Five New Schizophrenia Loci May Converge on the Same Cellular Mechanism: The AKT Pathway

To the Editor: The complexity of schizophrenia genetics raises new questions regarding the biological plausibility of findings from association studies (1). Is there a shared cellular mechanism for the diverse proteins encoded by the dozens of "schizophrenia genes"? The Schizophrenia Psychiatric Genome-Wide Association Study Consortium reported significant associations for five new gene loci (2). Here, we show that these loci are all associated with the neuregulin-1-induced activation of the phosphatidylinositol 3-kinase/protein kinase B/AKT1 intracellular system, which is an important convergence point for several putative factors of psychotic disorders including biogenic amines, synaptic proteins, and growth factors (3, 4). Decreased AKT1 protein levels and phosphorylation have been documented in lymphocytes and brains of individuals with schizophrenia (4–6). We genotyped 115 healthy volunteers for the following five loci: *MIR137*, *PCGEM1*, *CSMD1*, *MMP16* (also associated with cancer), and *CNNM2* (a metal ion carrier) (2). The AKT1 pathway, similarly to four of the five loci, is implicated in cell proliferation and differentiation. AKT1 activation was determined from peripheral lymphoblasts by using an immunoblot assay (5, 6). We also studied the extracellular signal-regulated kinase kinase (MEK-) extracellular signal-regulated kinase (ERK) pathway. Results revealed that the ratio of phosphorylated AKT1 (Ser473; 60 kDa) to total AKT1 was lower in risk-allele carriers (mean ratio averaged across the five foci, 0.21) relative to noncarriers (mean ratio, 0.39). This result was evident for all five foci ($p<0.001$ in all cases; Table 1). We did not observe similar changes in the case of ERK ratios. Our findings raise the possibility that the complex array of proteins encoded by "schizophrenia genes" converge on common intracellular molecular pathways that convert information from the environment to the biological system.

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TABLE 1. AKT and Extracellular Signal-Regulated Kinase (ERK) Activation Relative to the Risk Alleles of Five New Schizophrenia Loci[a]

Gene	Chromosome	Single-Nucleotide Polymorphism	Alleles	N (Risk)	Risk-Allele Carriers pAKT/AKT Mean	Risk-Allele Carriers pAKT/AKT SD	Noncarriers pAKT/AKT Mean	Noncarriers pAKT/AKT SD	Mann-Whitney Test (AKT Ratio) Z	Mann-Whitney Test (AKT Ratio) p	Risk-Allele Carriers pERK/ERK Mean	Risk-Allele Carriers pERK/ERK SD	Noncarriers pERK/ERK Mean	Noncarriers pERK/ERK SD
MIR137	1p21.3	rs1625579	TG	95	0.22	0.15	0.45	0.11	–5.45	<0.0001	0.38	0.19	0.37	0.17
PCGEM1	2q32.3	rs17662626	AG	105	0.27	0.13	0.53	0.17	–3.37	0.0001	0.41	0.12	0.43	0.16
CSMD1	8p23.2	rs10503253	AC	69	0.26	0.14	0.36	0.14	–3.41	0.0007	0.40	0.14	0.44	0.14
MMP16	8q21.3	rs7004633	GA	18	0.14	0.15	0.32	0.14	–3.94	0.0001	0.36	0.13	0.36	0.11
CNNM2	10q24.32	rs7914558	GA	19	0.16	0.15	0.29	0.13	–3.39	0.0007	0.37	0.19	0.35	0.12

[a] The table shows data from 115 healthy volunteers of Central-Eastern European descent with a negative family history for schizophrenia and major mood disorders (mean age=45.6 years, SD=8.7; mean education=12.4 years, SD=4.8; 57 female participants). Genotyping was performed using a TaqMan assay (Applied Biosystems, Foster City, Calif.; duplicate run, error rates <2%; no deviation from the Hardy-Weinberg equilibrium). In alleles, the first one is the risk allele from stage 1 of the genome-wide association study (1). "N (Risk)" refers to the number of participants with the risk allele. Means and standard deviations for the ratios of neuregulin-1-induced phosphorylated AKT and ERK (pAKT and pERK) and total AKT and ERK are shown in the case of risk-allele carriers and noncarriers. Groups were compared with Mann-Whitney U tests. In the case of pERK/ERK ratios, risk-allele carriers and noncarriers did not differ ($p>0.5$ in all cases).