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Reply to Kock et al.

To the Editor:

In their study, Kock et al. (2002 [in this issue]) investigated two families from South Tyrol, to test for linkage with a restless legs syndrome (RLS)–susceptibility locus, on chromosome 12q, that was recently identified by our group (Desautels et al. 2001). They genotyped a total of 51 subjects by use of four markers spanning a 17-cM interval on the candidate region. Assuming both a dominant and a recessive mode of inheritance, Kock et al. failed to replicate our reported linkage on chromosome 12q in the families that they studied. In addition, aiming to reproduce our original results, they subsequently analyzed the same family that we studied by use of our marker data and the published recessive model, assuming a phenocopy rate of 80%. Being unable to replicate our findings by use of our own material, Kock et al. have raised some concerns regarding the recessive model described in our article.

Unfortunately, the published version of our original article reporting linkage between RLS and a locus on chromosome 12q (Desautels et al. 2001) contained an error. Indeed, the information presented for the penetrance values and phenocopy rates in the published table (p. 1267) does not correspond to the values used in our analyses. The genetic models used by our group were based on realistic assumptions, which are listed below, in the rectified version of the table (table 1; for the recessive model, the disease-allele frequency was set at 0.25 with a reduced penetrance of 0.8 and an estimated phenocopy rate of 0.005). The error involves only the presentation of the table, not the parametric analyses per se. Therefore, this will clarify the issue pertaining to our model raised by Kock et al., since their criticisms were based on misinterpretations induced by this unfortunate error.

Table 1

Genetic Models Used in the Parametric Analysis

Model of Inheritance	Allele Frequency		Penetrance		
	p	q	f_1	f_2	f_0
Dominant 1	.99	.01	.9	.9	0
Dominant 2	.95	.05	.5	.5	.005
Recessive	.75	.25	.8	.005	.005

NOTE.—θ Between males and females was considered to be equal.

The nonreplication of our positive linkage in two South Tyrolean families' results raises the hypothesis that genetic heterogeneity is present. Accordingly, since the publication of the original study, additional families have been recruited and investigated for the candidate interval. Although linkage to chromosome 12q has been confirmed in some kindreds, our analyses indicate that a number of families are definitely not linked to this region, further supporting the heterogeneity hypothesis (A. Desautels, G. Turecki, J. Montplaisir, A. S. Walters, B. L. Ehrenberg, K. Brisebois, A. K. Desautels, W. G. Johnson, E. Lugaresi, G. Coccagna, D. L. Picchietti, A. Lazzarini, Y. Gingras, and G. A. Rouleau, unpublished data). Taken together, these data suggest that other putative loci, besides the locus on chromosome 12q that has recently been identified by our group, could be involved in the etiology of this common sleep disorder.

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