## MICROCEPHALY RESEARCH UPDATE

Currently there is a lot interest in the causes of mental retardation and of brain development. It has become clear that humans as a species not only have a much bigger brain than any of their nearby primate relatives, such as chimpanzees and gorillas, but also that our brains work more efficiently and quickly. However, a huge number of different genes function in the brain and it is very difficult to tell which have an essential role and what these roles are. In our research group we have concentrated on a group of individuals who have a small brain at birth and no other abnormal physical findings. When we have been able to do brain scans it has always shown a small brain that has a normal structure. Also in our research of individuals with microcephaly we have ruled out chromosome problems, severe infections and accidents, metabolic diseases etc. So we are left with a group of people who have got a defect in the growth of the human brain in the second part of pregnancy. In the past this condition has been called autosomal recessive primary microcephaly (MCPH). It is MCPH on which I will concentrate upon in the rest of this article, although there are many other types of microcephaly.

Currently we know that there are at least eight genes which can each cause primary microcephaly. The first gene found was called *MICROCEPHALIN*. The person who found this gene and has subsequently worked upon it intensively is Dr Andrew Jackson, now in Edinburgh. He has made a number of discoveries about the function of the gene; in particular he has picked up a very important clinical fact. Children who have a handicap normally have a test called chromosome analysis. In this test, white cells are grown and after a few days they are fixed to stop them growing and their chromosomes analysed. As cells grow and divide their chromosomes come together, are doubled in number, split efficiently into equal halves and then the cell divides. In Microcephalin (MCPH1) patients this process happens too quickly, *and this can be seen on standard chromosome analysis.* This is an important finding from two points of view. Firstly it allows us to distinguish the microcephalin form of primary microcephaly from all the other types and is useful for family testing. Secondly it has given Dr Jackson a great insight into one of the main roles of the microcephalin gene.

My own group has been working on the other microcephaly genes that have been found which are called *CDK5RAP2, CENPJ and ASPM*. Their names all originate from previous work that had been done on these genes before their role in microcephaly was discovered. Interestingly all of these three genes seem to be important for the function of the part of the cell known as the centrosome. The centrosome is a small area, usually in the middle of cells, which is important in the control of the direction of cell division. That is, for certain cells at certain times it is very important whether they divide left and right or up and down and this process is used by the body to generate either two cells of the same type or two cells of different types. We know that this goes on within the brain because for quite a long time cells that are produced in the brain are able to produce neurones but have not yet done so. Then there is a change that occurs and these cells then start to produce neurones. In humans it is critical to keep cells from producing neurones and build up the supply of cells prior to the production of neurones. This is because once the cell commits to producing neurones it can only make a limited number of neurones, so the best way to make all the neurones you need for a human brain is to build up your stock pile of neurone precursors. (For those of you into mathematics, the number of neurons = 2n versus number of cells able to produce neurons = $2^n$ situation, where n is the number of cell divisions!). Quite how the primary microcephaly genes control this is unknown but the centrosome does appear very important in directing this type of cell division.

Work in mice has shown that *Aspm* (in mice the gene names are always written as *Abcd*, and in humans as *ABCD*!) is critical for stopping cells switching too early from the left right cell division to the up down cell division. Work on the fruit fly *Cenpj* gene has shown that this is also critical for the production of sufficient neurones. So a recurring theme is that the same genes that cause microcephaly have a role in brain growth and neurone number in all species so far tested.

We are continuing to try and find further microcephaly genes and also to look at their function. However, now that people have become more interested in this field, many more scientists are working on this problem of how these genes work, usually using animals rather than, as we do, human cells.

The final area of research excitement recently has been evolutionary. It has been reasoned that if genes were important in normal brain growth in humans, maybe these same genes have been manipulated during evolution to control the different relative brain sizes of different mammals. So far three genes have been examined; *ASPM, MICROCEPHALIN* and *CDK5RAP2*. All three of these genes have a pattern of evolution which suggests that they have been strongly selected during the monkey/primate/human lineage in mammals. Selection can be detected by looking at changes in the gene that lead to an altered protein, compared to changes that do not. Usually you would expect a protein to be efficiently made and not need to change, but if it has changed that infers that the protein has gained a new function; this is what has been detected in MCPH genes. Even more unexpectedly, in the *ASPM* gene it appears that the evolutionary changes have been occurring not only in our past history as monkeys and primates evolved, but also in our recent history as human beings. What remains to be discovered however is exactly how these evolutionary changes have altered the way the microcephaly genes or proteins function.

Finally back to more practical matters. Testing for microcephaly genes by NHS laboratories is becoming increasingly available. Some *MICROCEPHALIN* mutations can be tested for in Leeds and testing for *ASPM, CENPJ* and *CDK5RAP2* has been started in Cambridge. Our current work suggests that the *ASPM* gene will account for about half of the cases of primary microcephaly with the other genes being much rarer as causes. We still cannot see any way of developing new therapies or management yet for MCPH. However, it is possible that what we learn about the primary microcephaly genes will be very important for a new area of human treatment; that is stem cell biology. People have long considered that it would be useful to be able to replace destroyed neurones in the brains of individuals with diseases like Parkinson's or dementure. Such natural stem cells exist and we are starting to understand how to manipulate them. It seems very likely that the primary microcephaly genes will be important here, both to identify these human neural stem cells and to control how they can be made to either grow or start to produce neurones.

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