The *TAF1/DYT3* Multiple Transcript System in X-Linked Dystonia-Parkinsonism

To the Editor: The X-linked dystonia-parkinsonism syndrome (XDP or DYT3 [MIM #314250]) is a severe adult-onset movement disorder that originated by founder effect in the Philippine island of Panay.[1] The disease gene was identified in 2003 and was described as a "multiple transcript system." It is composed of several of the 38 known *TAF1* (TATA-box binding protein–associated factor 1) exons and an additional 5 of the then-unknown exons that lie 3′ of *TAF1* exon 38.[2] The latter five exons can either be spliced to known *TAF1* exons (variants 1 and 2) or be transcribed separately (variants 3 and 4). Five disease-specific single-nucleotide changes (DSCs) and a small deletion were detected within this transcript system. One of the DSCs (DSC3) is located in a transcribed exon. These findings have now been confirmed by Makino and coworkers in the March issue of the *Journal*.[3] Whereas, in the original study, the *DYT3* critical region was sequenced by PCR in a patient, Makino et al.[3] resequenced this region in BAC clones constructed from a patient's DNA. The resequencing confirmed the DSCs described elsewhere[2] and detected a previously unrecognized retrotransposon (SVA [SINE, VNTR, and *Alu*] element) in intron 32 of *TAF1* in close proximity to DSC10. Makino et al.[3] also confirmed the various splice variants of *TAF1* that were found earlier.[2] Furthermore, the study by Makino et al.[3] validates our use of several DSCs in the routine molecular genetic diagnosis of XDP.[4]

It is currently not known whether or to what extent the DSCs in *TAF1/DYT3* are involved in the disease process. Makino et al.[3] implicate the SVA retrotransposon in intron 32 of *TAF1* in the pathology of XDP. They present several findings supporting an important role for SVA in XDP. In particular, they provide evidence that the SVA affects expression of a transcript splice variant described elsewhere[2] that includes exon 34′ of *TAF1*. However, the data are not entirely convincing.

1. The article by Makino et al.[3] implies that there is only one splice variant of *TAF1* that includes exon 34′. This is not accurate. There are other splice variants of *TAF1* that also include exon 34′—for example, splice variants including exons 34′ and 32′ and splice variants including exons 34′, 3, and 4.[2]

2. Figure 5*a* in the work of Makino et al.[3] shows dramatic reduction of expression of an exon 34′–containing transcript but also demonstrates reduced expression of the common form of *TAF1* in a patient's caudate nucleus. Although antibodies were directed against TAF1 polypeptides (and not specifically against the exon 34′ isoform), their figure 5*f* implies complete absence of TAF1 in the patient's caudate. This cannot be explained by gliosis alone, since calcineurin antibodies definitely identified neurons in the patient's caudate (see their figure 5*f*).

3. Although hypermethylation was shown at CpG sites of SVA, a correlation between this epigenetic modification and the postulated specifically reduced expression of the exon 34′ transcript was not shown.

4. When postmortem brain is used for the quantitative ascertainment of gene expression, a high degree of variation has to be kept in mind. Apart from biological reasons, different postmortem times, storage conditions, etc. account for this variation. This might explain why transcript variant 34′ of *TAF1* is specifically reduced in some experiments but the common form of *TAF1* is also affected in others (their fig. 5*a* and 5*f*).

5. Makino et al.[3(p402)] indicate that the decrease in expression of the exon 34′ transcript is "the cause rather than the result of neuronal loss in the caudate nucleus…." This argument is not entirely convincing, since this transcript is also reduced in cortex and nucleus accumbens that do not show major neuronal loss. Makino et al.[3] do not provide evidence of neuronal subtype-specific expression and function of the exon 34′ transcript that might explain the discrepancy.

Obviously, the molecular pathological mechanism in XDP remains unknown. The involvement of one or several of the described DSCs, either alone or in concert with the SVA retrotransposon, certainly cannot be ruled out. Here, a function of DSC3 is intriguing, since it is located in an exon that can be part of all major splice variants of the *TAF1/DYT3* transcript system. However, intronic SNPs can also affect gene expression, as was recently shown with the *SORL1* susceptibility gene for late-onset Alzheimer disease.[5]

Several other aspects of the article need further clarification. In figure 3, patients are shown carrying the "disease-specific" 6.1-kb SVA fragment, but other patients (right panel of fig. 3) show the "wild-type" fragment. Can the SVA fragment occur in healthy persons as well, or has a sample mix-up occurred? Makino et al.[3] claim that exon 2, described elsewhere[2] (3′ of *TAF1* exon 38), is derived from *ING2*. This is not the case, since the *ING2* pseudogene overlaps with exon 2 on the opposite strand. Exon 38 of *TAF1* is skipped when further 3′ exons are used in a transcript. This was shown in cDNAs isolated from a brain cDNA bank and in RT-PCR experiments.[2] Makino et al.,[3] however, report the presence of this exon in these alternative transcripts. Provided that this is no RT-PCR artifact, this does not disprove previous findings of the absence of exon 38 in some splice variants that include additional 3′ exons.

In conclusion, many issues remain unresolved as to both the normal function of *TAF1* variants in various tis-

sues and the role of disease-specific changes in the *TAF1/DYT3* multiple transcript system in patients with XDP.

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Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for XDP or DYT3)

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