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X-Linked Dystonia-Parkinsonism

Synonyms: DYT3, DYT-TAF1, Lubag

Virgilio Gerald H Evidente, MD[1]

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Summary

Clinical characteristics

Individuals with X-linked dystonia-parkinsonism (XDP) have dystonia of varying severity and parkinsonism. XDP afflicts primarily Filipino men and, rarely, women. The mean age of onset in men is 39 years; the clinical course is highly variable with parkinsonism as the initial presenting sign, overshadowed by dystonia as the disease progresses. Features of parkinsonism include resting tremor, bradykinesia, rigidity, postural instability, and severe shuffling gait. The dystonia develops focally, most commonly in the jaw, neck, trunk, and eyes, and less commonly in the limbs, tongue, pharynx, and larynx, the most characteristic being jaw dystonia often progressing to neck dystonia. Individuals with pure parkinsonism have non-disabling symptoms that are only slowly progressive; those who develop a combination of parkinsonism and dystonia can develop multifocal or generalized symptoms within a few years and die prematurely from pneumonia or intercurrent infections. Female carriers are mostly asymptomatic, though a small minority may manifest dystonia, parkinsonism, or chorea.

Diagnosis/testing

The diagnosis of XDP is suspected in a male with typical clinical findings, family history consistent with X-linked inheritance, and maternal ancestral roots from the Panay Islands in the Philippines. Molecular genetic testing for variants that tag a disease-associated haplotype of the multilocus transcript system termed *TAF/DYT3* is required to confirm the diagnosis in those with no known family history of XDP, very early symptoms, and/or a phenotype of pure parkinsonism, pure tremor, or chorea without dystonia. Olfactory testing indicates olfactory dysfunction early in the disease and may be used to support the diagnosis when molecular genetic testing is not available.

Management

Treatment of manifestations: Pharmacologic agents are used to treat dystonia or parkinsonism or both. Anticholinergic agents, benzodiazepines, and sometimes neuroleptics are used in the early stages of dystonia;

Author Affiliation: 1 Director, Movement Disorders Center of Arizona Scottsdale, Arizona; Email: vevidente@movementdisorders.us.

zolpidem and tetrabenazine are used after dystonia becomes multifocal or generalized. Botulinum toxin injections improve focal dystonia but may worsen swallowing in individuals with preexisting dysphagia. Parkinsonism is treated with levodopa and dopamine agonists to control tremor. Bilateral pallidal deep brain stimulation may be used to treat advanced disease and medically refractory dystonia, although it may have less effect on parkinsonism.

Prevention of secondary complications: Swallowing evaluation to guide diet modification and swallowing techniques to minimize risk of aspiration. Physical therapy, coupled with maximal medical and surgical therapy, may help delay immobility and its complications.

Surveillance: Annual clinical evaluations in males with the disease-related haplotype who are not yet symptomatic, biannual evaluation for symptomatic males to monitor medications, and periodic swallowing evaluation, especially in those with subjective dysphagia.

Genetic counseling

XDP is inherited in an X-linked manner. Approximately 94% of affected individuals have a known family history of the condition. *De novo* occurrence of the disease-related haplotype associated with the disorder has not been observed to date. Males with XDP pass the *TAF1/DYT3* disease-associated haplotype to all of their daughters and none of their sons. Women who are carriers have a 50% chance of transmitting the *TAF1/DYT3* disease-associated haplotype in each pregnancy: males who inherit the *TAF1/DYT3* disease-associated haplotype will be affected; females who inherit the *TAF1/DYT3* disease-associated haplotype are mostly asymptomatic, although a small percentage may manifest symptoms. Carrier evaluation of at-risk female relatives is possible if the *TAF1/DYT3* disease-associated haplotype has been identified in the family. Once the *TAF1/DYT3* disease-associated haplotype has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for XDP are possible. Caution should be exercised in interpreting the results of prenatal testing as the c.94C>T (p.Arg32Cys) variant that marks the disease haplotype has not been proven to be the molecular cause of XDP.

Diagnosis

Clinical Diagnosis

The diagnosis of X-linked dystonia-parkinsonism (XDP) **should be suspected** in an individual with the following clinical findings, neuroimaging results, and neurophysiologic test results.

Clinical findings

- Dystonia of varying severity, ranging from focal to generalized typically starting in early adulthood
- Parkinsonism
- Family history consistent with X-linked inheritance
- Maternal ancestral roots from the Panay Islands in the Philippines where XDP originated as a genetic founder effect. All known affected individuals to date are of Filipino descent.

Neuroimaging. CT and brain MRI in 20 individuals with symptomatic XDP did not reveal significant striatal or brain stem atrophy [Evidente, personal observation]. Generalized cerebral atrophy (usually mild) may be seen in some individuals. Caudate atrophy on brain imaging can be seen in individuals with more advanced disease similar to that seen in Huntington disease, though this is not a consistent finding.

Neurophysiologic testing

- **Olfactory.** The degree of olfactory impairment in XDP can be as severe as that seen in Parkinson disease. Evidente et al [2004a] administered a culturally corrected University of Pennsylvania Smell Identification Test (ccUPSIT) consisting of 25 odor items to 20 symptomatic males with XDP and 20 controls. The mean ccUPSIT score of individuals with XDP (18±3.19) was significantly lower (p=0.003) than that of controls (20.5±3.02). The olfactory scores did not correlate with phenotype, severity of dystonia, or duration of disease. Nine of 20 individuals with XDP (45%) had ccUPSIT scores below the mean, with the lowest score being 11, suggesting that olfactory dysfunction may occur in individuals with XDP even early in the disease.

  As genetic testing is often not available in the endemic rural areas in the Philippines, olfactory testing may support the diagnosis in symptomatic (and possibly presymptomatic) individuals with XDP, though this possibility needs to be studied further.

- **Other.** Nerve conduction studies, somatosensory evoked potential studies, electroencephalography, blink reflex studies, and brain stem evoked potential studies in ten symptomatic males with XDP with dystonia and parkinsonism have revealed no abnormalities [Evidente, personal observation].

Establishing the Diagnosis

Male proband. The diagnosis of XDP **is established** in a male proband with typical clinical and neuroimaging findings. In those with no known family history of XDP, very early symptoms, and/or a phenotype of pure parkinsonism, pure tremor, or chorea without dystonia, molecular genetic testing is required to confirm the diagnosis. A single haplotype of the multilocus transcript system termed *TAF1/DYT3* is the only locus associated with XDP. The molecular cause of XDP has not been determined; therefore, variants on the *TAF1/DYT3* disease-associated haplotype are used as a marker for XDP (see Table 1).

Female proband. The diagnosis of XDP **is usually established** in a symptomatic female proband with a family history of XDP who presents with either chorea, pure parkinsonism, focal dystonia, or (rarely) generalized dystonia; it is confirmed by identification of a *TAF1/DYT3* disease-associated haplotype (see **Male proband** and Table 1).

Molecular genetic testing. Approaches can include **targeted analysis** for a *TAF1/DYT3* disease-associated haplotype and use of a **multigene panel**:

- **Targeted analysis** for the XDP-disease-specific sequence variant c.94C>T (p.Arg32Cys) is consistent with the diagnosis in all affected males; however, this is an indirect test. See Note (1).

  Note: (1) Although detection of c.94C>T (p.Arg32Cys) in a symptomatic individual is considered diagnostic, this is an indirect finding. Variants at this locus not previously associated with XDP cannot be interpreted as disease associated (see Genetically Related Disorders). (2) This variant has only been associated with XDP in individuals of Filipino ancestry. (3) Recent data suggest that a haplotype-tagging SVA (*s*hort interspersed nuclear element, *v*ariable number of tandem repeats, and *A*lu composite) retrotransposon insertion in *TAF1*, which contains an unstable repeat expansion, may be the causative variant. Note that due to the context of the sequence, testing for this SVA and repeat expansion poses a technical challenge for molecular testing [Makino et al 2007, Bragg et al 2017].

- **A multigene panel** that includes XDP-specific sequence variants and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in

genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in X-Linked Dystonia-Parkinsonism

Gene/ Locus [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TAF1/DYT3	Targeted analysis for the XDP-specific sequence variant c.94C>T (p.Arg32Cys) [3]	100% in affected persons of Filipino descent [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. A variety of molecular methods may be used to detect a specific variant. If sequence analysis is performed, variants other than the c.94C>T (p.Arg32Cys) may be detected. For issues to consider in interpretation of sequence analysis results, click here.
4. The common c.94C>T (p.Arg32Cys) variant (historically known as disease-specific single-nucleotide change 3 (DSC3) is the only DSC embedded in a predicted coding region; see Table 2). Four additional DSCs and a 48-bp deletion that were unique to XDP were identified [Nolte et al 2003]. In addition, an SVA retrotransposon insertion in *TAF1* has also been identified on the XDP haplotype [Makino et al 2007]. The molecular cause of XDP is unknown. See Molecular Genetics for details on the multilocus transcript.

Clinical Characteristics

Clinical Description

X-linked dystonia-parkinsonism (XDP) or *lubag* afflicts primarily adult Filipino men and, rarely, women. The male-to-female ratio is 99:1. The mean age of onset in men is 39 years, with a range of 12 to 64 years. The mean age of onset in women is 52 years, with a range of 26 to 75 years [Evidente et al 2004b]. The time from onset of dystonia to generalization ranges from one to 23 years, with a mean of 3.8 years.

The clinical course in men with XDP is highly variable. Although the presenting finding was traditionally thought to be dystonia in most cases [Lee et al 2002], a longitudinal follow up of asymptomatic or early symptomatic individuals with genetically confirmed XDP revealed that the initial presenting sign is almost universally parkinsonism [Evidente et al 2002c]. In particular, abnormality of rapid alternating limb movements (which can be asymmetric) can often be appreciated on neurologic examination in early symptomatic (or soon to be symptomatic) individuals.

Parkinsonism. Individuals with XDP may present predominantly with one or more of the cardinal features of Parkinson disease, including resting tremor, bradykinesia, rigidity, and postural instability. Shuffling gait, in the absence of lower-limb dystonia, can be severe enough to cause recurrent falls and significant impairment of walking.

Some individuals may have pure parkinsonism and no dystonia for many years [Evidente et al 2002c]. In some of these individuals, the dystonia develops very late in the course and is usually focal or segmental. When the dystonia becomes advanced (i.e., multifocal or generalized in distribution), the parkinsonism remains, although it is overshadowed by the dystonia.

Some individuals with XDP (both male and female) may have all the cardinal features of parkinsonism, asymmetric findings, and levodopa responsiveness. These individuals may initially be misdiagnosed as having Parkinson disease [Evidente et al 2002c, Domingo et al 2014].

Dystonia. The dystonia develops focally, most commonly in the jaw, neck, trunk, and eyes, and less commonly in the limbs, tongue, pharynx, and larynx.

The most characteristic dystonia seen in males with XDP is jaw dystonia, more commonly presenting as more difficulty with jaw opening than jaw closing. Jaw dystonia often progresses to neck dystonia, with retrocollis being more common than torticollis. Retrocollis can be so severe that the neck is extended more than 90 degrees, and the trunk is hyperextended. Cervical dystonia may be accompanied by a dystonic head tremor. Extension dystonia of the trunk is far more common than flexion or lateral dystonia of the trunk.

Blepharospasm is only rarely the initial symptom of XDP. It tends to be more common as the disease progresses. It can coexist with mid- or lower-facial dystonia.

Limb dystonia, rarely an initial presenting finding, is more commonly seen as disease advances. It affects the upper limbs as often as the lower limbs and is usually bilateral, although severity can be greater on one side of the body than the other. Unlike DYT1 torsion dystonia, XDP only rarely presents with dystonia of the foot.

Tongue dystonia may also be seen, manifesting as either involuntary tongue protrusion or limitation in tongue protrusion. Pharyngeal dystonia, manifesting as difficulty swallowing, usually affects those with orolingual dystonia. Pharyngeal dystonia often leads to significant weight loss, aspiration pneumonia, and early death.

Laryngeal dystonia leading to stridor (a rare finding) can also lead to sudden death. Individuals with orolingual, pharyngeal, or laryngeal dystonia may present with respiratory sounds [Evidente et al 2002a]. Such vocalizations can be observed during both inspiration and expiration.

Sensory tricks (improvement in dystonia by touching certain areas) have been observed in individuals with XDP with dystonia, particularly those with cervical dystonia.

Other neurologic findings. Traditionally, XDP was thought to be a combination of dystonia and parkinsonism only [Evidente et al 2002a]; however, with genotypic correlation, other neurologic findings including pure tremor, chorea, athetosis, and myoclonus have been recognized:

- **Resting tremor or action tremor** can be seen in either the early or later stages of disease. In some individuals, an asymmetric resting tremor of a limb with an oscillation of 3-6 Hz (similar to that seen in Parkinson disease) can be observed. Some individuals may also have a coarse, relatively symmetric upper-limb tremor or head tremor similar to that in individuals with essential tremor. The tremor can involve not only the limbs and head, but also the trunk, craniofacial region (lips, jaw, or facial muscles), and voice. Distal limb tremor can sometimes be of slow frequency (1-3 Hz), reminiscent of myorhythmia [Evidente et al 2002a].
- **Chorea** usually occurs in the distal upper limbs in the early stages and is combined with subtle dystonia, thus resulting in athetotic movements. Chorea can also be seen with the generalized dystonic movements.
- **Action myoclonus** can be present in the limbs or even in the craniofacial region. Myoclonus is characterized by a combination of rapid, brief, lightning-like muscle contractions and is often mistaken for tremor.

  Electrophysiologic studies show muscle bursts ≤50-100 milliseconds in duration. Back-averaging may show a jerk-locked pre-movement surface-positive cortical electroencephalographic potential in the contralateral sensorimotor area, supporting the cortical origin of the myoclonus.

General cognition often remains intact although there may be problems with frontal executive functions [Domingo et al 2011].

Depression is also a common feature, most likely related to the profound disability and loss of employment that XDP causes, especially in more advanced cases [Morigaki et al 2013]. Impulse control disorder in the form of pathological gambling has been described in XDP [Gillian 2013].

Disease progression. Those with pure parkinsonism with little or no dystonia have the best prognosis; they have non-disabling symptoms that are slowly progressive or non-progressive.

Those who develop a combination of parkinsonism and orobuccolingual dystonia and cervical dystonia in the first year or two of the disease have the worst prognosis. Such individuals develop multifocal or generalized symptoms from the second to fifth year after onset, rapidly become bedridden, and die prematurely from aspiration pneumonia, laryngeal stridor, and/or intercurrent infections resulting from immobility.

Phenotype in women. Female XDP carriers are mostly asymptomatic, although a small percentage may manifest symptoms. Compared to men, women with XDP often do not present with dystonia, or if they do, the dystonia is usually focal, non-progressive, and non-disabling [Evidente et al 2004b]. The dystonia can subtly manifest in the neck or limbs. However, there have been rare cases of women with XDP who have generalized dystonia similar to that seen in affected men [Lee et al 2011].

Other manifestations in women include chorea (which can be in a hemi-distribution), focal tremor (usually limb), or parkinsonism. The parkinsonism is usually mild, non-progressive, and non-disabling. Rarely, levodopa-responsive parkinsonism very similar to Parkinson disease can be observed.

Neuroimaging studies have revealed the following:

- Normal findings on CT and brain MRI in the majority of patients, although generalized cerebral atrophy (usually mild) may be seen in some individuals and caudate atrophy in more advanced disease [Evidente, personal observation]
- Evidence for strong involvement of the white matter and putamen based on diffusion-weighted imaging [Brüggemann et al 2016]
- Evidence of both postsynaptic [Eidelberg et al 1993] and presynaptic nigrostriatal involvement [Waters et al 1993] on [^{18}F] fluorodopa PET scan studies
- Putaminal abnormalities on fluorodeoxyglucose (FDG) PET scan in affected men with early or mild symptomatic *lubag* despite normal brain CT or MRIs [Evidente et al 2002d]
- Results on presynaptic single-photon emission computed tomography (SPECT) studies using either [^{123}I]-β-carbomethoxy-iodophenyl-nortropane (CIT) or ioflupane I-123 dopamine transporter (DaT scan) which can be similar to those seen in individuals with Parkinson disease, with the putamina involved more severely than the caudate, and one side more affected than the other [Tackenberg et al 2007; Evidente, personal observation]. DAT scan abnormalities are noted even in early XDP with pure parkinsonism, or with only mild dystonia.
- Functional decline of postsynaptic dopaminergic transmission related to disease duration and ongoing degeneration function on [^{123}I] (IBZM)-SPECT studies [Brüggemann et al 2017].
- Hyperechogenicity of the substantia nigra in 79% and of the lenticular nuclei in 81% of individuals with XDP on transcranial brain sonography studies [Walter et al 2017]. Abnormal substantia nigra hyperechogenicity was more frequent in individuals with prominent parkinsonism (100%) compared to those without (68%). Thus, substantia nigra hyperechogenicity may be regarded as a preclinical risk marker of parkinsonism-predominant XDP.

Thus, it appears that by functional imaging, individuals with XDP may have one of the following:

- **Postsynaptic striatal involvement.** Affected individuals may represent the majority of XDP, with pure dystonia or combined dystonia-parkinsonism from the early stages; this group does not respond to levodopa.

- **Presynaptic nigrostriatal involvement.** Affected individuals may represent those few who have pure parkinsonism for a considerable number of years, with dystonia setting in late in the course; this group appears to be more responsive to levodopa.

Neuropathology. Little information is available on the neuropathology of XDP.

The earliest neuropathology report on XDP, from one Filipino male with dystonia-parkinsonism, showed neuronal loss and a multifocal mosaic pattern of astrocytosis in the caudate and lateral putamen [Waters et al 1993]. This information has been updated by Pasco et al [2011], who report that "[i]n the neostriatum, the dystonic phase of XDP shows the involvement of striosomes and matrix sparing, while the later, i.e., parkinsonian phase, shows matrix involvement as well. In the dystonic phase, the loss of striosomal inhibitory projections lead to disinhibition of nigral dopaminergic neurons, perhaps resulting in a hyperkinetic state; while in the parkinsonian phase, severe and critical reduction of matrix-based projection may result in extranigral parkinsonism."

Neuropathologic examination on an individual with severe generalized dystonia and parkinsonism confirmed the mosaic pattern of striatal gliosis as reported earlier, but also noted that the gliotic patches showed gradients that were dorsal to ventral, rostral to caudal, and medial to lateral [Evidente et al 2002b]. The caudate was more affected than the putamen, and the accumbens was largely spared. The head of the caudate was more affected than the tail. The patchy areas of striatal gliosis were not associated with microglial activation. The more marked involvement of caudate and putamen than of the ventral, limbic striatum (i.e., nucleus accumbens) suggests that striatal synaptic input from the limbic lobe is less affected than the synaptic input from the sensorimotor and association cortices. With synaptic immunostaining, it was noted that the patchy areas of gliosis corresponded to the areas of poor synaptophysin staining, suggesting that the basis for the patchy gliosis is synaptic loss rather than neuronal loss. The synaptic loss and gliosis were also observed in the globus pallidus interna and externa. Some focal gliosis was also noted in the substantia nigra pars reticularis, but not in the pars compacta.

Postmortem analyses of the basal ganglia based on striatal compartments (i.e., the striosomes and the matrix compartment) showed that in the neostriatum of individuals with XDP, the striosomes are severely depleted while the matrix component is relatively spared [Goto et al 2005]. Thus, the disproportionate involvement of the neostriatum compartments and their efferent projections may be responsible for dystonia in XDP and possibly in other neurodegenerative disorders.

Neuropathologic studies have shown a neostriatal defect of the neuropeptide Y system in individuals with XDP, suggesting that the neuropeptide Y system may play a role in the progressive loss of striatal neurons [Goto et al 2013].

Genotype-Phenotype Correlations

All symptomatic individuals have the same disease-associated *TAF1/DYT3* haplotype regardless of phenotype [Nolte et al 2003], which comprises a spectrum including pure parkinsonism, focal dystonia, segmental dystonia, multifocal dystonia, and generalized dystonia in symptomatic men and chorea, pure parkinsonism, and focal or multifocal dystonia in symptomatic women.

Recently, Bragg et al [2017] have further analyzed the sequence of the SVA in *TAF1* and detected polymorphic variation in the length of a hexanucleotide repeat domain, (CCCTCT)n, which varies from 35 to 52 repeats. The length of the repeat correlates inversely with age at disease onset [Bragg et al 2017].

Anticipation

Anticipation is not observed in XDP.

Nomenclature

XDP was first described by Lee et al [1976] as "dystonia musculorum deformans."

In the local Filipino dialect, *lubag* describes intermittent twisting or posturing. Other terms used include *wa-eg* (sustained postures) and *sud-sud* (shuffling gait), which are commonly seen in persons with XDP.

Prevalence

The first epidemiologic study was by Lee et al [1976]. More than 500 cases of XDP have been described in the literature. XDP is believed to have originated ancestrally in the Philippines, particularly in the Panay Islands through a founder variant some 50 meiotic generations (~1,000 years) ago. The prevalence rate is 5.24:100,000 in the Panay Islands, with the highest rate of 18.9:100,000 in the province of Capiz, where it is endemic [Lee et al 2002].

The prevalence in the general population in the Philippines is estimated at 0.34:100,000.

Although maternal ancestry can be traced to the Panay Islands in most cases, some individuals have no such traceable ancestry.

Genetically Related (Allelic) Disorders

Hemizygous, usually *de novo*, pathogenic variants in *TAF1* (other than the c.94C>T (p.Arg32Cys) variant) have been associated with a congenital neurodevelopmental disorder characterized by global developmental delay, intellectual disability, and dysmorphic facial features (OMIM 300966).

Differential Diagnosis

See Dystonia Overview.

Individuals with X-linked dystonia-parkinsonism (XDP) with tremor can be misdiagnosed as having Parkinson disease or essential tremor, especially in the early stages in which dystonia may be absent or subtle. Individuals with XDP with all the cardinal features of parkinsonism, asymmetric findings, and levodopa responsiveness are often diagnosed as having Parkinson disease or Parkinson-plus syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked dystonia-parkinsonism (XDP) syndrome, the following evaluations are recommended if they have not already been completed:

- Neurologic examination
- Assessment of speech
- Assessment of swallowing
- Nutritional assessment
- Surface electromyography study
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Pharmacologic Treatment of Dystonia

Anticholinergic agents and benzodiazepines. In the early stages of the disease when dystonia is focal or segmental in distribution, individuals may respond significantly to anti-dystonia medications, particularly to anticholinergic agents and benzodiazepines.

- The two most commonly prescribed anticholinergic drugs are trihexyphenidyl (Artane™) and biperiden (Akineton™). Trihexyphenidyl appears to have a more consistent and beneficial effect than biperiden, especially in the moderate-to-advanced stages.
- The benzodiazepine associated with the best response is clonazepam.
- Even greater improvement in dystonia is noted when anticholinergic drugs are combined with clonazepam.

Zolpidem. Once the dystonia is multifocal or generalized in distribution, even polypharmacy offers only partial relief of the dystonic symptoms. In such states, zolpidem has been observed to be potentially effective [Evidente 2002].

Zolpidem is particularly useful in individuals with a predominantly phasic type of generalized dystonic movements and no contractures. In such cases dramatic improvement can occur: some individuals experience nearly 100% improvement of dystonia for a few hours.

- The clinical effect of zolpidem may last six to eight hours per 10-mg dose in the first few weeks. Subsequently, the effect becomes progressively shorter, decreasing to two to three hours.
- Zolpidem was previously reported to have modest effects on parkinsonism in some individuals with progressive supranuclear palsy (PSP) [Daniele et al 1999] and Parkinson disease [Daniele et al 1997]; its effect on dystonia in individuals with XDP is more robust than its effect on parkinsonism.
- Individuals with XDP who take frequent doses of zolpidem either overcome its soporific effects rapidly or develop tolerable daytime sleepiness.

Neuroleptics, particularly those with strong dopamine D_2 antagonistic properties, are often prescribed because they are relatively cheap and widely available.

- Haloperidol is often used by primary care physicians who see individuals with XDP *de novo* in the Panay Islands. Although haloperidol may be effective initially for mild-to-moderate dystonia, its effect in more advanced dystonia remains dubious, as it is unclear if the progression of the dystonia is caused by the disease alone or partially caused by the extrapyramidal side effects (EPS) of haloperidol.
- Risperidone appears less effective than haloperidol in controlling dystonia. At doses of 6 mg/day or higher, risperidone may also be associated with EPS including tardive dyskinesias and parkinsonism.
- Of the atypical neuroleptics, clozapine has the greatest potential to be effective, at least for a limited period. However, its clinical use is limited by its potential to cause aplastic anemia and the need to do frequent complete blood counts, which is impractical in the rural areas of the Panay Islands where XDP is most prevalent.

Tetrabenazine (a non-neuroleptic presynaptic dopamine depleter) also benefits some individuals with clinically advanced dystonia [Evidente et al 2002a]. Similar to zolpidem, tetrabenazine best helps individuals with phasic dystonia and no contractures.

Botulinum toxin injections improve focal dystonia, particularly cervical dystonia, blepharospasm, tongue dystonia, and jaw dystonia. It can, however, dramatically worsen swallowing in individuals with preexisting dysphagia if injected in the cervical or tongue area. The prohibitive cost of botulinum toxin also limits its use in individuals with XDP in rural areas. Rosales et al [2011] using botulinum toxin-A injections in 109 persons with

XDP found substantial improvement for oromandibular and lingual dystonias and moderate improvement for truncal-axial dystonias as well as a significant reduction in associated pain.

Injections of ethanol and lidocaine for afferent blocking of muscle are far less costly than botulinum toxin and have been attempted in individuals with XDP with cervical dystonia. They only offer clinical benefits for one to two weeks and are associated with undesirable side effects including severe pain during injections and muscle fibrosis and contractures with repeated use.

Pharmacologic Treatment of Parkinsonism

Levodopa. Individuals with XDP, particularly those with pure parkinsonism, may be responsive to levodopa. Persons with parkinsonism who develop dystonia may become increasingly less responsive to levodopa as the dystonia progresses. Of note, long-term use of levodopa does not lead to development of levodopa-associated dyskinesias.

Dopamine agonists are also effective in controlling tremor in individuals with XDP but are less effective than levodopa in controlling bradykinesia or shuffling gait. Rarely, levodopa or dopamine agonists may exacerbate the dystonia in persons with XDP.

Surgical Treatment of Dystonia and Parkinsonism

Deep brain stimulation (DBS). XDP was successfully treated in one individual using DBS of the globus pallidus interna (GPi) bilaterally [Evidente et al 2007]. The individual had parkinsonism and generalized dystonia, with severe disabling jaw-opening dystonia, drooling, dysphagia, and dysarthria (speech was unintelligible). He received only partial relief of his symptoms with a combination of levodopa, piribedil (a dopamine agonist), trihexyphenidyl, and zolpidem. His generalized dystonia and parkinsonism improved markedly within the first week after surgery, with sustained benefits at 13-year follow up. Thus, it appears that bilateral pallidal stimulation may be the best option for symptomatic improvement in individuals with XDP with advanced disease and medically refractory dystonia [Wadia et al 2010, Aguilar et al 2011, Patel et al 2014].

DBS has been done so far primarily on individuals with more advanced dystonia, either multifocal or generalized. However, a Filipino male age 45 years with only three years of relatively mild symptoms of unilateral big toe extension dystonia, mild jaw-opening dystonia, mild parkinsonism, and dysarthria underwent bilateral pallidal GPi DBS, with significant improvement of his symptoms immediately post-op [Evidente, unpublished data]. As of latest follow up 18 months after DBS, his symptoms remain well controlled with no further spread of dystonia to other parts of the body. This individual is the earliest known with XDP to have undergone DBS during the initial stages of the disease. Long-term follow up as well as identification of other cases treated early in the course of the disease may help determine if performing DBS early in the stages of XDP may have a disease-modifying effect.

Although dystonia uniformly improves in individuals with XDP undergoing bilateral pallidal DBS, the parkinsonism may be less responsive [Oyama et al 2010]. In one individual with XDP rapidly progressive dystonia was noted to have early and marked benefit with bilateral GPi DBS [Martinez-Torres et al 2009]. In another individual with XDP who underwent bilateral pallidal DBS, an impulse control disorder similar to what is observed in people with Parkinson disease who have undergone DBS was described [Piano & Tan 2013].

Prevention of Primary Manifestations

See Treatment of Manifestations.

Prevention of Secondary Complications

The secondary complications of significant dysphagia and immobility are usually related to progression of dystonia.

Swallowing evaluation, especially in those with subjective dysphagia, can guide diet modification and use of swallowing techniques that minimize the risk for aspiration pneumonia.

Physical therapy, coupled with maximal medical and surgical therapy, may help delay the bedridden state and its complications.

Although traditional neuroleptics may initially help focal or segmental dystonia, they may eventually exacerbate the underlying parkinsonism in individuals with XDP and also lead to tardive dystonia with chronic use. Thus, it may be difficult to determine with chronic therapy if traditional neuroleptics actually help or worsen dystonia in individuals with XDP.

Surveillance

Presymptomatic males known to have the disease-associated haplotype may need yearly clinical evaluations after age 30 years to identify the onset of symptoms in order to institute appropriate therapy as early as possible.

Once an individual is symptomatic, biannual follow ups are recommended in order to adjust medications to assure best management of dystonia and/or parkinsonism.

Periodic swallowing evaluation, especially in those with subjective dysphagia, is appropriate.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Other sleep medications such as zaleplon (Sonata™) have had no beneficial effect on dystonia in individuals with XDP.

Drugs that have been used anecdotally with poor or inconsistent effects on dystonia in individuals with XDP include gabapentin, topiramate, baclofen, and tizanidine.

Brain surgeries for advanced dystonia in individuals with XDP that have failed in the past include four thalamotomies, two pallidotomies, and one cerebellar implantation [Lee et al 2002].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

X-linked dystonia-parkinsonism (XDP) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the *TAF1/DYT3* disease-associated haplotype.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- Approximately 94% of affected individuals have a known family history of the condition.
- When an affected male is the only affected individual in the family (i.e., a simplex case), it is likely that his mother has the *TAF1/DYT3* disease-associated haplotype that she inherited from a maternal female ancestor.

Sibs of a proband. The risk to sibs depends on the carrier status of the mother:

- Most often, the mother of the proband is a carrier and the chance of transmitting the *TAF1/DYT3* disease-associated haplotype in each pregnancy is 50%. Male sibs who inherit the *TAF1/DYT3* disease-associated haplotype will eventually develop symptoms; female sibs who inherit the *TAF1/DYT3* disease-associated haplotype will be carriers and will usually not be affected.
- There is no evidence to date of *de novo* occurrence of the disease-related haplotype associated with XDP, although it remains a possibility. In the unlikely circumstance that the mother of the proband is not a carrier, the risk to the sibs is low, but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a male proband. Males with XDP will pass the *TAF1/DYT3* disease-associated haplotype to all of their daughters and none of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and of being mildly affected, and the aunt's offspring, depending on their sex, may be at risk of being carriers and/or of being affected.

Carrier (Heterozygote) Detection

Carrier evaluation of at-risk female relatives is possible if the *TAF1/DYT3* disease-associated haplotype has been identified in the family.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk male relatives is possible once the *TAF1/DYT3* disease-associated haplotype has been identified in an affected family member. Note: Caution should be exercised in interpreting the results of predictive testing as the c.94C>T (p.Arg32Cys) variant that marks the disease haplotype has not been proven to be the molecular cause of XDP.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, there is concern as to the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of XDP, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *TAF1/DYT3* disease-associated haplotype has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for XDP are possible.

Note: Caution should be exercised in interpreting the results of prenatal testing as the c.94C>T (p.Arg32Cys) variant that marks the disease haplotype has not been proven to be the molecular cause of XDP.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Parkinson Disease Association (APDA)**
  Phone: 800-223-2732
  Fax: 718-981-4399
  Email: apda@apdaparkinson.org
  www.apdaparkinson.org

- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org

- **Parkinson's Foundation**
  Phone: 800-4PD-INFO (473-4636)
  Email: contact@parkinson.org
  www.parkinson.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Dystonia-Parkinsonism Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TAF1	Xq13.1	Transcription initiation factor TFIID subunit 1	TAF1 @ LOVD	TAF1	TAF1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Dystonia-Parkinsonism Syndrome (View All in OMIM)

313650	TAF1 RNA POLYMERASE II, TATA BOX-BINDING PROTEIN-ASSOCIATED FACTOR, 250-KD; TAF1
314250	DYSTONIA 3, TORSION, X-LINKED; DYT3

Molecular Pathogenesis

Though first described in 1976, it was only in 1990 that X-linked dystonia-parkinsonism (XDP) was formally shown through segregation and biochemical analyses to be inherited as an X-linked trait [Kupke et al 1990b]. This dispelled previous theories that XDP may be caused by environmental factors (similar to the then-prevailing theory on the cause of Guamanian ALS-parkinsonism) or by metabolic defects. Confirmation of X-linked inheritance of XDP came with the assignment of the disease locus to Xq21 by linkage analysis [Kupke et al 1990a].

XDP Critical Region

The locus identified with *lubag* (DYT3) was proposed to be a multiple transcript system within the XDP critical region. In this complex transcriptional unit, different transcript isoforms share some of the 3' *TAF1* exons as well as additional exons downstream (termed exons d1-d5). These latter exons can also be transcribed independently [Nolte et al 2003, Herzfeld et al 2007]. The genomic and transcriptional structure of the XDP critical region is being refined; some conflicting results remain to be resolved [Muller et al 2007, Tamiya et al 2007].

It is difficult to predict cellular pathways which are affected in XDP cells. Vaine and colleagues assayed expression of defined gene sets in XDP versus control fibroblasts to identify networks of functionally related transcripts which may be dysregulated in XDP cells [Vaine et al 2017]. The analysis derived a 51-gene signature distinguishing XDP versus control fibroblasts which mapped strongly to nuclear factor-kappa B (NFκB), a transcription factor pathway also implicated in the pathogenesis of other neurodegenerative diseases, including Parkinson and Huntington disease.

Gene structure. *TAF1* (reference sequences NM_004606.3, NP_004597.2) has 38 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nolte et al [2003] described five XDP-specific changes (DSC) (DSC1, 2, 3, 10, and 12) as well as a 48-bp deletion in the XDP critical region that mark a *TAF1/DYT3* disease-associated haplotype. These DSCs as well as the 48-bp deletion were found in all Filipino individuals with XDP, but not in normal Filipino

controls with no family history of XDP or in other populations with similar phenotypes. Nolte et al [2003] suggested that it is likely that DSC3 plays a pathogenic role in XDP, although the other XDP-specific sequence changes may also contribute to the disease.

None of the DSCs was located within a structural or regulatory region of a known gene. Rather, most changes occurred within repetitive DNA:

- DSC1 is located within an Alu repeat, DSC2 within a LINE2 repeat, and DSC10 within a LIMB2 repeat in intron 32 of *TAF1*. DSC12 is located in intron 18 of *TAF1*, whereas the 48-bp deletion is located in intron 2 of *TAF1*.
- Only DSC3 (c.94C>T (p.Arg32Cys) in *DYT3*) is embedded in a predicted exonic DNA sequence, located in exon "d4." The DSC3 variant was not detected in unaffected Filipino or other non-Filipino populations and is the only molecular alteration detected in a mature transcript within the XDP core haplotype. Nolte et al [2003] concluded that it is likely that DSC3 plays a pathogenic role in XDP, although other XDP-specific sequence changes may also contribute to the disease (e.g., by influencing splicing of transcripts). To date, XDP is known only in persons of Filipino descent, suggesting genetic homogeneity.

Using genomic sequencing analysis followed by expression analysis of XDP in brain tissues, Makino et al [2007] reported a disease-specific *s*hort interspersed nuclear element, *v*ariable number of tandem repeats, and *A*lu composite (SVA) retrotransposon insertion in intron 32 of *TAF1*, with significantly reduced expression of *TAF1* and *DDR2* (encoding the dopamine receptor D_2) in the caudate nucleus of individuals with XDP [Makino et al 2007].

Table 2. Selected Variants within the XDP Critical Region

Gene/Locus	Variant Classification	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
TAF1/DYT3	Pathogenic / Marker	c.94C>T	p.Arg32Cys (DSC3)	AJ549245.1 [2]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. The variant c.94C>T (p.Arg32Cys) is named on the reference sequence for *DYT3*.

Bragg et al [2017] have further analyzed the sequence of the SVA in *TAF1* and detected polymorphic variation in the length of a hexanucleotide repeat domain, (CCCTCT)n, which varies from 35 to 52 repeats. The length of the repeat correlates inversely with age at disease onset [Bragg et al 2017].

Molecular mechanisms in symptomatic women with XDP. The majority of symptomatic women with *lubag* are heterozygous for the *TAF1/DYT3* disease-associated haplotype, thus suggesting extremely skewed X-chromosome inactivation. Rarely, females may be symptomatic due to homozygosity for the *TAF1/DYT3* disease-associated haplotype [Evidente et al 2004b, Domingo et al 2014].

The loss of one X chromosome in a subset of cells or X-chromosome monosomy (45,X / 46,XX) has also been noted in a female with XDP and a phenotype similar to Turner syndrome [Westenberger et al 2013].

Normal gene product. Unknown

Abnormal gene product. Whether an abnormal protein product results from the DSC3 (c.94C>T;p.Arg32Cys) variant in *DYT3* is unknown. Nolte et al [2003] hypothesized that the *DYT3*-specific sequence changes could contribute to the disease by influencing splicing of transcripts. However, Makino et al [2007] suggested that the SVA retrotransposon insertion into *TAF1* may cause XDP by altering expression of *TAF1* isoforms (including the

neuron-specific TA14-391), possibly through DNA methylation alterations. The decreased expression of the TA14-391 isoform (and possibly other *TAF1* isoforms) in XDP brains may result in transcriptional dysregulation of many neuronal genes, including *DRD2*.

Although the individual or combined roles of DSC3, the other DSCs, and the SVA retrotransposon in pathogenesis of XDP remain to be determined, more recent work by Herzfeld et al [2013] suggests that the DSC3 in *TAF1/DYT3* interferes with dopamine processing and function, as well as calcium metabolism leading to impaired vesicular neurotransmitter release.

Ito and colleagues generated XDP and control fibroblasts and induced pluripotent stem cells (iPSCs) in order to further probe cellular defects associated with XDP [Ito et al 2016]. They compared expression of TAF1 and MTS transcripts in XDP versus control fibroblasts and iPSC-derived neural stem cells (NSCs). Compared with control cells, XDP fibroblasts exhibited decreased expression of TAF1 transcript fragments derived from exons 32-36, a region spanning the SVA insertion site. N-TAF1, which incorporates an alternative exon (exon 34'), was not expressed in fibroblasts, but was detectable in iPSC-differentiated NSCs at levels that were three times lower in XDP cells than in controls. Thus, not only do these new data support the previous findings that N-TAF1 expression is impaired in XDP, but additionally indicate that this aberrant transcription could occur in neural cells at relatively early stages of development that precede neurodegeneration.

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