parently, the A→C substitution is more common in the normal Mediterranean population. We had missed this because of the error in the study by Figus et al. (1995), as is noted in the letter by Loudianos et al. (1998 [in this issue]). Promoter studies are currently in progress to determine the nature of the mutations reported by us.

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Reply to Burghes

To the Editor:

In his recent editorial entitled "When Is a Deletion Not a Deletion? When It Is Converted" Burghes (1997) correctly ascribes the cause of spinal muscular atrophy (SMA) to the loss or mutation of the telomeric copy of the *SMN* (survival motor neuron) gene. The reduction in SMN protein, as Burghes recognizes, most likely leads to motor-neuron death, by unknown mechanisms (Coovert et al. 1997; Lefebvre et al. 1997). He also outlines the probable role of centromeric copies of SMN in the modulation of disease severity (Campbell et al. 1997; Velasco et al. 1996; McAndrew et al. 1997). However, concerning a second SMA candidate gene, known as *NAIP* (neuronal apoptosis–inhibitory protein), Burghes states that "it appears likely that the deletion of *NAIP* marks the extent of the [genomic] deletion and that different forms of SMN_{cen} modify the SMA phenotype," thereby rejecting a role for *NAIP* in SMA pathogenesis.

On this final point we strongly disagree. During the past 2 years, our group, our collaborators, and other laboratories have shown that NAIP could be involved in SMA pathogenesis in several ways. First, in most populations the *NAIP* gene is deleted in the majority of type I SMA individuals. In some type I SMA populations, the deletion of SMN_{tel} extends to *NAIP* in >80% of affected chromosomes (Morrison 1996; Samilchuk et al. 1996; Velasco et al. 1996). Second, in the CNS, NAIP is expressed in at least eight distinct neuronal populations, including the motor neurons, all of which are affected in type I SMA (Towfighi et al. 1985; Murayama et al. 1991; Peress et al. 1986; Xu et al. 1997*b*). A number of NAIP-positive neuronal types (e.g., cholinergic neurons of the striatum), when subjected to ischemia, demonstrate both a significant increase in NAIP levels (Xu et al. 1997*a*) as well as a marked resistance to apoptotic death. Third, NAIP exerts an antiapoptotic effect in cultured cells (Liston et al. 1996) and affords hippocampal neuroprotection in vivo when overexpressed from a transgene (Xu et al. 1997*a*).

In view of these data, we find the assertion surprising that the *NAIP* gene serves merely as a marker of genomic-DNA deletion size. Clearly, formal proof of NAIP involvement in SMA pathogenesis must await further analysis (e.g., exacerbation of an SMA phenotype in SMN-deficient mice when expression of NAIP is compromised). However, we feel that it is likely that motor neurons from SMA individuals with deletions of both *NAIP* and SMN_{tel} are prone to apoptosis. As a result, the cells are less able to withstand the stress of SMN depletion and die earlier than they would otherwise, resulting in a more severe form of SMA.

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Reply to Mackenzie

To the Editor:

MacKenzie suggests that, in my editorial "When Is a Deletion Not a Deletion? When It Is Converted" (Burghes 1997), I have not ascribed sufficient significance to the role of the neuronal apoptosis inhibitory protein (NAIP) gene in spinal muscular atrophy (SMA). In particular, MacKenzie takes issue with the following statement: "Further work is required to clearly define the mechanism by which the converted alleles modify phenotype, and it is possible that deletion of adjacent genes, such as NAIP, could influence the exact severity of the phenotype. However, it appears most likely that the deletion of NAIP marks the extent of the deletion and that different forms of SMN^C modify the SMA phenotype" (Burghes 1997, p. 13).

It is my opinion that this is a fair reflection of our current knowledge of the situation and that, at present, there is not adequate evidence to implicate NAIP as a major SMA-modifying gene. The first and foremost argument against involvement of NAIP comes from genetic studies. MacKenzie indicates that, in some type I SMA populations, the rate of NAIP deletion approaches 80%. However, in most cases in which a noninbred population has been studied, the rate of NAIP deletion in type I SMAs is 45%–50% (Cobben et al. 1995; Hahnen et al. 1995; Roy et al. 1995; Thompson et al. 1995; Velasaco et al. 1996; DiDonato et al 1997*b*). MacKenzie states that "we feel it likely that motor neurons from SMA individuals with deletions of both NAIP and SMN_{tel} are prone to apoptosis. As a result, the cells are less able to withstand the stress of SMN depletion and die earlier than they would otherwise, resulting in a more severe form of SMA." This would predict that the disease in those patients without a deletion of the NAIP gene would be mild, whereas the disease in those patients with a NAIP gene deletion would be severe. Patients with SMN^T intragenic mutations that still retain the NAIP gene would also be predicted to have a mild form of the disease. So a critical question is, Do the type I SMA cases without NAIP deletions show a clinical progression different from that seen in patients with an NAIP deletion? There is no clear difference between these two populations. In addition, type II/III SMA cases can have deletions of NAIP, as can carriers with no clinical phenotype (Cobben et al. 1995; Hahnen et al. 1995; Roy et al. 1995; Thompson et al. 1995; Rodrigues et al. 1996; Campbell et al. 1997; DiDonato et al. 1997*b*). Therefore, it does not always seem to be the case that motor neurons lacking NAIP are more sensitive to the loss of SMN^T. It could be argued that the type I SMA cases with an intact NAIP gene have another mutation, which is not detectable by current assays—and that they therefore are phenotypically equivalent—whereas type II/III SMA patients with a deletion of NAIP somehow make the NAIP protein in the motor neurons. This indicates two critical studies that are needed to substantiate NAIP as a major modifier of SMA. First, there must be detection of intragenic NAIP mutations in the type I SMA patients who have an intact NAIP gene. Second, there must be studies at the protein level that show reduction of the NAIP protein in motor neurons of type I SMA patients who do not have a deletion of the NAIP gene.