genes may make us 'moley'.

Putting the two things together means that we probably inherit a tendency to moles, and sun exposure probably plays a role in 'bringing them out'.

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WHAT DOES HAVING THE ATYPICAL MOLE SYNDROME PHENOTYPE (AMS) MEAN IF I HAVE NO FAMILY HISTORY OF MELANOMA?

The Atypical Mole Syndrome Phenotype is more common in people who have had a melanoma, occurring in around 1 in 7 patients who have melanoma. We therefore think that **people with the AMS are more likely to have a melanoma** than people who do not. However, the risk of melanoma is likely to be fairly small in people without a family history of melanoma.

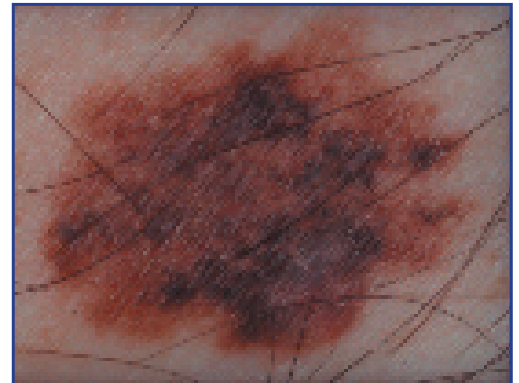
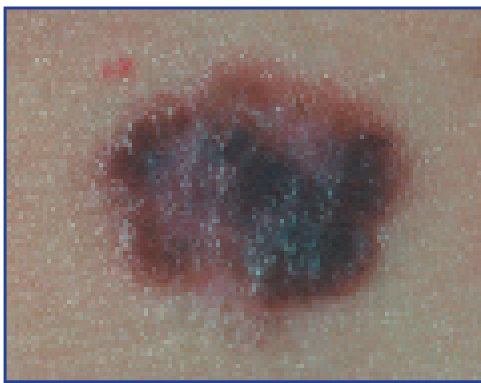
People with the AMS who have no history of melanoma in their family are about 10 times more likely to develop a melanoma, than people with very few moles. However, as the lifetime risk of melanoma in the UK is only around 1 in 200, this means that people with the AMS have a lifetime risk of melanoma of, at most, 1 in 20. That is, approximately **1 in 20 people with the AMS will develop a melanoma** at some time during their life. To put this in context, the risk of developing breast cancer of every woman in the UK is significantly higher at 1 in 12 by the age of 80 years.

WHAT DO MELANOMAS LOOK LIKE?

WHAT SHOULD I BE LOOKING FOR?

- A mole that is changing over weeks and months.
- A mole, which is, or is becoming, irregular in shape, size or colour.

These three pictures show melanomas with characteristically irregular colours and shape:



WHAT DOES IT MEAN FOR MY FAMILY IF I HAVE THE AMS AND I HAVE HAD A MELANOMA, BUT THERE HAVE BEEN NO OTHER MELANOMAS IN THE FAMILY?

It isn't really clear as yet what this means in terms of risk. It seems likely that family members may be at some increased risk and so it is sensible for them to keep out of the sun and to keep an eye on their moles. However, the strength of that risk is impossible to guess. It may be that the risk is low: we simply cannot say at the moment. It seems prudent to take the "safe" view and protect the skin, without undue anxiety.

WHY DOES MELANOMA RUN IN FAMILIES?

In our studies we have gathered information from many families where there are only two family members who have had a melanoma. However, we have also seen families in which there have been anything from three to nine relatives who have had melanomas.



GENES DISCOVERED

Many of these families have given blood samples for the research, and we have used these samples to search for genes which might make a person more likely to have a melanoma. Genes are made out of DNA and are the programming or blueprints for the cell. Genes are passed from parent to child and are the reason why children look like their parents. The role of some genes is to prevent cancer. A few families have a change in a gene (we call it a mutated gene) which doesn't prevent cancer as well as it should do. We have found that mutations in two genes makes some families more likely to develop melanoma. These two genes are known as CDK4 and CDKN2A. These two genes have been studied in several countries including the UK, Europe, the USA and Australia. Findings indicate that the alterations in the CDK4 gene are very rare and, in fact, no mutations in this gene have been found in our laboratory. However, changes in CDKN2A gene have been found in families all around the world. The chances of finding a mutation

are higher the more cases of melanoma there are in the family. Conversely, the chances are small if there are only 2 cases of melanoma.

In the period of time since these gene mutations were found we have been running extra experiments to make sure that what we have found is significant. That is, as far as we can tell, such gene mutations that we have found really are what makes people more likely to develop melanoma. We have also been trying to find out as much as we can about what having such a mutation really means for someone. The things we really need to know, for example, include what the risk of melanoma is for people who have such a mutation. People often worry that if they have a mutated gene it is inevitable that they will get a melanoma: we have shown that it is certainly not inevitable. We have taken some time to work out what the risks of developing melanoma are during different decades of life.

We cannot tell you directly if you have a mutation or not, on the basis of what we found in our research for three reasons

- First, because your blood sample was taken for research. The separation of research from clinical practice is important to protect your confidentiality. The ethics committees, which oversee research, take this confidentiality very seriously indeed.
- Second, because in order to be absolutely sure if you have a mutation or not, a fresh sample should be taken from you. We would also need another sample to be taken from a member of your family who has had a melanoma, if you have not had one yourself.
- Third, because testing is not for everyone. Many people decide they don't want to know their blood test result after they have discussed the pros and cons of testing with a geneticist.

We would like to emphasise that this newsletter is not intended to suggest in any way that we feel gene testing is to be recommended. Internationally there is a view, which we share, that it is premature to move towards gene testing because there is much we still have to learn about the CDKN2A gene. Furthermore there are pros and cons to any gene testing and many family members will decide it's not for them. The purpose of the newsletter is to give family members access to more information if they wish about the research they so kindly helped us with.

You may feel that testing would be right for you and in this case you would first go for genetic counselling. We should emphasise that counselling would be the reason for referral in the first instance, not testing. You might find counselling without a test helpful or you might decide after counselling that a test isn't for you. Having a genetic test may have implications in the future, for example with insurance. Usually insurance companies base their assessment on family history anyway so that attending a genetic counselling service however, prior to testing is unlikely to be

prejudicial in any way. However if you feel that you would like to talk confidentially to a geneticist on the telephone even before seeing your GP about this, then you could call Dr Carol Chu on 0113-2066970.

If you do wish to proceed to genetic counselling, your first step should be to make an appointment to see your GP and talk with him/her about whether or not you want to be referred to your local genetics department. If you both agree that this would be best for you then your GP can refer you to a hospital. I should emphasise that gene testing would only take place from a new blood sample taken later in the process if you were sure you wished to proceed.

Many melanoma families do not have as yet an identifiable mutation and then it would not be possible to offer gene testing. This might just mean that it was a coincidence that the melanomas occurred in more than one person. However, this does not necessarily mean that there is nothing to be found in your family or that there is an abnormality which hasn't been discovered yet. The geneticist would talk this through with you.

Are the members of my family who have abnormal moles the ones with the mutated gene?

We have done lots of work to try and sort out the relationship between moles and genes. The research has shown that 'moley' members of families are more likely to carry the faulty gene. However, the relationship is not quite that simple. We have found the mutated gene in patients with entirely normal moles, and we have failed to find mutations in many people with the AMS. Therefore it is not possible to predict who has the gene just from their moles alone. *All* first degree relatives of melanoma patients (where there are three or more cases of melanoma in the family **OR** two cases, one of whom has had more than one melanoma) should be considered at risk. These relatives should be referred to dermatologists for education about self examination, and some will require long term follow up.



WHAT ABOUT THE SUN?

It seems likely that the risk of melanoma in people who have the AMS, and in families with melanoma, is increased by excessive sun exposure. For example, we have some evidence that in AMS families living in hot countries, such as Australia, the numbers of cases of melanoma are higher.

It seems sensible that all members of families in whom melanoma occurs should heed the advice commonly given to fair skinned people about the sun. That is:

- Keep your clothes on when the sun is high: clothing is safer than sunscreen
- Keep out of the sun when the sun is highest in the sky, between 11.00 am and 3.00 pm
- Wear potent sunblock which is at least SPF15 and 4 stars UVA protective

We hope that you have found this newsletter informative and understandable. However, the concepts we are trying to explain are sometimes difficult to understand, so if you would like me to clarify anything please call me: I am usually available on 0113-2064668 on Tuesdays or on Friday mornings.

Thank you again for your help. Dr. Julia Newton-Bishop

Linda Whitaker 0113-2066117 (Research Sister)