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Presentation Abstract

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Abstract: In polygenic traits and diseases, such as schizophrenia (SCZ), individual genetic loci account for only a very small portion of the phenotypic variance. Therefore, in addition to increasing the sample size, a key to improved yield from SCZ genome-wide association studies (GWAS) is the application of refined statistical methods, providing greater power for detection of small genetic effects, for a given sample size. To this end, we have recently developed a novel statistical methodology that improves power for gene discovery in GWAS by using a priori information about relative “enrichment” of statistical association based on genomic annotations (1). Application of this approach to summary statistics from the published Psychiatric Genomics Consortium SCZ GWAS indicated approximately three-fold increase in gene discovery over standard methods. The analysis revealed gene loci spanning multiple biological themes including numerous receptors for neurotransmitters and

ion channels. Each gene has been discovered individually and independently of its function. The presence of hits across different neurotransmitter systems and channels for various ions begs the question of whether these hits reflect independent mechanisms, or are tied together through common biological pathways and functions. To address this question, we have examined the identified gene loci for the presence of putative elements of previously described “neurotransmitter integration network” (2). Our results show that many of these genes indeed are mapped onto a common network, where the signaling cascades triggered by activation of GPCRs can modulate ion channels and ionotropic receptors. This may be achieved by activation of the intracellular kinases and phosphatases ensuring the appropriate level of excitability, and thus neuronal output, given the intensity and modality of the input. Taken together, the spectrum of molecular risk factors identified in our study supports the concept of SCZ as an “associative” disorder: a breakdown in the communication across different slow and fast neurotransmitter systems through intracellular signaling pathways. This emergent model may unify a number of currently competing hypotheses, e.g., Dopaminergic, Glutamatergic, Calcium and (a more general) Second Messenger Hypothesis and explain why effective antipsychotic drugs have a “rich pharmacology”, i.e. affinity for several receptors. 1. Schork AJ, et al. (2013). PLoS genetics 9(4):e1003449. 2. Greengard P (2001). Science 294(5544):1024-1030.

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