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Recently-derived variants of brain-size genes *ASPM*, *MCPH1*, *CDK5RAP* and *BRCA1* not associated with general cognition, reading or language

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ABSTRACT

Derived changes in genes associated with primary microcephaly (MCPH) have been suggested to be "*currently sweeping to fixation*" i.e., increasing in frequency in most populations, with the likely outcome that the derived allele will completely displace the ancestral allele over time. Possible causes for this sweep include effects on human reasoning and language. Here we test the hypothesis that these derived alleles are associated with current variation in spoken or written language and related traits. The association of derived alleles of the *ASPM*, *MCPH1*, *CDK5RAP2* and *BRCA1* genes was tested against well-validated measures of dyslexia, specific language impairment, working memory, IQ, and head-size in a family-based association study of over 1776 subjects from 789 families of twins. No evidence for association was found for any gene to any trait. The results strongly did not support the hypothesis that derived alleles in MCPH-related genes are related to the evolution of human language or cognition. Results were compatible with the alternate hypothesis, suggesting that adaptations in these genes associated with a dramatic increase in brain size have long since reached fixation and are now maintained by stabilizing selection.

1. Introduction

Primary microcephaly (MCPH) is a genetic neurodevelopmental disorder characterized by dramatic (70%) reduction in cortical volume and influenced by at least 6 genes (Bond & Woods, 2006). Based on an analysis suggesting that derived alleles (i.e., new mutations) of genes *ASPM*, *MCPH1*, *CDK5RAP2* and perhaps the *BRCA1* gene are undergoing strong selection and are therefore "currently sweeping to fixation", workers in the Lahn laboratory predicted that derived changes in these genes would be related to cognitive changes coinciding with the cultural explosion related to agriculture and civilization and overlapping with the introduction of these new alleles some 37,000 and 5800 years ago. Current variation in human cognition was predicted to be associated with variation at these loci (Evans et al., 2005; Evans, Vallender, & Lahn, 2006b; Mekel-Bobrov et al., 2005). We test this hypothesis, examining the relationship of the derived alleles of *ASPM*, *MCPH1*, *CDK5RAP2*, and *BRCA1* to well-validated and highly heritable measures of reading and spelling (dyslexia), phonological storage (an endophenotype for specific language impairment), working memory, general intelligence (full scale IQ) and head-size in a family-based association study of 789 families.

The MCPH phenotype and its genetic basis have recently been reviewed (Cox, Jackson, Bond, & Woods, 2006b). Briefly, MCPH is diagnosed from a reduction in head circumference measured around the nasion (top of the bridge of the nose) to the inion (occipital bulge), and associated with a correspondingly large reduction in neuron numbers. Neuronal count is largely determined by the number of symmetric progenitor cell divisions, each of which doubles the progenitor cell count, and MCPH-associated mutations appear to code for an earlier-than-usual switch to asymmetric mitosis in which each

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division creates one neuronal cell and one progenitor cell. This atavistic brain size reduction is present prenatally, persists throughout life, and is associated with mild to severe mental retardation. *MCPH* genes have been identified at four of six known loci: autosomal recessive primary microcephaly 1 (*MCPH1*), abnormal spindle-like, microcephaly associated (*ASPM*), cyclin-dependent kinase 5 regulatory subunit-associated protein 2 (*CDK5RAP2*) and centromere protein J (*CENPJ*). All are autosomal recessive, and most cases have been identified in cultures in which consanguineous mating is encouraged (Cox et al., 2006b).

In 2002, Bond et al. (2002) reported an analysis of *ASPM* in flies, mice and humans showing that the gene differed across these species predominantly in the insertion of domains coding for increased brain volume in the primate lineage. This finding was followed by reports that *ASPM*, among other genes, had undergone accelerated evolution in primates, especially in man. Kouprina et al. (2004) examined changes in *ASPM* across the chimpanzee, gorilla, orangutan, and rhesus macaque, and found evidence for strong selection in the 'IQ' domains identified by Bond et al. (2002) beginning over 2 million years ago. Zhang (2003) subsequently demonstrated that there appeared to have been strong positive selection over a 2 million-year period during time which the human brain tripled in size. Zhang's analyses, however, suggested that brain-size related changes in *ASPM* were complete well before the development and migration of modern humans out of Africa, with the derived allele reaching fixation some 2–4 hundred thousand years ago with evidence for stabilizing selection since this time. Evolution of the human *ASPM* gene, may, then, have played a major role in the increase of brain size from the common ancestor of humans and chimps through to *Homo rhodesiensis* (Woodward, 1921) or *Homo sapiens idaltu* (White et al., 2003), but not for more recent changes related to modern humans.

A second group active in the new field of evolutionary cognitive genetics is that of Bruce Lahn, and has recently produced several very high impact reports on the possible genetic changes and origins of human cognitive function. Contrasting strongly with the analyses of Zhang, Mekel-Bobrov et al. (2005) found that one ASPM haplotype arose in humans only around 5800 years ago, with high positive selection pressure driving it to an average frequency of 21% since that period. Simultaneously, Evans et al. (2005) reported a similar haplotype in MCPH1 arising approximately 37,000 years ago and also implicated the *BRCA1* gene in recent human cognitive evolution. Shortly afterwards, a similar analysis was undertaken for the remaining two MCPH-related genes *CDK5RAP2* and *CENPJ*, concluding that *CDK5RAP2* molecular evolution paralleled that for *MCPH1* and *ASPM* (Evans, Vallender, & Lahn, 2006a).

Having identified these derived alleles (i.e., more recent forms of the gene derived from the ancestral form) the Lahn group argued that selection for these derived changes in MCPH-related genes was ongoing and possibly related to changes in human life-history strategy with the advent of civilization. They suggested selection for intelligence or language, specifically reading and writing, as possible drivers of this most recent selective sweep. Recently Dediu and Ladd (2007) demonstrated that the geographical distribution of variation in *MPCH1* and *ASPM* maps closely onto the global distribution of linguistic *tone*—the use of voice pitch to convey lexical or grammatical distinctions. They hypothesize that these genes may, then, be related to brain-function changes facilitating the use of non-tonal languages, with their increased demand on short-term storage of longer phonological sequences. Both the Lahn and Ladd groups, then, predict an association of spoken or written language ability to recently derived alleles of MCPH-related genes.

There are, however, good reasons to suspect that *MCPH* genes are unrelated to modern human variation in language, intelligence, or even brain size. While human brain volume is heritable (Toga & Thompson, 2005) and related to IQ (McDaniel, 2005), Woods et al. (2006) recently reported that neither *MCPH1* nor *ASPM* were associated with variation in MRI-assessed brain volume in 120 normal subjects. If MCPH-related genes do not cause normal variation in brain size, this cannot be the mechanism of their effect on intelligence. Finally, a combined group including authors of the present study, found that *ASPM* and *MCPH1* derived alleles were not associated with general cognitive ability (Mekel-Bobrov et al., 2007).

While refuting any association of the derived MCPH-related alleles to intelligence or to brain size, the preceding analyses do not completely discount the Lahn group's speculation, as they suggested further that *MCPH* and *ASPM* may relate to specific linguistic or written language innovations. There is considerable variance among modern humans in their ability to read and write, even in societies such as Australia and in Europe where schooling is both adequate and compulsory till after the normal acquisition of written language. In this environment, reading and spelling skills remain highly heritable (Bates, Castles et al., 2007), and work in both affected families (Fisher, 2006) and unselected normal samples (Bates, Luciano et al., 2007) suggest upwards of a dozen chromosomal regions linked to this heritable variance in reading and writing, which do not include the *ASPM*, *MCPH1* or *CDK5RAP2* loci (Chromosomes 1q31, 8p23, and 9q33 respectively (Bates, Luciano et al., 2007; Fisher, 2006)).

The purpose of this paper therefore was to test the hypothesis that the derived alleles in MCPH-related genes are associated with heritable variance in spoken or written language or the manipulation of symbolic information (working memory). The diagnostic SNPs that distinguish the adaptive derived allele and ancestral alleles of these genes were genotyped in a sample of over 700 Australian families. We extended previous reports by including the derived alleles of *CDK5RAP2* as well as *ASPM* and *MCPH1*. In addition, we collected head-size (as a proxy measure of brain size which is correlated with intelligence) and working memory data, and genotyped the *BRCA1* derived allele also speculated to be related to cognition (Vallender & Lahn, 2004). Our analyses failed to find any association of the derived alleles studied to any element of human cognition studied: brain size, IQ, working memory, dyslexia, or language impairment. The hypothesized phenotypic effect size for these genes is not known but the dramatic sweep to ~30% prevalence over a large geographical region within perhaps just 6000 years implies either a medium effect size and selection pressure, or extremely intense selection if the effect is small. Power in these different case varies, but the power of the present study to detect an effect of even 1% of variance exceeded 90% at