TAF1 as the Most Plausible Disease Gene for XDP/DYT3

To the Editor: We address the concerns of Dr. Müller and his colleagues[1(in this issue)] regarding our recent article in the *Journal*.[2] Previously, Müller et al. reported that five disease-specific single-nucleotide changes (DSCs) in a "multiple transcript system" (*MTS*) were associated with XDP (MIM #314250).[3] Our article was the first to report *TAF1* (MIM *313650) as the most plausible disease gene,[2] and it is regrettable that no one has succeeded in confirming *MTS* transcripts by any standard technologies, such as northern blot, to provide the information on length and abundance of the transcripts. Therefore, the term "*TAF1/DYT3* multiple transcript system" is ambiguous and misleading. *TAF1* and *MTS* are different genes that have distinct functions, although some alternative splicing exons of *TAF1* are shared with some *MTS* transcripts. In particular, we claim that the neuron-specific isoform of *TAF1* was discovered by us.[2]

The following are the responses to the points raised by Müller et al.[1]

1. As listed in our table 5, the splicing variant of *MTS* that includes exons 32′ and 34′ was never detected by our TaqMan assay.[2] Our results from long RT-PCR analysis consistently show that exons 3 and 4 may be just an additional part of the 3′ UTR of *TAF1,* rather than part of *MTS* (fig. 4*a*).[2]

2. As described in the figure legend, our figure 5*f* shows weak immunoreactivity of *TAF1* in neurons in the patient's caudate and glial cells in both tissues but never implies complete absence of *TAF1* in the patient's caudate.[2]

3. The possible mechanism between the epigenetic modification and the reduced neuron-specific expression of the *TAF1,* including the neuron-specific isoform that contains exon 34′, which we discovered, were described in the "Discussion" section of our article.[2]

4. The postmortem brain was immediately frozen after the patient's death, so the point raised about our postmortem sample seems to be excessively speculative.[2] However, we are ready for a confirmatory examination of other frozen specimens, to give credence to our findings.

5. We hypothesize that neuronal death depends on difference of local conditions in various brain tissues—for example, free radical production, calcium flux, local temperature, and dominant neurotransmitters, as illustrated for dopamine receptor D2 (*DRD2* [MIM *126450]) in figure 5*c*.[2]

For the family shown in the upper right of figure 3,[2] the picture scanned from the x-ray film was accidentally misaligned when the margin was trimmed. Our original x-ray film exactly shows the concordant signal with all other patients, as described in our article.[2] For the disease-specific SVA retrotransposon insertion, there is a striking discrepancy between the results from of our work[2] and the work reported by Nolte et al.[3] Nolte and colleagues stated that they sequenced 260 kb of the critical interval in a patient with XDP[3]; however, they did not find the insertion. We studied[2] the patients with XDP who had the same STR/DSCs haplotype as that of the patients examined by Nolte and colleagues.[3] It might be argued that the element was inserted only in the families we studied who carried no etiological significance in XDP. Nolte and colleagues claimed that they determined the genomic sequence beyond 260 kb by "cycle sequencing of overlapping PCR products,"[3(p10347)] without presenting any detailed information about the experimental conditions and without submitting their genomic sequence to any public database. Such a mutation search analysis requires the *completeness* of the sequence to justify its conclusion in the published work,[3] so readers such as us might interpret the sequence determined by Nolte and colleagues to be continuous and complete. It is, however, commonly believed that it is extremely difficult or almost impossible to determine such a large genomic sequence with use of the PCR-based sequence method, because of the complexity of the human genome and the well-known technical limitations, especially for long-range PCR. We ask Dr. Nolte and colleagues to submit their completed sequence to a public database, to strengthen the quality of their findings and to enable any researcher interested in this field to compare with our complete sequence (DNA Database of Japan accession number AB191243).

We hope that Dr. Müller and colleagues will succeed in determining the complete and accurate structure and abundance of *MTS* transcripts by means of various standard experiments, including northern blot, probe-hybridization screening of unbiased cDNA libraries, and TaqMan assay, and then present a hypothesis about what leads to the loss of striatal neurons by DSC3 on the *MTS* gene.

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Web Resources

The accession number and URLs for data presented herein are as follows:

DNA Database of Japan, http://www.ddbj.nig.ac.jp/Welcome-e.html (for the complete genomic sequence of the *DYT3* region [accession number AB191243])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for XDP, *TAF1,* and *DRD2*)

References

1. Müller U, Herzfeld T, Nolte D (2007) The *TAF1/DYT3* multiple transcript system in X-linked dystonia-parkinsonism. Am J Hum Genet 81:415–417 (in this issue)

2. Makino S, Kaji R, Ando S, Tomizawa M, Yasuno K, Goto S, Matsumoto S, Tabuena D, Maranon E, Dantes M, et al (2007) Reduced neuron-specific expression of the *TAF1* gene is associated with X-linked dystonia-parkinsonism. Am J Hum Genet 80:393–406
3. Nolte D, Niemann S, Müller U (2003) Specific sequence changes in multiple transcript system *DYT3* are associated with X-linked dystonia parkinsonism. Proc Natl Acad Sci USA 100: 10347–10352

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Am. J. Hum. Genet. 2007;81:417.

0002-9297/2007/8102-0025$15.00
DOI: 10.1086/519531