



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

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### ARTICLE INFO

#### Article history:

Received 11 September 2007

Received in revised form 1 February 2008

Accepted 9 April 2008

Available online 16 May 2008

#### Keywords:

Intelligence

Brain size

Evolution

Dyslexia

Reading

Language impairment

ASPM

### 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.

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### 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 *MCPH1* 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 cases varies, but the power of the present study to detect an effect of even 1% of variance exceeded 90% at

$p=.05$  (Purcell, Cherny, & Sham, 2003), suggesting that the current report is well-powered to detect the effect in most plausible scenarios.

## 2. Materials and methods

Participants were recruited as part of ongoing twin studies of cognition and melanoma risk factors, with recruitment predominantly through mail-outs to secondary schools in the Brisbane region (Wright et al., 2001). The largest sample (those with dyslexia phenotypes) included 1776 subjects (840 males) from 789 families. There were 144 MZ pairs, 447 DZ pairs, 177 unpaired twins (data collected from one twin of pair) and 416 siblings (24 of who were from families where twins did not participate). The least amount of data were available for IQ phenotypes and included 463 families (99 MZ pairs, 302 DZ pairs, 58 unpaired twins, 160 siblings) with roughly 53% of the sample female. Mean age at the time of testing was 17.5 (SD=3) for dyslexia phenotypes and 16.4 (SD=0.7) for IQ phenotypes. Participation in this study included a voluntary agreement to donate a blood sample for DNA isolation and genotyping. Parental genotypes but not cognitive scores were available.

### 2.1. Phenotyping

A dyslexia phenotype was constructed using the first principal component of the Core Skills of Reading Examination (CORE (Bates et al., 2004)), a revised 120-item version of the standard Castles and Coltheart test of reading (Castles & Coltheart, 1993) which produces six correlated measures based on reading and spelling of regular, and irregular words and nonword-based phonological decoding. The specific language impairment endophenotype of phonological storage efficiency was assessed using a standardised battery combining scores on the Gathercole, Willis, Baddeley and Emslie (1994) and Dollaghan and Campbell (1998) measures of nonword-repetition (NWrep). NWrep a heritable trait, previously linked to at least two genetic loci involved in specific language impairment (SLI Consortium, 2004). General ability was assessed using sub-tests of the Multi-dimensional Aptitude Battery (MAB) (Jackson, 1998). Short-term symbolic storage and working memory (the ability to manipulate the short-term contents of consciousness) were assessed using

the Digits-Forward, Digits-Backward, and Letter-Number Sequencing sub-tests of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997). Head circumference was measured by the research nurse, using a flexible inelastic tape with 1 mm precision and aligned with the nasion and inion positions of the head. All measures were normal, or transformed to normal prior to analysis.

### 2.2. DNA collection and genotyping

Zygosity was assessed using 9 polymorphic microsatellite markers (DZ|conc)  $<10^{-4}$ . Genotyping was performed blind to familial status and phenotypic data. Four assays were designed using the Sequenom MassARRAY Assay Design software (version 3.0): rs2297457 (*MCPH1*, Glu219-His), rs8176160 (*BRCA1*, intronic), rs930557 (*CDK5RAP2*, intronic) and rs41310927 (*ASPM*, Ser2562Gly). Primer information is available on request. Genotyping was performed using standard methods (Zhao et al., 2006) for iPLEX™ chemistry on a Compact MALDI-TOF Mass Spectrometer (Sequenom Inc, San Diego CA). Assay quality and genotype calls were assessed in the SpectroTYPER software (Sequenom). Genotypes were analyzed using PEDSTATS (Wigginton & Abecasis, 2005) to check Mendelian errors, sample identity and zygosity as well as Hardy-Weinberg equilibrium. Where zygosity or sample identities were suspect, sample histories were reviewed and when necessary, genotyping was repeated with DNA isolated from a backup sample.

### 2.3. Statistical analyses

For the family-based samples quantitative transmission disequilibrium tests were conducted using the program QTDT (Abecasis, Cardon, & Cookson, 2000). QTDT uses all the information in the sib data to decompose the genotypic effect into orthogonal between and within-family components, and also models the residual sib-correlation as a function of polygenic or environmental factors. MZ twins can be included and are modelled as such, by adding zygosity status to the data file. They are not informative to the within-family component (unless they are paired with non-twin siblings), but are informative for the between-family component; all siblings within a family were used in the analysis. The

**Table 1**

Means and SDs for each cognitive trait, deviation from the mean under the derived allele, and  $p$ -value for tests of total association for each of the four studied genes

Trait	Trait mean (SD)	Mean trait deviation (effect of the derived allele)				$P$ -value for additive (and dominant) models			
		<i>MCPH1</i>	<i>BRCA1</i>	<i>CDK5RAP2</i>	<i>ASPM</i>	<i>MCPH1</i>	<i>BRCA1</i>	<i>CDK5RAP2</i>	<i>ASPM</i>
		rs2297457	Rs8176160	rs930557	rs41310927	rs2297457	rs8176160	rs930557	rs41310927
Head-size	56.02 (3.03)	0.230	0.415	-0.075	-0.377	0.8 (.2)	0.7 (.4)	0.6 (.9)	0.9 (.3)
Full-scale Intelligence	112.6 (12.91)	-1.295	-0.729	0.920	0.739	0.1 (.3)	0.3 (.3)	0.2 (.3)	0.2 (.06)
Nonword-repetition	0.028 (1.74)	0.137	-0.068	0.023	-0.091	0.1 (.09)	0.3 (.1)	0.7 (.9)	0.2 (.2)
Irregular word reading	0.028 (0.98)	0.045	-0.037	0.083	-0.005	0.06 (.1)	0.3 (.3)	0.2 (.1)	0.9 (.7)
Regular word reading	0.085 (0.98)	0.015	-0.012	0.033	-0.014	0.3 (.5)	0.6 (.5)	0.9 (.9)	0.9 (.1)
Nonword reading	0.008 (0.99)	-0.007	-0.018	0.050	0.005	0.5 (.4)	0.7 (.7)	0.7 (.9)	0.7 (.9)
Irregular word spelling	0.055 (0.98)	0.007	-0.023	-0.021	0.014	0.6 (.8)	0.5 (.8)	0.8 (.6)	0.7 (.8)
Regular word spelling	0.073 (0.98)	-0.024	-0.063	0.055	-0.035	0.2 (.5)	0.7 (.2)	0.5 (.4)	0.3 (.4)
Nonword spelling	0.027 (0.99)	0.029	0.016	0.054	0.034	0.3 (.4)	0.7 (.1)	0.4 (.7)	0.3 (.5)
Digits-backward	7.20 (2.66)	-0.052	0.015	0.042	0.006	0.7 (.7)	0.9 (1)	0.7 (.5)	0.7 (.9)
Digit-letter sequencing	10.37 (3.08)	-0.073	-0.191	0.109	0.050	0.6 (.5)	0.1 (.2)	0.4 (.6)	0.6 (.6)

between-family association component is sensitive to population admixture, while the within-family component is unaffected by spurious associations due to population structure. Thus, if population structure creates a false association, the test for association using the within-family component is still valid, though usually less powerful. Both additive and dominance models were tested within this variance components framework.

### 3. Results

All subjects were genotyped for the diagnostic *ASPM*, *MCPH1*, *CDK5RAP2* and *BRCA1* derived alleles. The obtained frequencies for each of the four genes were .19, .33, .30, and .44 for *MCPH1*, *BRCA1*, *CDK5RAP2*, and *ASPM* respectively. An exact test of random mating indicated that the alleles in all four genes were in Hardy–Weinberg equilibrium (Guo & Thompson, 1992; Haldane, 1954).

Table 1 shows the means and standard deviations for each phenotype and, separately for each gene, the average trait deviation associated with the derived allele for that trait. The trait deviation simply represents the difference between heterozygote and homozygote groups. Scores are corrected for age and sex. To test for association between the derived alleles of *ASPM* and *MCPH1*, *CDK5RAP2*, and *BRCA1*, and cognitive variables, both additive and dominant models were tested using quantitative transmission disequilibrium test (qTDT) (Abecasis et al., 2000; Fulker, Cherny, Sham, & Hewitt, 1999). Genotypic effects were decomposed into between- and within-family components providing a test of population stratification (admixture), which if detected allows a family-based test using the within-family variance component on its own. There was no evidence for population stratification at any of the alleles under study (data available upon request), therefore, the test of total association which provides the most statistical power is reported.

These association results (i.e., *p*-values) are presented in Table 1. Neither the *ASPM*, *MCPH1*, *CDK5RAP2*, nor *BRCA1* derived alleles showed any statistically significant association with head-size, IQ, reading, spelling, phonological storage, or working memory. The null result for IQ previously reported was confirmed and extended to two previously unexamined genes *CDK5RAP2* and *BRCA1*. As no significant findings were observed we do not correct for multiple testing, although it should be noted that the cognitive tests (and especially the reading and spelling tests) were significantly correlated (*r* ranging .08 to .76) with the exception of the IQ nonword-repetition correlation.

### 4. Discussion

The results showed no association between the adaptive alleles of any of the four genes assessed with any of the several measures of language function tested, with or without correction for multiple testing. While a null result could reflect low power to detect an effect of possibly modest magnitude (though necessarily sufficient to drive its apparent adaptive sweep), the power of the present analysis (80% to detect effect sizes of half a percent) makes it more likely that the null finding is real, i.e., that recently selected MCPH-related alleles are unrelated to human language function. The

results also confirm the report by Woods et al. (2006) of a null association of *MCPH1* and *ASPM* to variation in brain size (assessed here by head circumference in a much larger sample), extending this also to show that neither *CDK5RAP2* nor *BRCA1* are related to the MCPH-diagnostic trait of head-size. This further weakens the Lahn hypothesis, as brain size was proposed as the prima-facie mechanism relating MCPH genes to recent human cognitive evolution.

We therefore conclude that there is no support for an association between the derived alleles of *ASPM* or *MCPH1*, *CDK5RAP2*, or *BRCA1* and human spoken or written language, working memory, IQ or brain size. Brain size is an important biological correlate of normal variation in intelligence (McDaniel, 2005), but normal variation in IQ and brain size appears unrelated to MCPH genes (Mekel-Bobrov et al., 2007). It seems highly likely that changes in MCPH-related genes were important in the tripling of hominid brain size over the last 2 million years, probably via regulation of the neural progenitor cell transition from proliferative to neurogenic division (Cox, Jackson, Bond, & Woods, 2006a; Fish, Kosodo, Enard, Paabo, & Huttner, 2006) as proposed by Rakic (1995). These adaptations, however, are likely to have spread to fixation by 2- to 4 hundred thousand years ago, with stabilizing selection since this time, suggesting that no MCPH-related variance in cognition is present in modern humans, except for (extremely rare (Cox et al., 2006b)) cases of MCPH mutation (Zhang, 2003).

These four genes were generated as candidates for study based on within- and between-species measures of selective pressure in the form of Ka/Ks data. The negative results reported here focus attention on the logic of such studies. A principal hope in this method is that signs of selection may provide inductive clues to gene functions important in human function and disease. This depends on researchers being able to induce functional targets of derived alleles from prior loss-of-function or model organism studies of gene function—as was done in the case of the *ASPM* (Mekel-Bobrov et al., 2005) and *MCPH1* (Evans et al., 2005) studies. Such reasoning is conventional, and a strong case has been made by Hill and others for the utility of this inductive strategy for disease research (Hill & Walsh, 2005; Sikela, 2006; Varki & Altheide, 2005). In contrast to this model, however, Mekel-Bobrov et al. (2007) suggest that negative phenotypic results despite evidence for current selection cast doubt on the utility of loss-of-function mutations in understanding and favor an empirical search for novel evolved functions for the genes (Mekel-Bobrov et al., 2007). If this were the case more generally, the value of comparative studies would be greatly diminished, as evidence for selection could not leverage knowledge of gene function, requiring instead a brute-force search for novel functions for the derived alleles. An alternative view of the present results is that the results can equally be taken as a warning of the limitations and possible false-positive signals of selection from studies of selection (Wang et al., 2007). This is compatible with the general utility of induction from loss-of-function studies as proposed by Hill and others (Hill & Walsh, 2005; Sikela, 2006; Varki & Altheide, 2005) and would suggest that the lack of association reported here and elsewhere (Mekel-Bobrov et al., 2007; Woods et al., 2006) indicates that the selection signal is a false-positive, unrelated to any selected function. It is noteworthy that MCPH-related genes do not appear as being under selection in

genome-wide studies of selection based on linkage-disequilibrium decay (LD decay), suggesting that the use of a small set of reference genes can generate false-positive results (Wang, Kodama, Baldi, & Moyzis, 2006). In addition, further analysis of the *MCPH1* “derived” allele suggests that it may be a neutral variant, which introgressed from Neanderthal into the modern Eurasian human line, hence the apparent disparity in frequency between sub-Saharan African and Eurasian population frequencies (Evans, Mekel-Bobrov, Vallender, Hudson, & Lahn, 2006), supporting the view that, in signal detection terms, the report of MCPH-related evolution was a “false alarm”, rather than the lack of phenotypic association being a “miss”. The original hypothesis that the derived alleles in MCPH-related genes studied here reflect recent cognitive selection for evolution in modern humans is likely false.

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