NEWS AND COMMENTARY

Evolutionary Genetics

Is brain evolution still continuing in modern humans?

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Bruce Lahn's team have recently published two back-to-back articles in *Science*, each of which primarily concerns a single SNP.^{1,2} While this might initially seem incongruous (a SNP = a paper!) it is the gene that each SNP is in and their recent evolutionary behaviour that is exciting.

The genes are Microcephalin and ASPM, which both control human brain size.³ Each SNP characterises one haplotype in these genes, which shows positive selection. Furthermore, each haplotype is young (in evolutionary terms) and has arisen after the appearance of anatomically modern humans. The authors suggest that the human brain is still evolving and that these haplotypes encode for cognitive phenotypic differences. These two publications have excited considerable interest and controversy in the world of evolutionary genetics.⁴

The most obvious difference between humans and other animals is the relative large size of our brains. Our brains are three times as large as those of other higher primates such as chimpanzees and gorillas. In evolutionary terms such 'large features' come at a considerable cost in terms of energy (eg the peacocks' tail, the giraffe's neck) and so must confer a considerable advantage to the species. In humans, the pay-off for this energetic expenditure is our increased cognitive ability, which has led to our adaptability and colonisation of almost all habitats on earth.

Clues to the identities of genes involved in the evolution of increased brain size in humans come from developmental disorders that affect brain size. For example

in MCPH (autosomal recessive primary microcephaly, OMIM 251200) foetal brain growth is reduced without any apparent change in brain structure.³ Affected individuals are born with a brain size often comparable to that of higher primates. So far, microcephaly-causing nonsense mutations have been identified in four genes: two of these are Microcephalin (MCPH1) and ASPM (MCPH5).³

The key question with respect to such genes that evolutionary biologists such as Bruce Lahn seek to address is 'if nonsense mutations in MCPH genes dramatically affected brain development, may missense mutations have occurred during evolution and caused more subtle (but still cumulatively important) changes in brain size?' The first step towards answering this question was to seek evidence that MCPH genes had been subjected to Darwinian selection in the primate lineages leading to humans.

Lahn and others have previously shown that parts of the Microcephalin and ASPM genes have indeed been under positive selection in humans compared with the great apes. That is amino acid changes in these genes have been selected for and maintained in the higher primates. However, the key advance of this new work is to show that these two genes not only have evolved but are continuing to evolve in anatomically modern humans.

Lahn's team sequenced an impressive number of human DNA samples to look for polymorphisms: 90 ethnically diverse individuals in both whole gene regions, later extending to more than 1000 individuals for more restricted haplotyping. The polymorphisms were analysed and

grouped into haplotypes (the arrangement of polymorphisms along a stretch of DNA that are inherited as one unit). In each of the genes, a single haplotype was found to predominate at a far greater incidence that would have been expected. In both cases a single SNP that caused an amino acid change defined these common haplotypes: G37995C characterised haplotype 42 in Microcephalin and A44871G characterised haplotype 63 in ASPM.^{1,2}

The next interesting observation was the worldwide population distribution of the two common haplotypes: in both cases the globally dominant haplotype was at its lowest frequency in Africa. The migration of modern humans from an East African population out of Africa 200–300 thousand years ago created a genetic bottleneck effect whereby a small pool of people become geographically isolated and expanded into a large, more genetically homogeneous population.⁴ So the present distribution of the common haplotypes in the two MCPH genes indicates that they most likely both arose after the human expansion from Africa. Microcephalin/G37995C was most prevalent in East Africans, Europeans, middle-easterners, Asiatic peoples and also South and Central Americans. This is in keeping with the estimated time of continental migration from Africa, between 30 and 60 000 years.⁵ By contrast, ASPM/A44871G haplotype has a more restricted geographical prevalence, mostly in Europe, the Middle East, East Africa, and Western parts of Asia, which accords with a more recent emergence of this haplotype.

Finally Lahn's team sought to date the emergence of the Microcephalin/G37995C and ASPM/A44871G haplotypes based on estimates of mutation rates in these genes. Amazingly they found the estimated age of the common Microcephalin/G37995C haplotype to be 37 000 years and the ASPM/A44871G haplotype to be only 5800 years! The authors make a tentative correlation between the emergence of ASPM/A44871G haplotype and the arrival of modern humans in Europe. ASPM gene evolution appears to have continued throughout the primate lineage and after the chimp-human split. However, the story of microcephalin's evolution is more enigmatic, appearing

to slow down once reaching the great apes but showing positive selection again in modern humans.

The independent emergence of the Microcephalin/G37995C and ASPM/A44871G haplotypes in more than one place at more than one time could also explain these results. However, the size and complexity of each common haplotype indicates this scenario would be very unlikely.

So, these findings provide strong evidence that Microcephalin and ASPM genes, are still evolving and that Microcephalin/G37995C and ASPM/A44871G haplotypes may be influencing brain function in modern humans. As Lahn's team have patents on both haplotypes it is clear that they will be undertaking phenotype studies in humans. However, they estimate that each haplotype need only have a very minor effect to have been so selected, which might mean the functional differences they confer might be hard to detect. Moreover, the authors have not been able to pinpoint which polymorphism(s) causes the functional change, which must underlie these findings: surely an important future goal.

There have been many examples of genes that cause severely deleterious effects when mutated but subtle changes can give rise to selective advantage, such as FOXP2 that can cause severe speech disorders in humans when mutated, and yet other subtle differences in FOXP2 show evidence for positive selection.^{6,7} Nevertheless the authors put little emphasis on any correlation of the Microcephalin/G37995C and ASPM/A44871G with brain size. Instead they suggest that these haplotypes have more subtle effects on brain function such as personality, cognition, or susceptibility to mental disease that might give a selective advantage. Others have suggested that the effect could be upon fertility; MCPH genes are expressed in brain and gonads and could have a role in the asymmetric cell division of gamete meiosis. Regardless this is an exciting set of findings, which leads to many testable hypotheses and may take us a step forward towards explaining ourselves ■

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