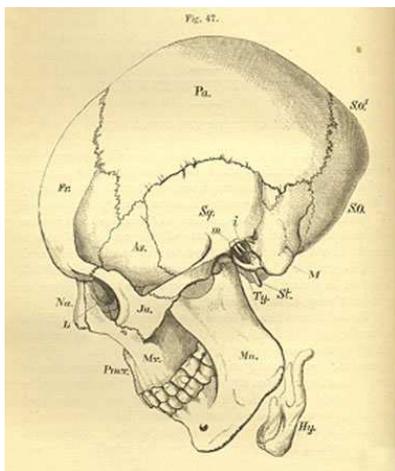


A grey matter

Vivienne Baillie Gerritsen

The human brain has been a hot issue for centuries. Physical anthropology flourished in the 19th century and with it the science of craniometry compounded by a growing belief in biological determinism. Intelligence – that intangible quality – was quantified and said to be dependent on brain size. Criminality was based on facial features and cranial particularities. And the notion of racism became a bodily measurement. Thankfully, the 20th century offered the necessary wherewithal to tone down all these beliefs thanks to an ever-growing knowledge of the molecular processes going on inside the human body. Intelligence is no longer quantifiable and cannot be defined according to the size of a human brain. Criminality has nothing to do with someone's looks and population genetics have demonstrated that the notion of race has no real meaning. Despite all this, it is clear that modern humans would not be where they are, were it not for the size of their brain, and its grey matter. And we now know of a number of proteins that are involved in such a process, one of which is a protein known as microcephalin.



The human skull

Lectures on the Elements of Comparative Anatomy
T.H. Huxley
(London, John Churchill & sons, 1865)

The human brain is big. It is bigger than our fellow primates' brains and it is bigger than our ancestors'. And its bigness is no doubt due to forces driven by increasing social complexity rather than mere adaptation to ever-changing geographical or meteorological surroundings. Comparatively, the relative size of our head is not all that different from a rat's. One of the

great differences however is the arrangement of our cerebral cortex – or 'grey matter' – under our protective skull. The cerebral cortex houses our neurons and their fibres. Over the millennia, it has become so large that – for spatial reasons – it has had to fold itself into a complex convoluted structure to fit into our skull. Such a structure does not exist in a rat's brain where the cerebral cortex is smooth and without pleats.

Diseases that affect the size of the brain can shed some light on the molecular processes at the heart of such largeness and convolution. Primary microcephaly is one. In primary microcephaly, babies are born with a brain far smaller than the average newborn's brain. It remains small throughout their life and those afflicted show signs of cognitive shortcomings. Surprisingly, there is no other flaw; every other function orchestrated by the brain is fulfilled normally. This finding has prompted scientists to qualify the condition as atavistic, i.e. people affected with primary microcephaly have a brain which can be compared to that of our ancestors'.

Though far from being the only protein involved, microcephalin clearly has a role in defining brain size. People with primary microcephaly bear a truncated form of the protein. Pruning part of a protein can be ruthless

– as is the case with microcephalin. The protein loses its function altogether and as a result the brain is not fully developed at birth. It is for this reason that some believe that such a mutation may zap the human brain backwards; to a time before the emergence of modern humans. But how could a protein have such a drastic effect on our brain?

Two events must have a marked effect on brain size: neuron proliferation and neuron apoptosis. Microcephalin may well have something to do with both. The protein has what is known as BRCT domains. These are domains which are found in proteins that belong to the animal kingdom, and are known to be involved both in protein-protein and DNA interactions. As a result, proteins with BRCTs are likely to be involved in DNA damage and repair mechanisms, and consequently in cell-cycle control leading to cell proliferation or apoptosis. Microcephalin has been shown to have a role in DNA damage response and probably goes about it by regulating a number of other proteins directly involved in DNA repair.

It is not unique to humans. Microcephalin orthologs are found in all other mammals, and some argue that others are also likely to be found in all chordates. What is particularly interesting is that microcephalin has evolved

rapidly within the primate lineages. What is more, there is a particular variant of human microcephalin that seems to have been – and may well still be – under the grasp of positive selection for the last 30'000 years. This is well after the emergence of modern man, and once modern man had left Africa to discover the rest of the world. This particular haplotype is, for the great majority, found in Eurasians. Some have even been so far as to suggest that the Eurasian microcephalin could be concomitant with novel forms of ‘art’ and symbolism...

So? Microcephalin is most likely involved in brain size but it cannot bear on its own the burden of modern human brain size and what such a notion implies. As a number of researchers have pointed out, though it is largely present in the foetal brain, it is also found in other tissues where it must have some other function. Likewise, there are – without doubt – many other proteins involved in brain size. Making a direct link between microcephalin and brain size is therefore a little hasty. However, what is sure is that the protein is involved in DNA repair mechanisms. Certain types of cancer are due to DNA damage and microcephalin may well have a tumour suppressor function – something researchers will be looking into...

Cross-references to Swiss-Prot

Microcephalin, *Homo sapiens* (Human): Q8NEM0

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