Title: DYT1 Early-Onset Isolated Dystonia *GeneReview* – PET Scan and DTI Studies

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PET scan studies and diffusion tensor imaging (DTI) studies in DYT1 dystonia

- Fluorodeoxyglucose (FDG) PET scan studies of individuals with a *TOR1A* pathogenic variant *with and without* dystonia show an abnormal network with relative increased metabolism in the lentiform nucleus, cerebellum, and supplementary motor cortex.
- Individuals with a *TOR1A* pathogenic variant with dystonia have been found to have a distinct metabolic pattern characterized by relative metabolic increases in the pre-supplementary motor area (SMA) and parietal association cortices and decreases in the inferior cerebellum, brain stem, and ventral thalamus [Carbon & Eidelberg 2009].
- Other imaging abnormalities (using [11^{C}] raclopride and PET imaging) detected in individuals with a *TOR1A* pathogenic variant include decreased striatal D2 receptor binding [Asanuma et al 2005].
- Studies combining PET scanning and psychomotor testing in individuals with a *TOR1A* pathogenic variant without dystonia show subtle sequence-learning abnormalities in motor performance and recruitment of brain networks [Carbon et al 2002, Ghilardi et al 2003, Carbon et al 2008]. This PET evidence suggests the presence of abnormal brain processing in individuals with a *TOR1A* pathogenic variant regardless of the presence or absence of dystonia [Carbon et al 2011].
- Diffusion tensor imaging (DTI) studies have shown microstructural changes involving the subgyral white matter of the sensorimotor cortex and the dorsal pons in manifesting and non-manifesting individuals with a pathogenic variant in *TOR1A* [Carbon et al 2004a, Carbon et al 2004b, Carbon et al 2008], with a greater degree of abnormality in the dorsal pons (in the region of the superior cerebellar peduncle) in the manifesting individuals [Carbon et al 2008], implicating abnormalities in the cerebello-thalamo-cortical pathways in the pathogenesis of dystonia.
- Subsequent studies using DTI in conjunction with probabilistic tractography showed that the presence or absence of clinical manifestations in individuals with a *TOR1A* pathogenic variant is determined by tract changes occurring along the course of the cerebello-thalamo-cortical pathways. Reductions in structural connectivity involving cerebellothalamic projections (the “proximal” pathway segment) are observed in individuals with a *TOR1A* pathogenic variant, whether or not they manifest signs and symptoms of dystonia. A second fiber tract abnormality involving thalamocortical projections (the “distal” pathway segment)

are also identified, but only in asymptomatic individuals with a *TOR1A* pathogenic variant [Argyelan et al 2009]. These findings suggest that the distal pathway segment regulates penetrance by controlling the transmission of aberrant cerebellothalamic signals to the cerebral cortex [Niethammer et al 2011].

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