Identical Twins with Leucine Rich Repeat Kinase Type 2 Mutations Discordant for Parkinson's Disease

Analysis of concordancy rates in monozygotic and dizygotic twins with Parkinson's disease (PD) has been an important subject for research into the disorder[1] and discordancy between twins has traditionally been interpreted as evidence against a genetic etiology of disease. Discordancy in late-onset diseases such as PD is complicated by the possibility that the disease onset may vary considerably between twins, and cases with up to 20 years of discordance have been reported.[2] Leucine-rich repeat-kinase type 2 (LRRK2) mutations are the most common Mendelian cause of PD,[3,4] with the G2109S mutation occurring in 1% to 2% of idiopathic cases in the UK.[5] Here we report the identification of a pair of identical twins with this mutation who are discordant by more than 10 years.

The twins, of English descent, are 70+ years old and were self-reported as identical. The proband developed the first symptoms of PD at age 60 years, with unilateral bradykinesia, rigidity, and rest tremor that became bilateral. The initial good response to levodopa therapy was followed in 5 years by development of motor fluctuations with wearing off, on-off effects, and peak dose and diphasic dyskinesias. The family had autosomal dominant inheritance of PD with a parent and 2 second-degree relatives affected by the disorder. On exam, the twin had a normal smell test and no signs of neurodegenerative disorder.

DNA from the proband was sequenced as part of the clinical workup and the heterozygous LRRK2 G2109S mutation was identified. DNA from the twin was sequenced and the mutation was confirmed in the sample. DNA from both twins was run on genomewide arrays (Illumina 660) to confirm that the twins were identical; this also revealed no major chromosomal abnormalities in either twin.

These data show that considerable variance in the penetrance of the mutation can occur even in the context of genetic identity. This suggests that the effects of other genetic loci in modifying the age at onset of disease must be minimal and, therefore, that identifying such loci through linkage or association methods will be extremely challenging because the variability in onset age between LRRK2 mutation carriers[6] must be largely nongenetic in etiology. Identifying environmental risk factors for disease is notoriously difficult and there is nothing in the personal or medical histories of these twins that provides obvious clues for the reasons behind the current discordance. Indeed, both twins have had similar life courses. The recent data implicating pathology spread in PD is consistent with the notion that the disease process can start at a single site.[7] If this is the case, then a stochastic initiation of disease may underlie the discordance as it may for prion disease.[8,9]

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Broad Spectrum of Dystonia Associated With a Novel Thanatosis-Associated Protein Domain-Containing Apoptosis-Associated Protein 1 Mutation in a Japanese Family With Dystonia 6, Torsion

To date, more than 37 pathological mutations have been discovered in thanatosis-associated protein domain-containing apoptosis-associated protein 1 (THAP1), and phenotypic variations have been revealed in dystonia 6, torsion (DYT6), including varied onset and progression of symptoms.[1–3] Accumulation of genotype/phenotype correlations would contribute to a better understanding of molecular mechanisms of dystonia and accompanying neurological features, such as cognitive dysfunction.[4,5] Here, we describe a Japanese family carrying a novel mutation in THAP1 showing a broad clinical spectrum of dystonia and additional neurologic features.

The study was performed according to a protocol reviewed and approved by the ethics committee of the Graduate School of Medicine, University of Tokushima (Tokushima, Japan). The proband is a 34-year-old man. He was born healthy to nonconsanguineous parents and grew up without any developmental delay. He noticed speech difficulties and occasional involuntary flexion of the arms and extension of the legs at the age of 15. Twelve years later, his dystonia had generalized and he was obliged to quit his job. Subsequent to bilateral globus pallidus internus (GPi) DBS at the age of 30, his Burke-Fahn-Marsden Dystonia Rating Scale-motor (BFMDRS-M) score changed from 55.5 to 21. Oral administration of zolpidem (40 mg/day) further eased the symptoms. Findings from neuroimaging, including brain MRI and tractography, were unremarkable; however, neuropsychological evaluation demonstrated a total IQ of 82 (Weschler Adult Intelligence Scale—Third Edition; performal: 86 [perceptual organization index: 89; processing speed index: 78], verbal: 82 [verbal comprehension index: 88; working memory index: 92), revealing mild neurocognitive dysfunction. He had responded favorably to GPi-DBS during the first 2 years of therapy; however, clinical response continued to decline later, as previously reported.[2,3,6,7] His latest BFMDRS-M score at the age of 34 was 42.

Clinical investigation of other family members demonstrated various types of dystonia (Fig. 1A). Three patients (III-1, III-2, and III-3) initially showed spasmodic dysphonia in their early teens. Afterwards, dystonia had gradually spread to the face, cervical region, and proximal upper limbs and become generalized in their middle twenties to their early thirties. In addition, mild cognitive dysfunction became prominent. The 59-year-old mother of the proband (III-6) and her deceased mother (II-6) showed very mild symptoms of laryngeal dystonia. The 61-year-old patient (III-5) developed segmental dystonia of the right upper extremity at the age of 19, which did not spread to other body parts later. All currently living family members were examined by movement disorder specialists (R.M., T.K., H.K., W.S., Y.I., and R.K.). Generalized dystonia in the deceased affected family members (I-2 and II-1) was ascertained by examining medical records.

Sequence analysis of THAP1 showed a novel heterozygous mutation c.389_390delCA in exon 3, resulting in premature truncation of the THAP1 protein (p.S130fs133X) (Fig. 1B), which provided further evidence that haploinsufficiency is the most likely disease-causing mechanism in DYT6. Polymerase chain reaction (PCR)/restriction fragment length polymorphism analysis using the restriction enzyme, *Dde* I, confirmed the mutation in the proband and other family members, including asymptomatic carrier IV-3 (Fig. 1C).

Our study demonstrated marked intrafamilial variations of dystonia in a single Japanese family with DYT6 and limited efficiency of GPi-DBS. Further investigations are needed to establish an effective therapeutic strategy based on the pathophysiology in DYT6.

Legends to the Videos

Video 1. Patient IV-7. The proband. DBS device was turned off for 3 days to reprogram the stimulation parameters (DBS OFF), 1 year after implantation. A marked lateral shift of the neck is present in the sitting position. Dyskinesia of the upper extremities and face become apparent with action. Speech is severely impaired and difficult to understand. While walking, there is dystonia of the face, arms, and trunk. His left arm is endorotated.

Video 2. Patient IV-7. The proband. After reprogramming of DBS device (DBS ON) and oral administration of zolpidem, partial improvement is observed in motor function and speech. Dystonia of the neck is still present, but less severe, compared to Segment 1.

Video 3. Patient III-6. The proband's mother. While reading and speaking, she shows very mild spasmodic dysphonia,

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Additional Supporting Information may be found in the online version of this article.

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