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Comment on Papers by Evans *et al.* and Mekel-Bobrov *et al.* on Evidence for Positive Selection of *MCPH1* and *ASPM*

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Evans *et al.* and Mekel-Bobrov *et al.* (Reports, 9 September 2005, p. 1717 and 1720, respectively) reported that human genetic variants of *Microcephalin* (*MCPH1*) and *abnormal spindle-like microcephaly associated* (*ASPM*) are under strong positive selection. We genotyped these variants in 9000 children and find no meaningful associations with brain size and various cognitive measures, which indicates that contrary to previous speculations, *ASPM* and *MCPH1* have not been selected for brain-related effects.

Homozygous null mutations in the genes *Microcephalin* (*MCPH1*) and *ASPM* (*abnormal spindle-like microcephaly associated*) cause primary microcephaly in humans, a condition in which brain size is reduced to a third, with no other symptoms except mental retardation (1). Sequence variation in humans strongly suggests that for both genes, a new haplotype emerged ~6000 (*ASPM*) and ~40,000 (*MCPH1*) years ago and rose to frequencies in Europe and Asia of ~40% (*ASPM*) and ~80% (*MCPH1*) as a result of positive selection (2, 3). Given the phenotype of the recessive null mutations, it has been speculated that some brain-related feature, such as brain size or cognitive function, was the selected phenotype. However, the phenotypic consequences of the selected alleles remain unknown (4, 5).

We genotyped nearly 9000 children from the ALSPAC study (Avon Longitudinal Study of Parents and Children) for two single-nucleotide polymorphisms that are characteristic for the selected haplogroups D of *MCPH1* and of *ASPM* (6). The selected alleles have a frequency of 42.7% (*ASPM*) and 81.4% (*MCPH1*), well in accordance with published frequencies (2, 3). Many phenotypic measurements are available for the majority of the ALSPAC children (7). We initially focused on head circumference at birth, which correlates well with brain size (1), especially during early development (8), as well as general cognition (total, verbal, and performance IQ), working memory, attention span, and motor performance (6). We found no meaningful differences across the genotypes for these measurements (Table 1).

We then extended our analysis to 30 other variables like weight, height, allergy, lung function, and occurrence of various psychological and physiological disorders (6). In none of these measurements (table S1), did we observe a robust effect of the genotype. An absence of an effect on brain size corresponds to the results of a study measuring brain volume using magnetic resonance imaging of 120 individuals (5) and with paleontological data indicating that human brain size has not changed in anatomically modern humans (9). The absence of an effect on IQ measures corresponds with the findings in a recent study with half as many individuals as analyzed here (4). Because the selected phenotype must be large enough to confer around 1 to 5% more offspring per generation on average (2, 3), and in view of our relatively large sample size, we conclude that it is unlikely that the haplogroups D of *ASPM* and *MCPH1* conferred some selective advantage due to the wide range of brain-size- and brain-function-related

phenotypes that we have investigated. Assuming that the two haplogroups D indeed rose to high frequencies because of positive selection [see (10), however], what could have been the selected phenotype? Because *MCPH1* and *ASPM* are widely expressed in fetal and adult tissues and are involved in functions such as spindle organization and DNA damage signaling not exclusive to the brain (1), the causes for selection may involve functions frequently found to be under positive selection in mammals, such as immunity and spermatogenesis (11). Although our present study only addresses the phenotypic consequences of the two human haplogroups D, such a scenario would also be compatible with the findings that amino acid changes in *ASPM* and *MCPH1* were repeatedly positively selected in nonhuman primate lineages for which there is no evidence of a change in brain size or cognitive function (12).

References and Notes

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13. We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them,

Table 1. Brain-related measurements and their association with ancestral and derived alleles of *ASPM* and *MCPH1* in children of the ALSPAC cohort.

Measurement*	Gene	N [†]	Mean A/A [‡]	Mean A/D [‡]	Mean D/D [‡]	P [§]
Attention (8)	ASPM	5500	5.27 ± 0.09	5.17 ± 0.07	5.2 ± 0.1	0.21
	MCPH1	5536	5.47 ± 0.39	5.21 ± 0.08	5.21 ± 0.06	0.4
Head circumference (0)	ASPM	6627	34.8 ± 0.06	34.8 ± 0.05	34.9 ± 0.09	0.21
	MCPH1	6666	34.8 ± 0.22	34.8 ± 0.07	34.8 ± 0.04	0.31
Motor performance (8)	ASPM	5526	1.37 ± 0.02	1.38 ± 0.02	1.37 ± 0.03	0.97
	MCPH1	5562	1.36 ± 0.07	1.38 ± 0.02	1.37 ± 0.01	0.92
Performance IQ	MCPH1	5245	98.3 ± 2.8	99.9 ± 0.8	100.2 ± 0.56	0.2
	ASPM	5210	99.9 ± 0.8	100.3 ± 0.6	99.1 ± 1.1	0.36
Total IQ	MCPH1	5196	102.8 ± 2.7	104.5 ± 0.8	105.0 ± 0.5	0.09
	ASPM	5161	104.8 ± 0.8	104.9 ± 0.6	103.6 ± 1	0.12
Verbal IQ	MCPH1	5603	106.2 ± 2.5	107.4 ± 0.8	107.7 ± 0.5	0.24
	ASPM	5569	107.8 ± 0.77	107.5 ± 0.62	106.9 ± 1.0	0.19
Working memory (10+)	ASPM	5300	3.45 ± 0.04	3.41 ± 0.03	3.43 ± 0.05	0.42
	MCPH1	5325	3.41 ± 0.14	3.42 ± 0.04	3.43 ± 0.03	0.65

*For a detailed description, see (6); age of assessment in years is given in parentheses. †Total number of individuals for which genotype and phenotype information was available. ‡Mean and 95% confidence interval of measurements for children carrying the ancestral (A) or the selected (derived, D) allele. §P value for the association of genotype and measurement (linear regression).

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and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The U.K. Medical Research Council, the Wellcome Trust, and the University of Bristol provide core support for ALSPAC. W.E. is supported by the Bundesministerium für Bildung und Forschung, the Max Planck Society,

and the European Commission's Sixth Framework Programme (PKB140404). This research was specifically funded by the Academic Research Collaboration program of the British Council and the German Academic Exchange Service (DAAD). We are grateful to S. Pääbo for providing resources and comments on the manuscript.

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Materials and Methods
Table S1

23 February 2007; accepted 25 June 2007
10.1126/science.1141705