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# Comment on “Genetically Determined Differences in Learning from Errors”

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Klein *et al.* (Reports, 7 December 2007, p. 1642) used individuals with a polymorphism adjacent to the dopamine receptor 2 gene as naturally occurring models for reduced brain dopamine receptor density in a probabilistic learning task. We raise the concern that this polymorphism resides in the gene for the kinase ANKK1, where it causes a nonconservative amino acid exchange.

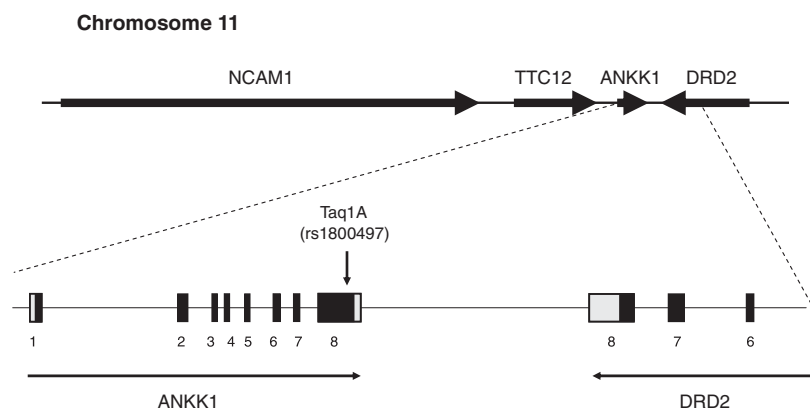
Klein *et al.* (1) reported an association between the dopamine receptor 2 gene (DRD2) TAQ-IA (rs1800497) polymorphism and a probabilistic learning task. To explain these results, they noted that reduced D2 receptor expression is associated with the TAQ-I A1 allele. Although these findings are intriguing, the causal reasoning deserves some cautionary notes. (i) The association of the TAQ-I A1 allele with receptor availability—a measure with con-

siderable variability—was not always replicated (2). Others reported that TAQ-I-A1 is associated with higher 3,4-dihydroxyphenylalanine uptake and increased decarboxylase activity, potentially resulting in higher dopamine levels antagonizing the lower receptor availability (3). (ii) The DRD2 gene is confined to a cluster of genes including neural cell adhesion molecule 1 (NCAM1); tetratricopeptide repeat protein 12 (TTC12), a potential scaffolding protein for multiprotein complexes; ankyrin repeat and protein kinase domain-containing protein 1 (ANKK1), a kinase presumably involved in cell signaling; and, finally, DRD2. Importantly, the TAQ-IA polymorphism is located 9489 base pairs downstream from the 3' end of DRD2, within the last exon of ANKK1, and causes a nonconservative amino

acid exchange (Glu<sup>713</sup>Lys) in a conserved ankyrin repeat (4, 5) (Fig. 1). The genetic block of the TAQ-IA polymorphism comprises portions of DRD2 and ANKK1. Dubertret *et al.* cloned ANKK1 from whole-brain RNA and reported transcript expression in adult and fetal brain, cerebellum, and spinal cord (5). (iii) In large part, the identification and characterization of DRD2-TAQ-IA results from numerous association studies on alcohol dependence with rather controversial results [reviewed in (6)]. Recent replication studies considering many variants in the NCAM1-TTC12-ANKK1-DRD2 region have provided evidence for stronger associations of polymorphisms located in TCC12 and ANKK1 with dependence than for those in DRD2 (6, 7). Indeed, there is good evidence for the contribution of the dopaminergic system to learning processes, as shown in a recent study of Parkinson's patients on and off dopaminergic treatment (8). However, the idea that signaling components—as suggested for ANKK1 and TCC12—also contribute to neural function and, ultimately, to learning, is also plausible. A refined genetic analysis that includes polymorphisms in TCC12 and ANKK1, as well as other functional DRD2 variants, could help to resolve this issue. The DRD2 C957T variant (rs6277) is one such polymorphism located within the DRD2 gene that has been associated with D2 receptor density and negative feedback learning (9). Pharmacological approaches and single-photon computerized tomography studies could further corroborate the findings by Klein *et al.* (1). In the absence of such data and in light of the complexities of this genetic locus, we suggest caution when considering the straightforward reasoning tightly linking TAQ-IA variants, dopamine receptor 2 expression, and the observed neuropsychological phenotype.

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**Fig. 1. (Top)** Genetic locus comprising the genes for NCAM1, TTC12, ANKK1, and DRD2 on human chromosome 11. **(Bottom)** Enlarged illustration for ANKK1 and part of DRD2. Arrows refer to the transcriptional orientation of these genes. Numbers indicate exons, black boxes coding exons, gray boxes nontranslated parts of these exons. TAQ-IA refers to the localization of this polymorphism in the last exon of ANKK1 within the coding sequence.

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18 January 2008; accepted 13 June 2008  
10.1126/science.1155372