WHAT'S HOT IN... BIOLOGY , September/October 2009

Two Studies Clarify the Genetic Disruptions in Schizophrenia

by Jeremy Cherfas

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Schizophrenia typically afflicts around 1% of the general population, and although it runs in families, the inheritance pattern, like the illness itself, is complex. Early claims to have identified a schizophrenia gene were fraught with difficulties of interpretation and replicability. Now, two recent papers shed light on why a schizophrenia gene has proved so elusive and, more importantly, on the true genetic basis of the disease.

Large teams, one led by Jon McClellan at the University of Washington in Seattle (paper #7) and the other by David St Clair of the University of Aberdeen in Scotland and Kari Stefansson of deCODE genetics in Iceland (H. Stefansson, *et al.*, *Nature*, 455[7210]: 232-7, 2008; currently ranked at #14, with 32 citations this period and 58 total), have shown that copy number variants (CNVs)—relatively large deletions and duplications that may disrupt the functioning of several genes—are common in patients with schizophrenia but not in their unaffected relatives or non-sufferers. McClellan's group started by comparing schizophrenics with controls, while the others looked for new mutations and then asked whether they were more prevalent in schizophrenics.

The Washington group scanned the DNA of 418 people—150 of whom had been

Biology Top Ten Papers

Rank	Papers	Cites Mar-Apr 09	Rank Jan-Feb 09
1	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	88	2
2	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	62	1
3	The ENCODE Project Consortium (E. Birney, *et al.*), "Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project," *Nature*, 447(7146): 799-816, 14 June 2007. [80 institutions worldwide] *178FV	55	†
4	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

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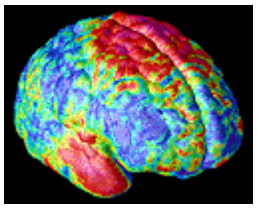

Mapping brain tissue loss in adolescents with schizophrenia. This map reveals the 3-dimensional profile of gray matter loss in the brains of teenagers with early-onset schizophr enia

Image by Paul Thompson, Christine Vidal, Judy Rapoport, and Arthur Toga.

diagnosed with schizophrenia or similar psychiatric illnesses—using the increasingly powerful and widespread tool of microarray analysis to look for variant DNA patterns associated with disease. (See also, for example, the discussion of autism and other conditions in the previous Biology Top Ten commentary, July-August 2009). Among the variants were 53 mutations that were by definition rare; they had not previously been reported in the literature. Not all of these variants changed the functioning of genes, of course, but of those that did, cases with schizophrenia were three times more likely to have one than unaffected controls. And cases that showed symptoms early, at less than 18 years of age, were four times more likely than controls to have a rare variant. Rare mutations that did not affect function were equally common in cases and controls.

5	V. Cherezov, *et al.*, "High-resolution crystal structure of an engineered human beta$_2$-adrenergic G protein-coupled receptor," *Science*, 318(5854): 1258-65, 23 November 2007. [Scripps Res. Inst., La Jolla, CA; Stanford U., CA] *233JG	40	5
6	E. Zeggini, *et al.*, "Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes," *Nature Genetics*, 40 (5): 638-45, May 2008. [5 U.S. and U.K. institutions] *293WS	39	†
7	T. Walsh, *et al.*, "Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia," *Science*, 320(5875): 539-43, 25 April 2008. [9 U.S. institutions] *292EM	39	†
8	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	38	4
9	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	37	6
10	J.A. Todd, *et al.*, "Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes," *Nature Genetics*, 39 (7): 857-64, July 2007. [7 institutions worldwide] *184CX	35	†

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The group went on to look for the rare variants in an independent group of severely affected cases with childhood onset schizophrenia, comparing their DNA with that of their parents. The same pattern emerged.

St Clair and Stefansson's team reasoned that the reduced fecundity associated with severe mental illness is continually selecting against the underlying mutations, which is why the variants are rare. So they screened almost 10,000 trios (two parents and a child) and parent-child pairs, looking for CNVs present in children but not their parents. This picked up 66 novel variants, which were then sought in 1,433 schizophrenia cases and 33,250 unrelated controls. Eight of the 66 were found in at least one schizophrenia patient, and three were statistically associated with the disease. Six other sets of patients and controls showed essentially similar results. The three mutations are between 2.5 and 10 times more common in cases than controls.

What of the genes that these mutations disrupt? The Washington group asked whether particular functional classes of genes were over-represented in the sample. The affected genes in schizophrenia cases did indeed over-represent pathways that are clearly important for brain development, including systems that regulate the growth of nerve axons and others related to specific neurotransmitters. By contrast, genes disrupted in the controls were not from any particular functional pathways.

The St Clair and deCODE group also examined the specific genes in the CNVs that they identified, and came up with very similar results. One deletion contains a gene associated with outgrowths that connect

nerves and is also important in the maintenance of neuronal structures. Another deletion contains a gene associated with working memory.

One of the fascinating aspects of the studies is that the symptoms associated with the rare CNVs are not limited to those associated with schizophrenia, even though that was the target illness. For example, in the deCODE study one of the controls who carried a deletion was autistic but not schizophrenic, and others showed dyslexia.

This opens the prospect of a much more nuanced approach to mental disorders with a genomic component. As the University of Washington group reported, "Our design does not prove the involvement with the illness of any specific variant or even the involvement of any specific gene." It does, however, dispel any simplistic notion of a gene "for" schizophrenia or any other complex mental illness. The CNVs identified in both studies, exciting though they are, do not account for a very large fraction of the genetic risk of schizophrenia. There must be many other factors involved.

Both studies also, in a roundabout way, illustrate the robustness of the development of the brain. Disruptions are indeed associated with illness. But many individuals harbor these variants and yet show no signs of abnormal function. There's obviously a lot we still have to learn.

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