Jacob Metcalf[1]
University of California, Santa Cruz
Dept. of Philosophy

When Evidential & Ethical Standards Intersect: Genomics, Human History, and Racial Ancestry, Human Intelligence

Summary

This project examines the intersection of ethical and evidential standards in claims made by genomics researchers regarding human evolution, human genetic differences, brain size, and cognitive capabilities. We focus on the claims made by Bruce Lahn and his collaborators at Univ. of Chicago in two articles published consecutively in *Science* in 2005 (Mekel-Bobrov, 2005; Evans, 2005; Vallender, 2004). In these articles, Lahn et al. claim to have identified two genes that are related to human brain size and IQ that show evidence of strong recent evolutionary pressure and difference across ancestral/racial groups. This research attracted substantial interest in the broader media and resulted in Lahn receiving early tenure and a personal profile in *Science* (Balter, 2005, 2006a, 2006b; Regalado, 2006; Wade, 2005). Lahn and the Univ. of Chicago immediately applied for a patent for a 'genetic intelligence test' to be marketed to employers. This research came under attack from quite a few genomics researchers and was challenged on multiple empirical fronts and criticized for overreaching in its speculative claims. The patent was eventually withdrawn and the University assisted Lahn with some surprising PR claims.

The Claims

In two papers published consecutively by Science in 2005 (and supported by previous and subsequent research), Lahn and his research group claimed that haplotypes[2] of two genes, *ASPM* and *microcephalin*, believed to be involved in fetal neurogenesis, show signs of recent positive selection (see Evans, 2004a, 2004b; Gilbert, 2005). Both of these genes are members of the MCPH family, a series of five loci in which lesions are known to cause primary microcephaly, a developmental defect marked by a dramatic reduction in the volume of the frontal cortex of the brain and subsequent cognitive disabilities (Jackson, 1998, 2002; Wang, 2004; Woods, C., 2005). This family of genes is especially interesting from a genomics perspective because it offers a focal point for molecular study of recent evolution of an important human trait. Lesioned

---

[1] This research is entirely a collaborative project with Sarah Richardson of Stanford's Modern Language and Thought Department. All mistakes here are mine, however.

[2] A haplotype consists of a series of alleles (genes) at multiple loci on a chromosome which is typically inherited together. The size and scope of a haplotype is defined by what interests the researchers. A haplogroup is a family of genealogically related haplotypes—there are variations within a haplogroup, but all the variations derive from an ancestral variation. A haplotype need not be responsible for a phenotypic trait—it may just be used as a functionally arbitrary marker for tracking ancestry—but in this case the haplotypes are under consideration because they are believed to specify a phenotypic trait.

variants (mutations that prevent the proper functioning of the protein specified by the gene) appear to interfere with functioning of the mitotic spindles in neural stem cells, resulting in very low numbers of neurons in the fetal brain's frontal cortex (for a broad literature review see: Woods, C., 2005). The haplotypes contended to have undergone recent positive selection were differentially distributed in the human population, showing the highest incidence in European and Asian populations and lowest incidence in sub-Saharan African populations. Lahn's group speculated that the possible role of these genes in neurogenesis, recent positive selection, and the haplotypes' demographic distribution altogether (may)[3] imply that these genes were positively selected for playing a role in the cognitive and linguistic advances related to the spread of agricultural societies from the Middle East 6,000 years before present. They thus contend that these genes are possible explanans for cultural and cognitive differences between human populations.

Controversy & Rebuttals

Perhaps the most contentious aspect of Lahn's research was the University of Chicago's decision to apply for a patent (later withdrawn) for a genetic test for the 'favorable' haplotypes to be marketed as a proxy intelligence test. As you will see below, because Lahn at that time lacked any data linking these haplogroups to phenotypic data about brain size or cognitive capacities (later research showed no correlation), this test would functionally be a test for ancestral groups. In other words, had this test become marketed based on the information known to Lahn at the time, it would have been a test that functionally only showed whether one's ancestors *probably* came from Europe, Africa, or Asia and yet it would have been marketed as a proxy for intelligence testing.

This research was immediately picked up by politically conservative commentators as evidence of the biological basis of the cognitive inferiority of African Americans and the pointlessness of attempts to address social inequalities, such as affirmative action or investing in urban education. For instance, John Derbyshire wrote in the *National Review* that Lahn's research demonstrated that "our cherished national dream of a well-mixed and harmonious meritocracy" is misguided (Derbyshire, 2005). The public relations office at Univ. of Chicago prepped Lahn with talking points and strategies for dealing with the press on such questions. One person in that office defended Lahn's work from charges of potential racism by claiming that neither Lahn nor his research could possibly be racist because he is Chinese and does not have the 'favored variant.' (Of course they had no phenotypic evidence of any variant being 'favored,' whatever that might mean.) And Lahn offered a rather bizarre statement in his *Science* profile that he next wished to study why Chinese people "are so boring" and favor social and political conformity (Balter, 2006; Regalado, 2006).

In addition to these problems at a social/political level, there proved to be numerous empirical and conceptual gaps in Lahn's account that should have been obvious at the

---

[3] See the bullet point at the end regarding Lahn's uses of qualifiers.

outset.[4] At the time of publication, there was no phenotypic evidence that the gene variants were correlated with larger brain sizes or cognitive capacities. Similarly, no causal account was even speculatively offered as to how non-lesioned variants of these genes play a role in brain size phenotypes. Later research (some done by Lahn's group) showed that indeed there was no phenotypic correlation, except between lesioned loci and primary microcephaly (Woods, R., 2006; Timpson, 2007; Mekel-Bobrov, 2007). As later critics noted, Lahn's group did not adequately rule out demographic scenarios to explain the variations in *ASPM* and *microcephalin* that do not include positive selection, thus challenging the notion that these genes are related to an evolutionarily advantageous phenotype (Currant, 2006; Yu, 2007; Mekel-Bobrov, 2006, 2007). The genes are expressed in multiple fetal tissues, but Lahn's group made no attempt to rule out the possibility that these genes show positive selection for other effects that appear to be common in mammals, such as spermatogenesis or immunological function (Ponting, 2006). A major reason that these genes were targeted for this research was early evidence of these genes playing a role in human–chimp speciation; however the premise that genes involved in speciation would therefore be candidate genes for humans' cognitive skills is not to be taken for granted when considering that coding changes in DNA appear to play a far smaller role than regulatory DNA.

Lahn's research also shows a propensity to misuse the term "determine" to describe the role of these genes—even using it in the title of a paper—without accounting precisely for its meaning either conceptually or empirically. This is symptomatic of a conflation between two notions of a gene: genes as directly determinant of a phenotype (such as the lesioned haplotypes that cause microcephaly) and genes as contributing to a massively complex developmental system (Moss, 2004). In other words, just because a gene when lesioned determines a diseased outcome (clinically small brains) in no way means that a non-lesioned variant gene determines the opposite of that outcome (larger brains). Indeed, there was a preponderance of evidence prior to Lahn's research that is the case (Woods, C., 2005). Etiological research into microcephaly had already indicated that the cause of the smaller brains in microcephalics was a failure of mitotic division in fetal neural stem cells. Typically, a neural stem cell will divide/differentiate into a daughter neuron and *another stem cell* for further division. In neural stem cells with lesioned version of *ASPM*, the stem cells produce two neurons, thus failing to provide another stem cell for further divisions. This was a well-established phenomenon that both physiologically explains the low volume of microcephalic brains and casts substantial doubt on the notion that variants of these genes *cause* (let alone *determine*) larger brains or cognitive advantages—healthy versions of the gene likely just supply properly working mitotic spindles and the explanation for variation in these genes lies elsewhere than cognitive advantage. For Lahn's research to coherently fit with this etiological account of microcephaly, they would have to demonstrate that

---

[4] We argue that to adequately understand this case (and others like it) it is inappropriate to assume a bright line between social/political factors and empirical factors. A thorough understanding of how this research came to be requires a careful tracking of the entanglements of "social" and "empirical" factors. It is, however, possible to hold the difference pragmatically in order to speak of it succinctly.

healthy variants of these genes cause or determine higher rates of fetal neurogenesis by controlling the mitotic spindles. Not only did Lahn's research lack such evidence and fail to address such a causal question, the papers show no evidence of Lahn et al. consulting the etiological data about microcephaly. Additionally, the bulk of evidence looking at brain size and IQ data demonstrate a very weak correlation, largely isolated to the margins of very large and very small brains. In order for these gene variants to have an evolutionarily significant effect there would likely need to be a substantial increase in brain size.

Questions

All of these errors raise a series of critical questions:

• How was such transparently shoddy research published in the most prestigious of science journals?

• Why did this research earn Lahn a Science profile and lauditory attention for his willingness to engage in bold (we would say unfounded) and politically sensitive research? How does such attention, focused on anti-PC, jockish personality traits, support bad research?

• How does Lahn's standpoint as a non-Caucasion Chinese immigrant function to add to the credibility of his research and shield it from criticism within and beyond the scientific community?

• The common thread in public criticism of Lahn's work was an emphasis on the possibility of mistaken "interpretation" of the data rather than on the values, conduct, and aims of the research itself. We argue that the data and interpretation are mutually implicated such that there must be a very strong conceptual infrastructure to justify and publish such research. While we applaud the effort to vigorously address the research and attendant controversies by some scientists, we suggest that this incident indicates the need for more rigorous standards for pursuing and publishing similar research. These standards necessarily require interdisciplinary insights from across the natural sciences, and should regularly incorporate work from philosophers and social scientsits. How can we reconceive scientific practice to incorporate heterogeneous knowledges?

• One of the interesting aspects of this case is Lahn et al.'s use of qualifiers such as "may" in their speculations, which Lahn dropped in his public statements. How exactly such speculation gets done in a peer reviewed work opens up an under-examined minefield of philosophical and political problems. On the one hand, speculations must always be appropriately qualified. On the other hand, there is a performative aspect of such qualifications that hides the ideologies which favor one speculation over others. The qualifications, even though appropriate on one level, function to support the institutional and infrastructural inertia of those ideologies that can do real harm. All of which raises a very pragmatic question: how can those of us who oppose those harms effectively support better standards of scientific practice that account for the ideologies sedimented within such speculations?

• Far from arguing against research that follows speculative leads or suggesting that controversial or "politically incorrect" research should not be pursued, we argue that there are deep conceptual concerns that must be addressed in order to adequately empirically test claims that link genes, human evolution, brains, and behavior. Indeed, we contend that even if Lahn's research had been about lactose intolerance—a thoroughly non–controversial topic—it would not have met appropriately rigorous evidential standards. (Note that this is not the same as claiming that lactose intolerance has the same burden of evidence as such sensitive claims about human cognitive differences.) In Lahn's case, there appears to be no attempt to account for the multiple conceptual steps necessary to move from a lesioned gene determining a disease phenotype to healthy haplotypes of the same gene even correlating with—let alone causing—differential cognitive phenotypes. However, there is a general lack of evidential and methodological standards that would have caught this dramatic and harmful error.

• What are the challenges for linking genomics—an algorithm-driven quantitative discipline—to genetics and then to complex cognitive and behavioral traits? This case study points out a number of pitfalls when genomics research fails to account for heterogeneous causal pathways properly, but it still isn't clear how this could be done successfully.

Works Cited

Balter, Michael. 2006. Links Between Brain Genes, Evolution, and Cognition Challenged. Science 214 1872.

Balter, Michael. 2006. Brain Man Makes Waves With Claims of Recent Human Evolution. Nature 314 1871-72.

Balter, Michael. 2005. Brain Genes Show Signs of Selection. Science 309 1662-63.

Currant, Mathias, Laurent Excoffier, Wayne Maddison, Sarah P. Otto, Nicolas Ray, Michael Whitlock, and Sam Yeaman. 2006. Comment on "Ongoing Adaptive Evolution of Aspm, a Brain Size Determinant in Homo Sapiens" and "Microcephalin, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans". Science 313 172a.

Derbyshire, John. 2005. The Specter of Difference. National Review, 40-42.

Dorus, Steve, Eric J. Vallender, Sandra L. Gilbert, Michael Mahowald, Gerald J. Wyckoff, Christine M. Malcom, and Bruce T. Lahn. 2004. Accelerated Evolution of Nervous System Genes in the Origin of Homo Sapiens. Cell 119 1027-40.

Evans, Patrick D., Jeffrey R. Anderson, Eric J. Vallender, Sun Chim Choi, and Bruce T. Lahn. 2004. Reconstructing the Evolutionary History of Microcephalin, a Gene Controlling Human Brain Size. Human Molecular Genetics 13 1139-45.

Evans, Patrick D., Jeffrey R. Anderson, Eric J. Vallender, Sandra L. Gilbert, Christine M. Malcom, Steve Dorus, and Bruce T. Lahn. 2004. Adaptive Evolution of Aspm, a Major Determinant of Cerebral Cortical Size in Humans. Human Molecular Genetics 13 489-94.

Evans, Patrick D., Sandra L. Gilbert, Nitzan Mekel-Bobrov, Eric J. Vallender, Jeffrey R. Anderson, Leila M. Vaez-Azizi, Sarah A. Tishkoff, Richard R. Hudson, and Bruce T. Lahn. 2005. Microcephalin, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans. Science 309 1717-20.

Gilbert, Sandra L., William B. Dobyns, and Bruce T. Lahn. 2005. Genetic Links Between Brain Development and Brain Evolution. Nature Reviews Genetics Advanced Online Publication 1-10.

Jackson, Andrew P., Helen Eastwood, Sandra M. Bell, Jimi Adu, Carmel Toomes, Ian M. Carr, Emma Roberts, Daniel Hampshire, Yanick Crow, Alan J. Mighell, Gulshan Karbani, Hussain Jafri, Yasmin Rashid, Robert Mueller, Alexander Markham, and C. Geoffrey Woods. 2002. Identification of Microcephalin, a Protein Implicated in Determining the Size of the Human Brain. American Journal of Human Genetics 71 136-42.

Jackson, Andrew P., Duncan P. McHale, David A. Campbell, Hussain Jafri, Yasmin Rashid, Jovaria Mannan, Gulshan Karbani, Peter Corry, Malcolm Levene, Robert Mueller, Alexander F. Markham, Nicholas J. Lench, and C. Geoffrey Woods. 1998. Primary Autosomal Recessive Microcephaly (Mcph1) Maps to Chromosome 8p22-Pter. American Journal of Human Genetics 63 541-46.

Lohmueller, Kirk E., Matthew M. Mauney, David Reich, and John M. Braverman. 2006. Variants Associated With Common Disease Are Not Unusually Differentiated in Frequency Across Populations. American Journal of Human Genetics 78 130-36.

Mekel-Bobrov, Nitzan, Patrick D. Evans, Sandra L. Gilbert, Eric J. Vallender, Richard R. Hudson, and Bruce T. Lahn. 2006. Response to Comment on "Ongoing Adaptive Evolution of Aspm, a Brain Size Determinatn in Homo Sapies" and "Microcephalin, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans". Science 313 172b.

Mekel-Bobrov, Nitzan, Sandra L. Gilbert, Patrick D. Evans, Eric J. Vallender, Jeffrey R. Anderson, Richard R. Hudson, Sarah A. Tishkoff, and Bruce T. Lahn. 2005. Ongoing Adaptive Evolution of Aspm, a Brain Size Determinant in Homo Sapiens. Science 309 1720-22.

Mekel-Bobrov, Nitzan, and Bruce T. Lahn. 2007. Response to Comments By Timpson Et Al. And Yu Et Al. Science 317 1036b-.

Moss, Lenny. 2004. What Genes Can't Do. Basic Bioethics. Cambridge, MA: MIT Press.

Ponting, Chris P. 2006. A Novel Domain Suggests a Ciliary Function for Aspm, a Brain Size Determining Gene. Bioinformatics 22 (9): 1031-35.

Regalado, Antonio. 2006. Head Examined: Scientist's Study of Brain Genes Sparks a Backlash. The Wall Street Journal Online.

Timpson, Nicholas, Jon Heron, George Davey Smith, and Wolfgang Enard. 2007. Comment on Papers By Evans Et Al. And Mekel-Bobrov Et Al. On Evidence for Positive Selection of Mcph1 and Aspm. Science 317 1036a.

Vallender, Eric J., and Bruce T. Lahn. 2004. Positive Selection on the Human Genome. Human Molecular Genetics 13 245-54.

Wade, Nicholas. 2005. Researchers Say Human Brain is Still Evolving. New York Times.

Wang, Yin-qui, and Bing Su. 2004. Molecular Evolution of Microcephalin, a Gene Determining Human Brain Size. Human Molecular Genetics 13 1131-37.

Woods, C. Geoffrey, Jacquelyn Bond, and Wolfgang Enard. 2005. Autosomal Recessive Primary Microcephaly (Mcph): A Review of Clinical, Molecular, and Evolutionary Findings. American Journal of Human Genetics 76 717-28.

Woods, Roger P., Nelson B. Freimer, Joseph A. De Young, Scott C. Fears, Nancy L. Sicotte, Susan K. Service, Daniel J. Valentino, Arthur W. Toga, and John C. Mazziotta. 2006. Normal Variants of Microcephalin and Aspm Do Not Account for Brain Size Variability. Human Molecular Genetics 15 2025-29.

Yu, Fuli, R. Sean Hill, Stephen F. Schaffner, Pardis C. Sabeti, Eric T. Wang, Andre A. Mignault, Russell J. Ferland, Robert K. Moyzis, Christopher A. Walsh, and David Reich. 2007. Comment on "Ongoing Adaptive Evolution of Aspm, a Brain Size Determinant in Homo Sapiens". Science 316 370b.