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Letter to the Editor

Case-control investigations of a *DRD2* missense variant in Asian populations: more noise, less signal

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Dear Editor,

I have read with interest the recent report by Liu et al. (2012) on risk-enhancing effects of a DRD2 missense variant with regard to schizophrenia in Asian populations. In their article, the authors summarize evidence from 16 case-control investigations in Japanese, Chinese, and Indian populations and concluded to significant effects on disease susceptibility. Multiple flaws, however, cast doubt on the validity of this claim. Genotype distributions have been incorrectly transcribed for numerous studies, e.g., for Itokawa et al. (1993), Hattori et al. (1994), Nanko et al. (1994), Arinami et al. (1994, 1996), and Chen et al. (1996). For other studies, allele frequency data do not match genotype data (e.g., Hori et al., 2001). It appears that the authors did not consult the original papers but relied on citations instead, which led to a carry-over of errors (e.g., incorrect genotypes given by Harano, 1997, for the studies by Nanko et al., 1994; Arinami et al., 1994). By their own exclusion criteria, the authors should have dropped studies that lack adequate information on genotypes for rs1801028 (see, e.g., Arinami et al., 1996; Hori et al., 2001; Morimoto et al., 2002). Intriguingly, genotype data of unknown origin were used to make up for these gaps and for calculations of pooled effects. Other studies that qualify by the inclusion criteria given were excluded for reasons not specified (e.g., Iwata et al., 2003; Vijayan et al., 2007; Srivastava et al., 2010). In contrast to the

authors' statement, violation of the Hardy-Weinberg equilibrium in controls did not lead to the exclusion of studies (see Hattori et al., 1994), and studies that confused major and minor alleles were also included despite earlier alerts (see the comment by Sand, 2007, on the study by Ohara et al., 1996). Whether or not letters should be considered unsound as a source of information for meta-analysis is certainly disputable. The length of a scientific report does not correlate with its quality as long as peer review is provided. However, once an exclusion criterion is defined, the authors should stand by it. This implies that the letter by Nanko et al. (1994) should have been dropped. Finally, methodologies for genotyping in Table 1 are in error for several of the studies that were referenced, e.g., Harano (1997) used allele-specific PCR, Gupta et al. (2009) used MALDI-TOF, and Fan et al. (2010) used Sanger sequencing.

The abundance of artefacts and arbitrary calculations rationalize the growing concerns over false-positive association claims (Macarthur, 2012). Ironically, Liu et al. (2012) themselves assigned a "quality score" to the studies they used, ranging from 18 to 26 points; but this score and the criteria used for grading remain entirely cryptic. While the idea behind this approach is laudable, the article does little to satisfy requirements of scientific quality.

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