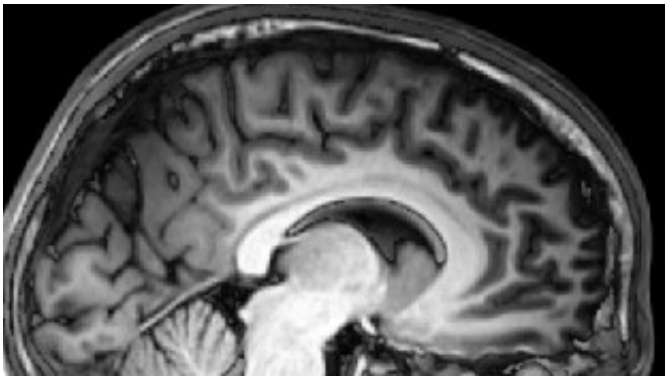
Brain Genetics Paper Retracted

A study that identified genes linked to communication between different areas of the brain has been retracted by its authors because of statistical flaws.

By Anna Azvolinsky | September 4, 2014



MRI image of the brain
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The authors of a June *PNAS* paper that purported to identify sets of genes associated with a specific brain function last week (August 29) retracted the work because of flaws in their statistical analyses. "We feel that the presented findings are not currently sufficiently robust to provide definitive support for the conclusions of our paper, and that an extensive reanalysis of the data is required," the authors wrote in their retraction notice.

The now-retracted study identified a set of gene ontologies (GO) associated with a brain phenotype that has been previously shown to be disturbed in patients with schizophrenia. Andreas Meyer-Lindenberg, director of the Central Institute of Mental Health Mannheim, Germany, and his colleagues had healthy volunteers perform a working memory task known to require communication between the hippocampus and the prefrontal cortex while scanning their brains using functional magnetic resonance imaging (fMRI). The volunteers also underwent whole-genome genotyping. Combining the fMRI and genomic data, the researchers identified groups of genes that appeared associated with communication between the two brain regions, which can be disturbed in some people with schizophrenia. The authors used gene set enrichment analysis to pick out genes associated with this brain phenotype, identifying 23 that could be involved in the pathology of the brain disorder.

The Scientist first learned of possible problems with this analysis when the paper was under embargo prior to publication. At that time, *The Scientist* contacted Paul Pavlidis, a professor of psychiatry at the University of British Columbia who was not connected to the work, for comment on the paper. He pointed out a potential methodological flaw that could invalidate its conclusions. After considering the authors' analyses, Pavlidis reached out to Meyer-Lindenberg's team to discuss the statistical issues he perceived.

The original analysis flagged a set of 11 genes in close proximity to one another within the genome using the same single nucleotide polymorphism (SNP), inflating the significance of the results. "The researchers found a variant near a genomic region that they say is correlated with the [working memory] task," explained Pavlidis. "But instead of counting that variant once, that variant was counted 11 times."

"When we re-analyzed the data, we saw that we had to retract because addressing the problem went beyond just an erratum," Meyer-Lindenberg told *The Scientist*. "The analysis could not be used to make

any conclusions with the required statistical confidence."

Elizabeth Thomas, who studies the molecular mechanisms of neurological disorders at The Scripps Research Institute in La Jolla, California, and was not involved in the work noted that the GO annotations used in the study were outdated. "GOs change every few months, and it's unfortunate for researchers that rely on a certain set of annotations. It makes you wonder whether the papers published in the past five to 10 years are still relevant," said Thomas. "This retraction raises the issue of how many papers may have falsely reported gene associations because of the constantly evolving changes in gene assemblies and boundaries. That's really alarming to me."

According to Meyer-Lindenberg, the researchers are re-evaluating their data using a different set of criteria and several updated sets of GO annotations.

In the meantime, however, Pavlidis lauded the researchers' swift decision to retract. "What the authors did was the right thing," he said.

Tags

schizophrenia, retraction, neuroscience, neuroimaging, gwas, genetics & genomics, fMRI and brain

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Comments

Judith Blake
Posts: 1

September 8, 2014

As noted by Dr. Pavlidis, concerns associated with the Meyer-Lindenberg et al. paper in regards to data processing have properly led to the paper being retracted. We want to avoid any inappropriate overgeneralization of the issues that led to the retraction of this paper. It is irrelevant whether the Gene Ontology annotations used in the analysis were old, as the data problem occurred upstream of any GO enrichment testing. Nevertheless, we wish to encourage the use of up-to-date Gene Ontology annotations for the most accurate results. GO annotations are constantly being added and revised as new scientific discoveries are made. The more general consideration here is in data processing and appropriate application of data analysis tools. This event also points to the necessity of providing, as part of the publication process, metadata (versions of software, downloading date for annotation sets, etc.) and intermediate analysis data (e.g. complete lists of P-values for all SNPs, and mapping of SNPs to genes) that enable rapid and accurate replication of the reported results.
Judith Blake (GO-PI, Jackson Laboratory), Paul Thomas (GO-PI, USC)

September 18, 2014

Posts: 0

Re: “This retraction raises the issue of how many papers may have falsely reported gene associations because of the constantly evolving changes in gene assemblies and boundaries. That’s really alarming to me.”

I am alarmed by those who report anything in terms of 'constantly evolving changes in gene assemblies and boundaries.' It seems that few people realize the importance of RNA-mediated events that link the epigenetic landscape to the physical landscape of DNA in the organized genomes of species from microbes to man. See: RNA and dynamic nuclear organization

Indirectly attributing anything to an evolutionary event when only RNA-mediated events have been detailed in the context of biologically-based cause and effect makes many papers published in the past 50 years irrelevant.

This is why: Dobzahsky (1964) claimed that "...the only worthwhile biology is molecular biology. All else is "bird watching" or "butterfly collecting." Others have continued to watch and collect data despite the clarify of Dobzahsky (1973). "...the so-called alpha chains of hemoglobin have identical sequences of amino acids in man and the chimpanzee, but they differ in a single amino acid (out of 141) in the gorilla."

Fixed amino acid substitutions differentiate all cell types in all individuals of all species, and the substitutions are nutrient-dependent and pheromone-controlled during life history transitions. See for review: Honey bees as a model for understanding mechanisms of life history transitions. "...we discuss the physiological and genetic mechanisms of this behavioral transition, which include large scale changes in hormonal activity, metabolism, flight ability, circadian rhythms, sensory perception and processing, neural architecture, learning ability, memory and gene expression."

Unless experimental evidence of biologically-based cause and effect suggests that an evolutionary event led to what obviously are RNA-mediated events in honeybees and humans, those who report their data as if gene assemblies and boundaries change via *EVOLUTION* stand to be corrected each time someone accurately represents cause and effect in the context of RNA-mediated events.

See also: Combating Evolution to Fight Disease and Starvation-Induced Transgenerational Inheritance of Small RNAs in C. elegans and Uncovering the Hidden Risk Architecture of the Schizophrenias: Confirmation in Three Independent Genome-Wide Association Studies

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