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Reply to Ogino and Wilson

To the Editor:

Drs. Ogino and Wilson (2002 [in this issue]) raised some issues regarding our paper on quantitative testing of *SMN1* and *SMN2* in spinal muscular atrophy (SMA) (Feldkötter et al. 2002). First, they raised some ethical issues regarding the testing of unaffected children for SMA. We are also aware of the controversial aspects of such testing and, in general, agree with Drs. Ogino and Wilson: the identification, at birth, of homozygous absence of *SMN1* in children, followed by the quantitative analysis of *SMN2,* should be offered as a prognostic tool only when a therapy for SMA is available. In this case, a newborn screening (similar to that in phenylketonuria) could—and possibly should—be considered. Since several drugs that up-regulate full-length *SMN2* have been found (Andreassi et al. 2001; Chang et al. 2001) and since the identification of many more is in progress, the development of a therapy for SMA seems likely to become a reality in the near future. Therefore, the development of a highly sensitive and fast method to determine the number of *SMN2* copies will be an essential prerequisite before starting a therapy. Furthermore, the identification, immediately after birth, of children who carry homozygous absence of *SMN1* will be equally essential, to start the therapy before the motor neurons are degenerated. On the basis of the number of *SMN2* copies, the dosage and starting-point of a therapy may significantly vary.

Since an efficient therapy has to be started early, we calculated the posterior probability that a child with an *SMN1* deletion would develop type I, type II, or type III SMA, under the assumption that the analysis is done immediately after birth. As a consequence, we have used a Bayesian-type analysis that is based on the odds ratios and a priori probabilities as chosen.

We reevaluated the sensitivity calculations, and we agree with Drs. Ogino and Wilson that the sensitivity of the test, for the detection of an SMA carrier from the general population without family history, is 95.9% (i.e., $1 - [0.024 + 0.017]$), since 2.4% of carriers have two *SMN1* copies per chromosome and 1.7% carry intragenic *SMN1* mutations. Therefore, there is a posterior probability of ~1:850 (i.e., $[4.1/100] \times [1/35]$) that a person from the general population who carries two *SMN1* copies is an SMA carrier. The carrier frequency of 1:35 is based on the results presented in our previous article (Feldkötter et al. 2002). The sensitivity of the test for the detection of an SMA carrier from a family with an affected patient who carries a homozygous absence of *SMN1* is 97.6% (i.e., $1 - 0.024$).

With reference to the primers designed to detect either *SMN1* or *SMN2,* the test is based on two nucleotide differences in exon 7 and in intron 7 (position +100). This implies that converted *SMN* genes may amplify with a decreased efficiency. At this point, it is important to mention that, in the large majority (42/44 [~95%]) of converted *SMN* genes, the complete gene, except for the region containing the nucleotide difference in exon 8, is converted (Hahnen et al. 1996). This means that, for most converted *SMN* genes, the two primers that we have applied lie in either *SMN1* or *SMN2* only and will not hamper the efficiency of the PCR. Additionally, the analysis of 20 patients with only homozygous absence of *SMN1* exon 7 showed identical number of *SMN2* copies analyzed with both methods—multiplex competitive PCR (Wirth et al. 1999) and LightCycler PCR (Feldkötter et al. 2002). Nevertheless, the efficiency of the PCR may be reduced for those rarely observed *SMN*

genes in which the breakpoint lies between the two primers used in the LightCycler PCR.

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The Power of Multivariate Quantitative-Trait Loci Linkage Analysis Is Influenced by the Correlation between Variables

To the Editor:

In a recent article, Sham et al. (2000) investigated the power of variance-components linkage analysis by deriving an analytic expression for the noncentrality parameter (NCP) of the linkage test. The authors demonstrated that the NCP—and, hence, the power of the test to detect linkage—was determined primarily by the square of the additive and dominance genetic components of variance due to the quantitative-trait locus (QTL) and by the residual correlation between siblings. However, Sham et al. presented calculations for the univariate case only. Recently, it has been demonstrated that the power of QTL linkage analysis may be increased by use of multivariate techniques that analyze the pleiotropic action of the QTL on several variables (Boomsma 1996; Martin et al. 1997). In particular, the power of multivariate linkage analysis is strongly influenced by the correlation between the variables, being greatest when the QTL induces covariation between the variables in the direction opposite to the residual correlation (Allison et al. 1998; Amos et al. 2001). Here, I follow the methodology of Sham et al., to demonstrate analytically, for the first time, how the power of a bivariate variance-components linkage analysis depends not only on the magnitude and direction of the correlation between variables but also on the source of this correlation.

The relationship between two observable variables is parameterized in terms of the path model displayed in figure 1. Observed variables for each sib pair (*square boxes*) are due to the combined action of several latent variables (*circles*), including a pleiotropic QTL (Q), poly-

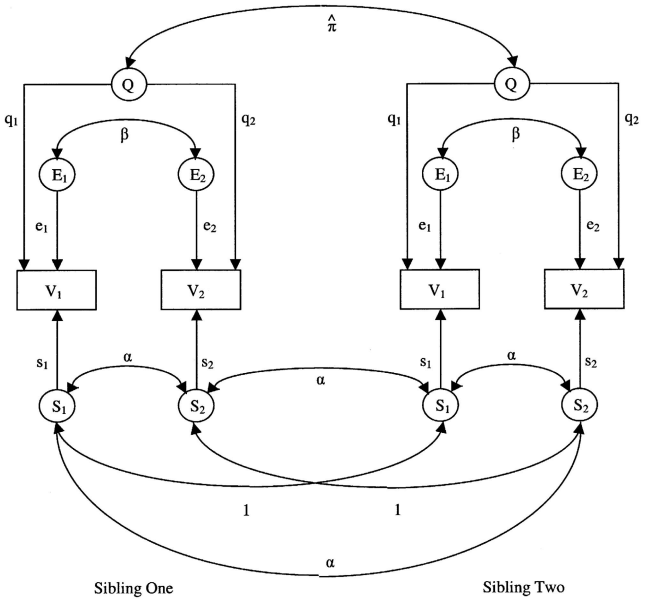

Figure 1 Path diagram showing the relationship between two observed variables (V_1 and V_2) for a pair of siblings. Covariation between the phenotypes is due to the QTL (Q), genetic and environmental sources that are shared among siblings (S_1 and S_2), and nonshared sources of variation (E_1 and E_2).