Molecular dissection and anatomical basis of dystonia:
X-linked recessive dystonia-parkinsonism (DYT3)

Ryuji Kaji¹, Satoshi Goto², Gen Tamiya¹, Satoshi Ando¹, Satoshi Makino¹, and LV Lee³

¹Department of Clinical Neuroscience, Institute of Health Biosciences, The University of Tokushima, Graduate School, Tokushima, Japan; ²Department of Neurosurgery, Kumamoto University, Kumamoto, Japan; and ³Philippines National Children’s Medical Center, Philippine

Abstract: Pathological findings in dystonia have been unclear. X-linked recessive dystonia-parkinsonism (XDP, DYT3), endemic in the Panay island, the Philippines, is characterized by the clinical onset with dystonia followed by parkinsonism. It provides a unique opportunity to explore the anatomical basis of dystonia, because it has discernible pathological changes even at its early phase of dystonia. After extensive searches for the anatomical basis in XDP, we found selective loss of striosomal neurons in the striatum in dystonic patients’ brain. Because striosomal neurons inhibit nigrostriatal dopaminergic neurons via GABAergic innervation, the striosomal lesion could account for dopamine excess in the striatum, which in turn causes a hyperkinetic state or dystonia. We also identified the causative gene as one of the general transcription factor genes, TAF1. XDP has certain similarities to Huntington disease not only in pathological and clinical findings, but also the molecular mechanism, which disturbs expression of genes essential for striatal neurons, such as DRD2. Therapeutic intervention may become possible through pharmacological measures that affect gene expression. J. Med. Invest. 52 Suppl.: 280-283, November, 2005

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Dystonia is defined as a syndrome of sustained muscle contractions frequently causing twisting or repetitive movements or abnormal postures(1). The onset of its focal form such as cervical dystonia is often preceded by psychological stress. Although dystonia has been regarded as a basal ganglia disorder, its precise pathology and molecular pathogenesis have not been clarified(2).

X-linked recessive dystonia parkinsonism (XDP) is an adult onset movement disorder characterized by severe and progressive dystonia with a high frequency of generalization (Fig.1a)(3). Although the striatal lesion has been the most striking pathology in this disease, the functional anatomy of the basal ganglia circuit in XDP has been a mystery. The mammalian striatum can be divided into two complementary and functionally distinct compartments, the matrix and the striosomes that are arranged in a mosaic pattern. Matrix compartment forms the matrix-based pathways (i.e., the direct and indirect pathways) that act as push-pull system to increase or decrease movement(4). Striosomes form the striosomal pathway that is thought to exert critical control over movement by modulating the nigral dopaminergic functions (Fig.1b). We obtained anatomo-pathological evidence that in the XDP neostriatum, the matrix compartment is relatively spared in a unique fashion while the striosomes are severely depleted(5). In view of the three-pathway basal ganglia model(6), we postulate that the differential involvement of

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Address correspondence and reprint requests to Ryuji Kaji, M.D., Ph.D., Department of Clinical Neuroscience, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax: +81-88-633-7208

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neostriatal compartments may underlie the manifestation of dystonia in patients with XDP.

XDP, first described in 1976 by Lee and colleagues as endemic in Panay, Philippines, is predominantly male movement disorder whose dystonia dominates the first 10 to 15 years of the illness and is associated or replaced with parkinsonism in the later years of life(3). To investigate its striatal pathology, we carried out postmortem analysis on multiple brain sections from male Filipino XDP patients who manifested dystonia. We have reported that the pathology of the XDP striatum is consistent with respect to the neostriatum (i.e. the caudate nucleus and putamen), but not the nucleus accumbens(3). Our current findings corroborate those reported earlier that the neostriatal lesion, characterized by neuronal loss and astrogliosis, was not diffusely but rather compartmentally distributed in a multifocal or mosaic fashion: the mosaic appearance resulted from islands (patches) of almost normal striatum sharply demarcated by gliotic area containing only a few neurons.

To assess the involvement of striatal projection neurons in XDP, we performed an immunohistochemical study using an antibody to calcineurin (CaN). CaN can be a neurochemical marker for striatal medium spiny neurons of both the matrix and striosomal compartments and for their axonal projections in the human basal ganglia. The medium spiny neurons account for up to 90% of the striatal neuron population. We found that macroscopically, there exist two distinct compartments in the XDP neostriatum, i.e., CaN-positive (CaN+) patches and inter-patch area devoid of CaN immunoreactivity.

To further elucidate whether the CaN+ patches found in XDP originated from the striatal matrix or striosomes, we used immunostaining with antibody to calbindin, an excellent marker for labeling the striatal matrix compartment. Double-immunofluorescence staining disclosed that CaN+ neurons represented a population that co-localized with calbindin. These findings indicated that in the XDP neostriatum, the matrix compartment was relatively spared in a mosaic pattern. However, the striosome compartment was markedly depleted because of severe neuronal loss in the inter-patch area.

Normally, efferent projections from the striosomes and matrix compartment differentially innervate the substantia nigra: striosomal cells provide inputs to the location of dopaminergic cells in the substantia nigra pars compacta (SNc) and islands of dopaminergic cells in the SNr, while matrix cells provide inputs to the location of non-dopaminergic (GABAergic) neurons in the SNr.

Our hypothesis on the differential temporal evolution of striosome and matrix involvement in XDP
is shown in Fig. 2a. We postulate that, as was suggested in Huntington’s disease (HD), neuronal loss may first occur predominantly in the striosomes at the early stage of disease progression. This may, in the late stage, result in the characteristic mosaic appearance presented by islands (patches) of remaining matrix cells. Based on the three-pathway model of the basal ganglia function, we postulate that at the earlier stage, when dystonia predominantly manifests, severe loss of striosomal GABAergic projection neurons that form the striosomal pathway leads to disinhibition of the nigral dopaminergic neurons and thereby to increased activity of striatal dopamine function. This then results in the hyperkinetic disorder dystonia. At the later stage when dystonia is less severe and is replaced by parkinsonism, the greater involvement of the matrix compartment leads to a severe and critical reduction of matrix-based projections and thus to the development of so called “extra-nigral form” of parkinsonism (Fig. 2b).

Among the basal ganglia disorders, XDP shares common features with HD, another adult onset genetic disorder; their progression of neurological signs and striatal pathology that includes the preferential loss of medium spiny projection neurons. In fact, we found the causative gene for XDP as TAFI (TATA-binding protein associated factor 1), which plays a critical role in gene expression. Similarly, in HD, polyglutamine accumulated in striatal neurons has been postulated to interfere with DNA transcription(7). Despite hypotheses to explain the occurrence of hyperkinetic symptoms (e.g. chorea) in HD, this intriguing issue continues to be debated. Until now, the focus in the functional anatomy of basal ganglia disorders has been directed at the direct and indirect pathways to explain the genesis of the disease-associated hyperkinetic or hypokinetic motor symptoms. Based on the present data, we suggest that the dystonia in XDP may result from an activity imbalance between the striosomal and matrix-based pathways, and that XDP, particularly at the earlier stage, can be a human disease model to study the implication of reduced striosomal pathway activity in the genesis of dystonia(8).

REFERENCES

