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Reduced Neuron-Specific Expression of the *TAF1* Gene Is Associated with X-Linked Dystonia-Parkinsonism

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Abstract

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X-linked dystonia-parkinsonism (XDP) is a movement disorder endemic to the Philippines. The disease locus, *DYT3,* has been mapped to Xq13.1. In a search for the causative gene, we performed genomic sequencing analysis, followed by expression analysis of XDP brain tissues. We found a disease-specific SVA (short interspersed nuclear element, variable number of tandem repeats, and Alu composite) retrotransposon insertion in an intron of the TATA-binding protein-associated factor 1 gene (*TAF1*), which encodes the largest component of the TFIID complex, and significantly decreased expression levels of *TAF1* and the dopamine receptor D2 gene (*DRD2*) in the caudate nucleus. We also identified an abnormal pattern of DNA methylation in the retrotransposon in the genome from the patient's caudate, which could account for decreased expression of *TAF1.* Our findings suggest that the reduced neuron-specific expression of the *TAF1* gene is associated with XDP.

X-linked dystonia-parkinsonism (XDP [MIM314250]) is characterized by severe progressive torsion dystonia followed by parkinsonism.[1] Its prevalence is high (5.24 in 100,000) on Panay Island, Philippines.[2] Dystonia is a syndrome of sustained muscle contractions causing twisting and repetitive movements or abnormal postures,[3] and its pathogenetic basis is still unclear. XDP has a well-defined pathology of extensive neuronal loss and mosaic gliosis in the striatum (caudate nucleus and putamen),[4,5] which appears to resemble that in Huntington disease (MIM 143100). Identification of the disease gene of XDP may contribute to the elucidation of the molecular basis underlying not only XDP itself but also other diseases in which basal ganglia show neurodegeneration, such as Huntington disease and Parkinson disease.

A series of linkage analyses has mapped the disease locus, *DYT3,* to Xq13.1 (fig. 1).[6,7] A linkage disequilibrium study narrowed the *DYT3* locus to within a 350-kb interval on Xq13.1.[8] Subsequently, Nolte et al.[9] used PCR-based sequencing and screening analyses to report four SNPs and five disease-specific sequence changes (DSCs) in the "multiple transcript system" (*MTS*) within 260 kb of the *DYT3* region. However, PCR often fails to detect large sequence