WHAT'S HOT IN... BIOLOGY , Jul/Aug 2009

Just Below a "Steady-State" Top Ten, a Trio Awaits

by Jeremy Cherfas

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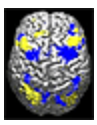
Can biology really have reached some sort of steady state? A glance across at the current What's Hot suggests maybe it has; not a single new entry in the lists. A couple are reappearing, having dropped out, but every paper has been here before. Things are not, however, standing still. Outside the Top Ten is a trio of papers that depends on the very papers which, because they remain so highly cited, are blocking access to the Top Ten.

Autism, type 1 diabetes, and breast cancer are just three of the diseases whose prevalence and complexity have by turns attracted and baffled researchers, and there they all are, revealing hitherto unimaginable details of their genetic links thanks to the new tools of molecular biology.

At #14, Jonathan Sebat and Michael Wigler, of the Cold Spring Harbor Laboratory, lead a team that has uncovered, for the first time, a genetic basis for autism (J. Sebat, *et al.*, *Science*, 316[5823]: 445-9, 20 April 2007; 34 citations this period, 110 overall). A genetic component has long been suspected; if one of a pair of identical twins is affected, there is a 70% chance the other will be too, almost 10 times the risk factor for non-identical twins and full siblings. And yet the actual mutations—or even links to specific genetic regions—have been very hard to pin down. Previous studies have implicated parts of 20 different chromosomes. The new paper indicates why. Rather than being



Biology Top Ten Papers

Rank	Papers	Cites Jan-Feb 09	Rank Nov-Dec 08
1	Intl. HapMap Consortium (K.A. Frazer, *et al.*), "A second generation human haplotype map of over 3.1 million SNPs," *Nature*, 449(7164): 854-61, 18 October 2007. [72 institutions worldwide] *221LY	83	3
2	K. Takahashi, *et al.*, "Induction of pluripotent stem cells from adult human fibroblasts by defined factors," *Cell*, 131(5): 861-72, 30 November 2007. [Kyoto U., Japan; CREST, Kawaguchi, Japan; Gladstone Inst. Cardio. Dis., San Francisco, CA] *243MG	76	†
3	A. Barski, *et al.*, "High-resolution profiling of histone methylations in the human genome," *Cell*, 129(4): 823-37, 18 May 2007. [NHLBI, NIH, Bethesda, MD; U. Calif., Los Angeles] *172FA	54	4
4	D.F. Easton, *et al.*, "Genome-wide association study identifies novel breast cancer susceptibility loci," *Nature*, 447 (7148): 1087-93, 28 June 2007. [87 institutions worldwide] *183HT	54	†

associated with particular genes, autism seems to be linked with copy number variations that are not present in the patient's parents.

The study depended on performing whole-genome scans on parents and their children, affected and unaffected, from 264 families, an unthinkable effort just a few years ago. With complex procedures for ensuring that observed mutations were indeed novel and not present in either parent, mutations, generally quite large deletions, were found to be present in 10% of patients with no affected relatives, certainly an underestimate. They were also widely spread across the genome, sometimes involving a single gene and sometimes several genes.

While these results are a far cry from understanding the genetic basis of autism or the mechanisms leading to the many variants of the condition, they do indicate that damage at several different sites can contribute to the syndrome. And they suggest differences between sporadic, or simplex, autism, in which no other family members are involved, and which is associated with *de novo* copy number variations, and multiplex autism, where more than one sibling is affected and which show much lower frequency of new mutations.

5	V. Cherezov, *et al.*, "High-resolution crystal structure of an engineered human ß$_2$-adrenergic G protein-coupled receptor," *Science*, 318(5854): 1258-65, 23 November 2007. [Scripps Res. Inst., La Jolla, CA; Stanford U., CA] *233JG	44	5
6	M. Wernig, *et al.*, "*In vitro* reprogramming of fibroblasts into a pluripotent ES-cell-like state," *Nature*, 448(7151): 318-24, 19 July 2007. [5 U.S. institutions] *191GC	41	6
7	T.S. Mikkelsen, *et al.*, "Genome-wide maps of chromatin state in pluripotent and lineage-committed cells," *Nature*, 448 (7153): 553-60, 2 August 2007. [6 U.S. institutions] *195XV	40	8
8	T. Korn, *et al.*, "IL-21 initiates an alternative pathway to induce proinflammatory T_H17 cells," *Nature*, 448(7152): 484-7, 26 July 2007. [Harvard Med. Sch., Boston, MA] *193VG	39	†
9	K. Okita, T. Ichisaka, S. Yamanaka, "Generation of germline-competent induced pluripotent stem cells," *Nature*, 448(7151): 313-7, 19 July 2007. [Kyoto U., Japan; Japan Sci. Tech. Agency, Kawaguchi] *191GC	38	7
10	Landgraf, *et al.*, "A mammalian microRNA expression atlas based on small RNA library sequencing," *Cell*, 129(7): 1401-14, 29 June 2007. [27 institutions worldwide] *188HQ	38	†

SOURCE: Thomson Reuters Hot Papers Database. Read the Legend.

The power of genomic analysis is further revealed in the paper at #15 (J. Todd, *et al.*, *Nature Genetics*, 39[7]: 857-64, July 2007; 33 citations this period, 162 overall), in which a team led by John Todd, director of the Juvenile Diabetes Research Foundation of the Wellcome Trust in Cambridge, England, has identified four chromosome regions associated with type 1 diabetes (T1D). This paper is in a sense the pin-up for a series of studies that emerged from the Wellcome Trust Case Control Consortium's publication of "A genome wide association study of 14,000 cases of seven common diseases and 3,000 shared controls," (*Nature*, 447[7145]: 661-78, 2007). The genome wide association study (GWAS) used the HapMap to identify links with common diseases. Todd's group went further, to screen the links and ensure that they truly are associated with T1D.

The big problem is statistical. If you are looking at 500,000 different potential sites that could be linked to the disease in question, five are going to be statistically highly associated just by chance. Todd's group used a range of techniques to narrow the field from twelve potential links to just four, adding a fifth from another GWAS. As the authors note, "[t]his study increases the number of T1D loci from six to at least ten." More than that, it rules out eight loci that might well have been a waste of time.

The final paper, at #16, conducts a GWAS for sporadic postmenopausal breast cancer (D.J. Hunter, *et al.*, *Nature Genetics*, 39[7]: 870-4, July 2007; 33 citations this period, 161 overall). This is the late-onset version of breast cancer, which usually affects women with no family history of the disease. Not surprisingly, it has been much harder to identify genetic factors. David Hunter, of Harvard Medical School, and his team identified four mutations, all affecting a "tumor-supressor" receptor gene that is often overexpressed in breast cancer. As with the diabetes study, the results are important also because they rule out four mutations that were false positives.

Three diseases, three papers, all taking advantage of the phenomenal power of modern molecular biology

and statistical techniques to offer improved targets for therapeutic research. If this is the steady state, long may it continue.

Dr. Jeremy Cherfas is Science Writer at Bioversity International in Rome, Italy.

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