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***RELN* rs7341475 and schizophrenia risk: confusing, yet somehow intriguing**

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The Reelin gene (*RELN*) is one of the more extensively examined schizophrenia candidate genes. Several lines of evidence have implicated the gene in etiology of the disorder, in particular the crucial role of the encoded glycoprotein in neurodevelopment (1), and the abnormalities in *RELN* methylation and expression that have been observed in some (2,3) but not all (4,5) patient populations. Further compelling support came from a recent genome-wide association study (GWAS) (6), which identified rs7341475G, a common variant in the fourth intron of *RELN*, as a female-specific risk factor for schizophrenia.

The finding has sparked considerable interest in the sex-specific genetic architecture of schizophrenia (7), and encouraged GWAS approaches with larger sample sizes and presumably higher statistical power. Subsequent reports, however, have dampened the initial enthusiasm (8), in particular a large meta-analysis (9) that included more than 30,000 individuals of different ethnicities. The study suggested, if anything, a disease association of much smaller effect size with significances well below current genome-wide accepted levels. These data were complemented by our own findings in Caucasian individuals of European ancestry (10), which did not provide any evidence for effects of rs7341475 on a broad array of intermediate phenotype measures linked to schizophrenia, further casting doubt on the pathogenetic significance of this locus. Curiously, however, positive findings continue to emerge, as demonstrated by the correspondence of Greenbaum and coworkers in this issue of *Biological Psychiatry*. The authors report significant effects of rs7341475 on prepulse inhibition, a potential intermediate phenotype measure of illness-related deficits thought to involve sensory gating, in a smaller cohort of Ashkenazi Jewish subjects.

Considered in their entirety, these data support a variety of interpretations, ranging from an unconvincing disease association to a hyper-complex genetic risk architecture. We tend to favor the latter hypothesis, as, on closer look, some consistency seems to emerge from this puzzling field of psychiatric genetics. Specifically, while prior association studies provide conflicting evidence on the pathogenetic relevance of rs7341475 in Caucasian populations (6,8–10), and seem to argue against a major impact of the variant in Han Chinese (6,9), fairly consistent associations with schizophrenia spectrum disorders have been observed in

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females of Ashkenazi Jewish descent (6,9,11,12). This raises the possibility that effects of population heterogeneity may contribute to these divergent findings (13).

In recent years, it has become increasingly evident that complex disease phenotypes (e.g., myocardial infarction) may be modulated by an ethnicity-specific constellation of susceptibility factors, a circumstance that complicates the dissection of their genetic underpinnings (14,15). If similar effects were true for *RELN* and schizophrenia risk, for example, through ethnically defined variations in haplotype composition or epistasis patterns (13,16), inconsistent findings and a “dilution” of population-specific outcomes in large multi-ethnic association studies would be expected. In this context, the behavioral work by Greenbaum et al. adds valuable information to the field, as it extends existing evidence for a role of rs7341475 in Ashkenazi Jewish populations and complements our own prior neuroimaging genetics findings in Caucasian individuals of European ancestry (10). While replications in larger samples are warranted, and the lack of a sex-specific association requires clarification, these data invite further research on potential ethnicity-specific effects of rs7341475 in brain circuits relevant to psychiatric disease.

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