ETHICAL & EVIDENTIAL STANDARDS IN GENOMICS CLAIMS ABOUT BRAIN SIZE, RACE, AND IQ

Jake Metcalf, UCSC Philosophy, jake.metcalf@gmail.com
Sarah Richardson, Stanford Modern Thought, richardson@stanford.edu

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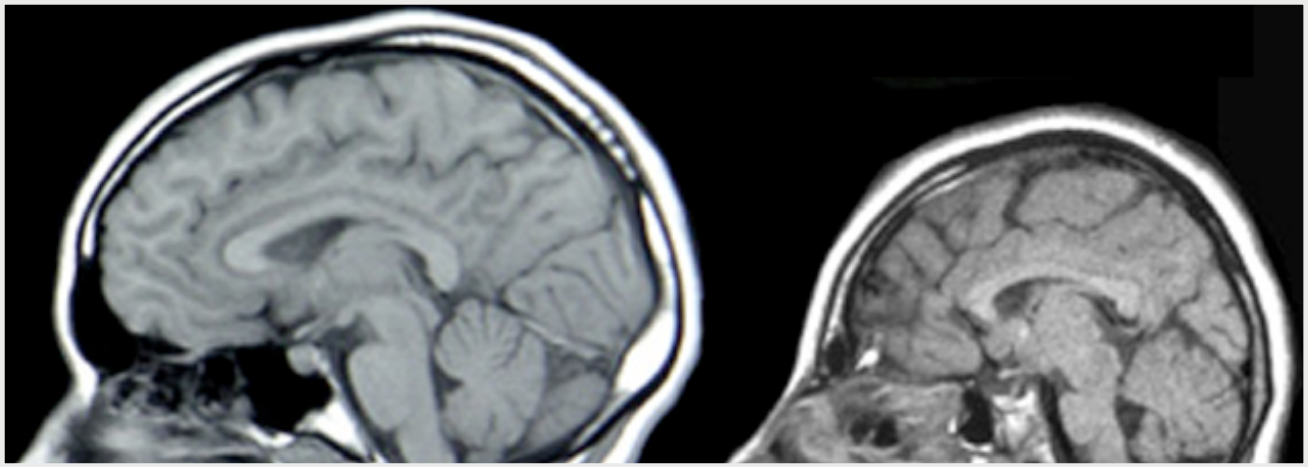


http://commons.wikimedia.org/wiki/Image:Microcephaly.png

LAHN ET AL., 2005

Ongoing Adaptive Evolution of *ASPM*, a Brain Size Determinant in *Homo sapiens*

Nitzan Mekel-Bobrov,[1,2] Sandra L. Gilbert,[1] Patrick D. Evans,[1,2] Eric J. Vallender,[1,2] Jeffrey R. Anderson,[1] Richard R. Hudson,[3] Sarah A. Tishkoff,[4] Bruce T. Lahn[1]*

The gene *ASPM* (*abnormal spindle-like microcephaly associated*) is a specific regulator of brain size, and its evolution in the lineage leading to *Homo sapiens* was driven by strong positive selection. Here, we show that one genetic variant of *ASPM* in humans arose merely about 5800 years ago and has since swept to high frequency under strong positive selection. These findings, especially the remarkably young age of the positively selected variant, suggest that the human brain is still undergoing rapid adaptive evolution.

Homozygous null mutations of *ASPM* cause primary microcephaly, a condition characterized by severely reduced brain size with otherwise normal neuroarchitecture (*1*). Studies have suggested that *ASPM* may regulate neural stem cell proliferation and/or differentiation during brain development, possibly by mediating spindle assembly during cell division (*1*, *2*). Phylogenetic analysis of *ASPM* has revealed strong positive selection in the primate lineage leading to *Homo sapiens* (*3*–*5*), especially in the past 6 million years of hominid evolution in which ASPM acquired about one advantageous amino acid change every 350,000 years (*4*). These data argue that *ASPM* may have contributed to human brain evolution (*3*–*6*). Here, we investigate whether positive selection has continued to operate on *ASPM* since the emergence of anatomically modern humans.

Human *ASPM* has 28 exons with a 10,434–base pair open reading frame (*1*) (fig. S1). We resequenced the entire 62.1-kb genomic region of *ASPM* in samples from 90 ethnically diverse individuals obtained through the Coriell Institute and from a common chimpanzee (*7*). This revealed 166 polymorphic sites (table S1). Using established methodology (*7*), we identified 106 haplotypes. One haplotype, numbered 63, had an unusually high frequency of 21%, whereas the other haplotypes ranged from 0.56% to 3.3% (fig. S2). Moreover, this haplotype differed consistently from the others at multiple polymorphic sites (save for a few rare haplotypes that are minor mutational or recombinational variants of haplotype 63, as discussed later) (table S2). Two of these polymorphic sites are nonsynonymous, both in exon 18, and are denoted A44871G and C45126A (numbers indicate genomic positions from the start codon, and letters at the beginning and end indicate ancestral and derived alleles, respectively). These two sites reside in a region of the open reading frame that was shown previously to have experienced par-

[1]Howard Hughes Medical Institute, Department of Human Genetics, [2]Committee on Genetics, [3]Department of Ecology and Evolution, University of Chicago, Chicago, IL 60637, USA. [4]Department of Biology, University of Maryland, College Park, MD 20742, USA.

*To whom correspondence should be addressed. E-mail: blahn@bsd.uchicago.edu

Microcephalin, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans

Patrick D. Evans,[1,2] Sandra L. Gilbert,[1] Nitzan Mekel-Bobrov,[1,2] Eric J. Vallender,[1,2] Jeffrey R. Anderson,[1] Leila M. Vaez-Azizi,[1] Sarah A. Tishkoff,[4] Richard R. Hudson,[3] Bruce T. Lahn[1]*

The gene *Microcephalin* (*MCPH1*) regulates brain size and has evolved under strong positive selection in the human evolutionary lineage. We show that one genetic variant of *Microcephalin* in modern humans, which arose ~37,000 years ago, increased in frequency too rapidly to be compatible with neutral drift. This indicates that it has spread under strong positive selection, although the exact nature of the selection is unknown. The finding that an important brain gene has continued to evolve adaptively in anatomically modern humans suggests the ongoing evolutionary plasticity of the human brain. It also makes *Microcephalin* an attractive candidate locus for studying the genetics of human variation in brain-related phenotypes.

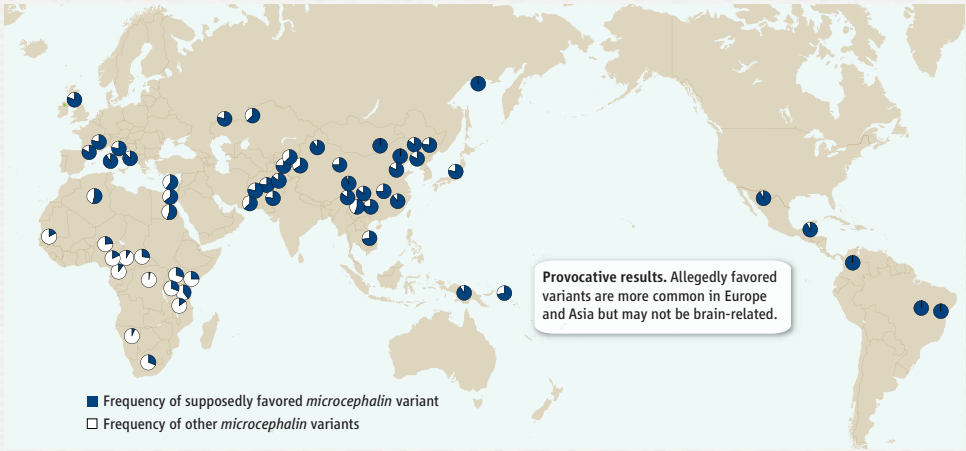
The most distinct trait of *Homo sapiens* is the exceptional size and complexity of the brain (*1*, *2*). Several recent studies have linked specific genes to the evolution of the human brain (*3*–*12*). One of these is *Microcephalin* (*7*, *8*); mutations in this gene cause primary micro-

CENPJ (*MCPH6*) (*14*, *21*, *23*). Patients with loss-of-function mutations in *Microcephalin* have cranial capacities about 4 SD below the mean at birth. As adults, their typical brain size is around 400 cm^3 (whereas the normal range is 1200 to 1600 cm^3), and the cerebral cortex

that it might have played a role in brain evolution (*16*, *28*). Consistent with this hypothesis, phylogenetic analysis of *Microcephalin* revealed signatures of strong positive selection in the lineage leading to humans (*7*, *8*). Here, we examine the possibility that positive selection has continued to operate on this gene after the emergence of anatomically modern humans.

The human *Microcephalin* locus has 14 exons spanning about 236 kb on chromosome 8p23 (*14*) (Fig. 1). We previously sequenced all the exons in 27 humans (*8*). When reanalyzing the data, we noticed that one haplotype had a much higher frequency than the other haplotypes. Additionally, this haplotype differed consistently from the others at position 37995 of the genomic sequence (counting from the start codon) or position 940 of the open reading frame. This polymorphism falls in exon 8 and changes amino acid residue 314 from an ancestral aspartate to a histidine. (This polymorphism is described as G37995C with G denoting the ancestral allele.)

To investigate whether positive selection has acted on the high-frequency haplotype, we resequenced 23.4 kb of a 29-kb region centered



Lahn's Argument

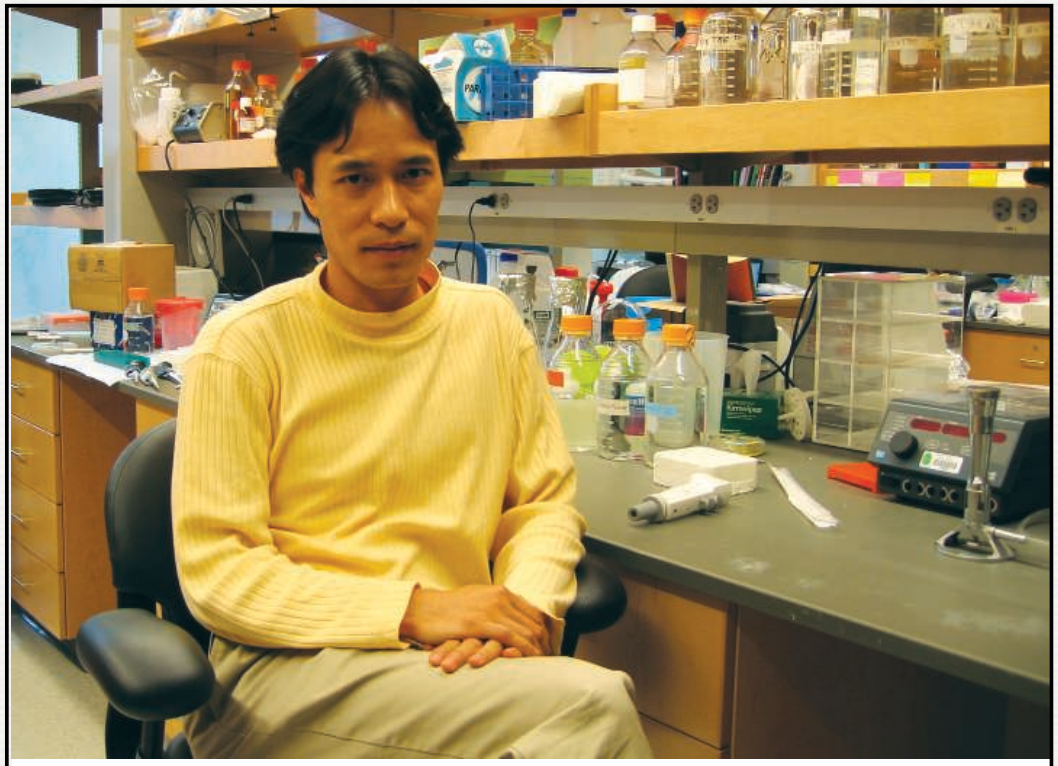
1. Positive selection for ASPM and microcephalin → advantage → high IQ.
2. Specifically, ASPM and microcephalin allele variants may have enhanced IQ by increasing brain size.
3. ASPM and microcephalin gene variants may explain cultural and cognitive differences among racial groups.

Researchers Say Human Brain Is Still Evolving

By NICHOLAS WADE
Published: September 8, 2005

Two genes involved in determining the size of the human brain have undergone substantial evolution in the last 60,000 years, researchers say, suggesting that the brain is still undergoing rapid evolution.

The discovery adds further weight to the view that human evolution is still a work in progress, since previous instances of recent genetic change have come to light in genes that defend against disease and confer the ability to digest milk in adulthood.

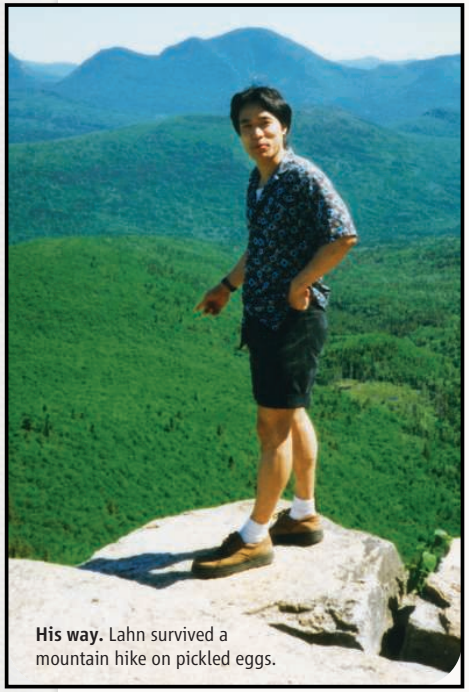


PROFILE: BRUCE LAHN

Brain Man Makes Waves With Claims of Recent Human Evolution

Geneticist Bruce Lahn's quest to understand the biology of human differences lands him in the minefield of debates over race and IQ

"GOLDEN HANDS"



His way. Lahn survived a mountain hike on pickled eggs.

- HHMI researcher
- Back-to-back papers in *Science*
- Lahn received tenure from University of Chicago shortly after their publication
- Celebrity treatment in reviews and profiles in science journals and magazines

RIGHT WING RESPONSE

■ SCIENCE

The Specter of Difference

What science is uncovering, we will have to come to grips with

JOHN DERBYSHIRE

IT is a longstanding cliché that human knowledge of the universe advances by a series of *dethronements*. There was a time when men thought that the whole world was alive with spirits whose main purpose and pleasure was to watch us. Great bonfires were lit to stir the sun from his midwinter torpor; kings were ritually slain and new kings proclaimed, so that the crops thus encouraged might rise from the ground. It took several thousand

block molecules. Other living things have genomes, too, of course, and the living creatures that most resemble us have genomes most like ours.

Of all living creatures, the one that resembles us most closely is the chimpanzee. A good approach to finding out what makes us humans so darn special would therefore be to get complete maps of the human and chimp genomes, and compare the two. Somewhere in the differences lies the secret of humanness—the thing that makes us more than just another great ape.

This work of comparison has now begun in earnest. Mapping of the human genome was completed in 2003. The chimp genome

> In seeking to understand what defines us, we cannot help learning about what divides us.

was published earlier this year. (That is, a database of all the components of all the genes of a particular chimp—an adult male

BOMBSHELL PAPERS

Two papers published in the Sept. 9, 2005, issue of *Science* illustrate my point. The actual titles of the papers are "*Microcephalin*, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans," and "Ongoing Adaptive Evolution of *ASPM*, a Brain Size Determinant in *Homo sapiens*." Since "ASPM" stands for "Abnormal SPindle-like Microcephaly-associated," both these genes have something to do with microcephaly, a congenital infant condition in which the brain fails to develop properly. More precisely, it is *defects* of these genes that lead to microcephaly. Genes, like celebrities, draw attention to themselves by misbehaving, and it is often from the conse-

John Derbyshire
National Review, 7/11/05

BEYOND THE PAGES OF *SCIENCE*

"The 37-year-old Dr. Lahn *says his research papers, published in Science last September, offered no view on race and intelligence. He personally believes it is possible that some populations will have more advantageous intelligence genes than others. And he thinks that 'society will have to grapple with some very difficult facts' as scientific data accumulate.*" (Regalado 2006)

BEYOND THE PAGES OF *SCIENCE*

"He [Lahn] said *he expected more such allele differences between populations would come to light,* as have differences in patterns of genetic disease. '*I do think this kind of study is a harbinger for what might become a rather controversial issue in human population research,*' he said." (Wade 2005).

BEYOND THE PAGES OF *SCIENCE*

"'You can't deny that people are different at the level of their genes,' Lahn says, citing the examples of skin color and physical appearance. 'This is not to deny the role of culture, but there may be a biological basis [for differences] above and beyond culture'" (Balter "Profile" 2006, 1871).

PROBLEMS

Positive selection for ASPM & *microcephalin*

↓

Advantage

↓

High IQ

1. POSITIVE SELECTION FOR ASPM AND MICROCEPHALIN → ADVANTAGE → HIGH IQ.

Statistical evidence for recent evolution of these gene variants under positive selection is disputed

1. POSITIVE SELECTION FOR ASPM AND MICROCEPHALIN → ADVANTAGE → HIGH IQ.

- No evidence that these allele variants correspond to any brain-related phenotype;
- Both genes are expressed in tissues other than the brain

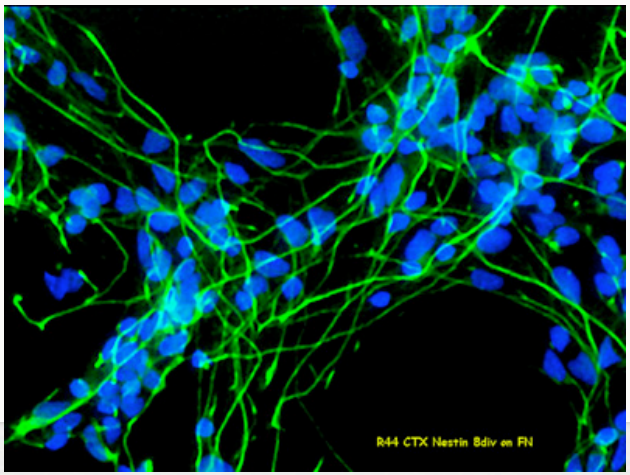
PROBLEMS

2. ASPM and microcephalin allele variants enhanced IQ by increasing brain size.

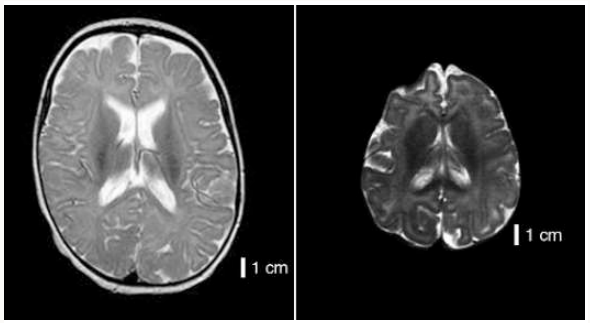
2. ASPM AND MICROCEPHALIN ALLELE VARIANTS ENHANCED IQ BY INCREASING BRAIN SIZE.

Assumptions:

- A gene that, if lesioned, causes small brains can be expected to, if normal or enhanced, cause big brains.
- Larger brain size can be expected to be associated with higher intelligence; there is a correlation between brain size and IQ.



Fetal neural stem cells, photo: Prof. John Sinden, Ectins project, Euopean Union.



Downsized. When mutated, brain genes cause microcephaly in humans (normal infant brain, *left*; microcephalic brain, *right*).

Primary microcephaly, *Science* 309, 9/15/05

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	ASPM	6627	34.8 ± 0.06	34.8 ± 0.05	34.9 ± 0.09	0.21
circumference (0)	MCPH1	6666	34.8 ± 0.22	34.8 ± 0.07	34.8 ± 0.04	0.31
Motor	ASPM	5526	1.37 ± 0.02	1.38 ± 0.02	1.37 ± 0.03	0.97
performance (8)	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	ASPM	5300	3.45 ± 0.04	3.41 ± 0.03	3.43 ± 0.05	0.42
memory (10+)	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).

Timpson et. al. (*Science 2007)* genotyped ~5000 individuals for ASMP and MCHP1 haplogroups D and phenotyped them against natal head circumference records and IQ, finding no correlation

PROBLEMS

3. ASPM and microcephalin gene variants may explain cultural and cognitive differences among racial groups.

3. ASPM AND MICROCEPHALIN GENE VARIANTS MAY EXPLAIN CULTURAL AND COGNITIVE DIFFERENCES AMONG RACIAL GROUPS.

"Although the age of haplogroup D and its geographic distribution across Eurasia roughly coincide with two important events in the cultural evolution of Eurasia—namely the emergence and spread of domestication from the Middle East ~10,000 years ago and the rapid increase in population association with the development of cities and written language 5000 to 6000 years ago around the Middle East—the significance of this correlation is not yet clear." (Mekel-Bobrov et al., 2005)

3. ASPM AND MICROCEPHALIN GENE VARIANTS MAY EXPLAIN CULTURAL AND COGNITIVE DIFFERENCES AMONG RACIAL GROUPS.

- "We note that the age of haplogroup D coincides with the introduction of anatomically modern humans into Europe about 40,000 years ago, as well as the dramatic shift in the archaeological record indicative of modern human behavior, such as art and the use of symbolism (i.e., the 'Upper Paleolithic revolution')." (Evans et al., 2005).

3. ASPM AND MICROCEPHALIN GENE VARIANTS MAY EXPLAIN CULTURAL AND COGNITIVE DIFFERENCES AMONG RACIAL GROUPS.

- Based on what is known about normal brain development, a few genes cannot be expected to have a dramatic effect on cognitive abilities in an otherwise healthy brain
- There are no sound reasons to expect that humans will differ in core genes involved in brain function between populations

3. ASPM AND MICROCEPHALIN GENE VARIANTS MAY EXPLAIN CULTURAL AND COGNITIVE DIFFERENCES AMONG RACIAL GROUPS.

- Time estimates of when the allele arose and underwent positive selection are highly speculative, large error bar.
- Assertions about a correlation between the rise of symbolic culture in European and Middle Eastern populations and alleles are ungrounded.

SUMMARY

1) Evidence of a correlation between haplotypes and phenotypic difference

- **Lahn presents no such evidence**

2) Deliberative consideration of several plausible causal stories that account for how this gene could cause phenotypic difference

- **Lahn considers no such plausible story**

COMMUNITY RESPONSE

Longino: Science as social knowledge

(1) there must be recognized avenues for the criticism of evidence, of methods, and of assumptions and reasoning

(2) there must exist shared standards that critics can invoke

(3) the community as a whole must be responsive to such criticism

(4) intellectual authority must be shared equally among qualified practitioners.

RESPONSES TO LAHN'S RESEARCH

1. "Damage Control"

2. "More Science"

3. "Community Standards"

1. DAMAGE CONTROL

"John Easton, head of media relations at the medical school … helped Dr. Lahn with talking points about his research."

-Wall Street Journal 2006

"We really don't want to end up on the front page ... for doing eugenics."

-Alan Thomas, University of Chicago Patent Director

"It's exactly what they were getting at. There was a lot of hallway talk. People said he's doing damage to the whole field of genetics."

-Pilar Ossorio, Wisconsin-Madison, Legal Scholar & Microbioligist

2. MORE SCIENCE

"Although they acknowledge such social concerns, most scientists who spoke to Science say that the only way to answer the questions posed by this research is to do more research. 'We should treat these genes just like any others,' says [Chris] Tyler-Smith."

"Even some researchers who scoff at racial differences in intelligence think the research should go on. Geneticist Michael Hammer of the University of Arizona in Tucson says he's not worried about the end result: 'I have no serious concerns that Europeans or Asians are going to be proven to be more intelligent, so I say go at it, let the chips fall where they may"

"The possibility that our brains are continuing to adapt is fascinating and important." (Huntington Willard)

- *Science* Profile Article by Balter (2005, pg. 1662)

3. COMMUNITY STANDARDS

- Broad's influential chief, Eric Lander, says scientists probing recent evolution run the risk of 'seeing a difference, and saying there is a story to fit it'" (Regalado 2006).
- "If greater human brain size is still undergoing evolutionary selection, how come we have no strong correlations between brain size and important functional attributes of the human nervous system? If the brain is still evolving in size, what are the conceivable selection pressures, given no apparent correlation between non-pathological brain size and function? *We're unhappy that the authors were not urged by the referees to make some statements about these questions*" (Science Week Editorial 2005).
- "The papers have such serious social implications that they needed to meet a higher standard of proof, says David Altshuler of the Broad Institute in Cambridge, Massachusetts—and they didn't. The links to cognition in particular were 'wild speculation,' he says. '*We have a powerful responsibility to think about how society will interpret [such work]*'" (Balter "Profile" 2006, 1871).
- "'There was no evidence whatsoever that these [genetic variants] have any effect' on differences between people, Altshuler says, adding that *the controversy over the work was 'easily anticipated*'" (Balter "Profile" 2006, 1872).

ETHICS PERSPECTIVES

- Lahn's work provides a case study to interrogate some tensions that exist between ethics and science
  - Traditional distinction: science (epistemology) produces empirical facts, ethics produces normative claims
    - This is both a logical and an institutional distinction
    - We work within the assumption that epistemology and ethics are inextricably linked; in other words, ethical and evidential standards are not wholly separate affairs

ETHICS PERSPECTIVES

- Consequences of the traditional distinction:
  - Temporality of ethics in science: ethics either comes before or after knowledge is produced
    - Early: Preventing dangerous human subject research, regardless of intellectual value
    - Late: Determining legitimate use of dangerous knowledge, i.e., how to engineer smallpox

ETHICS PERSPECTIVES

- Consequences of traditional distinction:
  - Scientists have little voice in ethical theory despite substantial stakes in ethics policies
  - Ethicists are excluded from epistemological or conceptual concerns, often taking for granted the naive or unnuanced understanding of science

ETHICS PERSPECTIVES

- In sensitive genomics brain research, this plays out predictably:
  - Ethicists panic about privacy or hypothetical dystopian futures or loss of human dignity
  - Scientists offer critical caveats, voice concerns about ethical or political "implications", suggest "more science or data" is needed

ETHICS PERSPECTIVES

- How should the ethicist respond to Lahn's research?

ETHICS PERSPECTIVES

- How should the scientist respond to Lahn's research?

ETHICS PERSPECTIVES

- Going beyond the data?
  - Title: "Ongoing Evolution of ASPM, Brain Size Determinant in *Homo sapiens*."
  - Alternate title: "Ongoing evolution of ASPM, a Gene Related to Microcephaly in *Homo sapiens*."

ETHICS PERSPECTIVES

- "Implications" model of ethical inquiry
  - When scientists or ethicists limit ethical theory and practice to the "implications" of "speculative" science, does that take for granted aspects of scientific practice that should be challenged?
  - What is the proper venue for challenging the deep conceptual errors at the core of Lahn's work *from an ethical-epistemological standpoint?* Does that venue yet exist?

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