PATHOPHYSIOLOGY AND ETIOLOGY OF DYSTONIA: FOCUS ON GENETIC FORMS AS CLUES TO PATHOPHYSIOLOGY

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A. Background:

Dystonia is a type of hyperkinesia, not a specific disease. It is characterized by sustained, muscle contractions causing repetitive postures and movements that are usually directional in nature, may be twisting, (Fahn 1987) and are often initiated or worsened by voluntary action and associated with overflow muscle activation (Albanese 2013). **The causes of dystonia are diverse**, including genetic etiologies that result only in dystonia (and sometimes tremor) as the only neurologic feature. Previously described as "primary dystonia", these **inherited dystonias with dystonia and tremor as the only features are now labeled as inherited isolated dystonias** (Albanese 2013). **Dystonia may also occur with other movement disorders (combined dystonia), and may also occur along with other neurologic findings (complex dystonia)** (Klein 2014). The varied and wide-reaching etiologies and include: medication-induced (e.g. dopamine-blocking agents used for nausea or for psychiatric conditions), inherited without a known metabolic abnormality, genetic causes leading to significant other neurological sequellae (e.g.glutaric aciduria type 1), severe degenerative disorders, stroke, or as the first feature or as the first presentation of early-onset Parkinson disease (PD), (both genetic or idiopathic PD). Clues regarding pathophysiology of dystonia are derived from multiple sources, including imaging of structural lesions (LeDoux 2003) and neuropathology. However in the inherited isolated forms of dystonia, both gross structural imaging and neuropathology are normal (Dauer 2014), therefore for these, as well as other etiologies of dystonia, functional imaging, electrophysiologic recordings, and systematic experimental studies lend additional insight. While the goal is to identify shared pathophysiological elements that will provide a common endophenotype for treatment, as befits a description of features with a wide range of etiologies, there is no single unifying pathophysiologic basis of dystonia. It is felt that variation in etiology may also contribute to some diversity of pathophysiology. After brief review of considerations of clinical approach to dystonia, this syllabus focuses primarily on emerging theories in pathophysiology of dystonia. This will be done, in part, through highlighting specific genetic forms of isolated dystonia.

Please see syllabus from Dr. Daniel Tarsy, for more detail on the overall approach to the patient with dystonia. As noted, the history includes determining whether there is a presumed structural or other etiology, such as a brain lesion from stroke, tumor, or metabolic disease, or a toxic etiology, such as tardive dystonia secondary to dopamine-blocking agent usage. Family history may yield tremendous clues with regard to etiology, although some individuals with identified genetic forms of dystonia may not have a known family history. This is particularly relevant in that many of the genetic forms of dystonia are transmitted in an autosomal dominant manner, but with reduced penetrance. Reduced penetrance means that the parent may be a gene carrier and never develop dystonia. For DYT1 dystonia, it is approximately 30% penetrant(Bressman 2002), and for DYT6/THAP1 approximately 50 or 60% penetrant (Saunders-Pullman 2007). Expression may also be variable. Variable expression describes the phenomenon that for a particular gene there may be a range in phenotype. This is particularly notable in DYT1 dystonia where one family member may have mild focal writer's cramp and another family member with the same gene, severe generalized dystonia with dystonic storm (Opal 2002). In the area of ascertaining the family history, this translates into that a parent may have a different expression of dystonia than the child. For example, the mother or father may have writer's cramp, never have presented to a physician, never diagnosed as dystonia, and the family history of dystonia not known to the child. Thus some cases with apparently "negative" family history may have disease. Another area with very notable difference in expression is dopa-responsive-dystonia, where the grandchild who harbors a GTPCH-1 mutation may have early onset dystonia, the gene carrying grandparent may present only in later life with parkinsonism (Nygaard 1990).

While the oral session will focus on genetics and update in genetics as a window to pathophysiology, this syllabus primarily on pathophysiologic mechanisms for which there is only limited time to discuss in the presentation.

Table 1 presents some of the major genetic determinants of isolated dystonia, as well as the combined dystonia syndromes. Focus on the pathophysiology will reference primarily related to DYT1/Tor1A and DYT6/THAP1 dystonia.

Table 1: Dystonia (DYT) Loci (Using HUGO Nomenclature)

HUGO Dystonia (DYT) Genetic Loci

Isolated Persistent

Locus	*Inheritance*	*Phenotype*	*Gene*
DYT1	**AD**	**Early, limb**	**Tor1A**
DYT6	**AD**	**"Mixed"**	**THAP1**
DYT25	**AD**	**"Mixed" cervical**	**GNAL**
DYT4	**AD**	**Whispering Dysphonia**	**TUBB4A**
DYT24	AD	Adult, cervical	CIZ
DYT23	**AD**	**Adult, mostly** cervical/cranial	**ANO3**
DYT2	AR	Early – upper	HPCA
DYT27	AR	Early – upper	COL6A3
DYT13	*AD*	*"Mixed"*	*unknown*
DYT21	*AD*	*"Mixed"*	*unknown*

Combined Persistent

Locus	*Inheritance*	*Phenotype*	*Gene*
DYT5/14	**AD**	**DRD**	**GCH1**
DYT11	**AD**	**Myoclonus-Dystonia (M-D)**	**SCGE**
DYT15	*AD*	*M-D*	*unknown*
(also KCDT17, CACNA18, RELN)			
DYT12	**AD**	**RDP** AHC/CAPOS	**Na+/K+ ATPase**
DYT16	**AR**	**Dystonia-parkinsonism**	**PRKRA**

Paroxysmal

DYT8	**PNKD**
DYT9	**PEI**
DYT10	**PKD**
DYT18	**PEI+**

Complex e.g., ATM, **DYT3**, Wilson's, others

Legend for Table 1: HUGO: Human Genome Organization; AD: autosomal dominant, and AR: autosomal recessive; H-ABC: hypomyelination with atrophy of basal ganglia and cerebellum; DRD: dopa-responsive-dystonia; AHC: Alternating Hemiplegia Childhood; CAPOS: Cerebellar ataxia Optic atrophy Sensorineural hearing loss; PKD: Paroxysmal kinesigenic dystonia; PNKD: paroxysmal non-kinesigenic dystonia; PEI paroxysmal exercise induced dystonia

An additional important factor that guides the differential diagnosis of dystonia is the determination as to whether dystonia and tremor are the only neurological features, or whether there are additional features.

Table 2 shows brief clinical pearls in the differential of genetic etiologies of combined dystonia syndromes.

As expanded below, there is a range of diseases that may present with dystonia but then progress to include other features. These include foot dystonia as an early feature of Parkinson disease due to mutations in the parkin gene, Huntington disease and cranial, cervical and/or limb dystonia in some forms of spino-cerebellar ataxia. Of special note, neuropsychiatric Wilson disease may present with isolated dystonia, especially cranial, oropharyngeal and other cranial, limb or other dystonia (Machado 2006), and should be considered in younger persons with dystonia (Soltanzadeh 2007). It is always important to consider the highly treatable forms of dystonia including Wilson disease, but also dopa-responsive-dystonia (consider l-dopa trial) and GLUT1 deficiency. Table 2 describes some of the features that may be seen in addition to dystonia, and the genetic diseases in which dystonia co-occurs with them.

Table 2:

Clinical pearls in consideration of combined and complex dystonias-- features in addition to dystonia and tremor:
Careful examination facilitates determining whether there are features other than dystonia. As noted below, diseases which may present with dystonia include foot dystonia as an early feature of Parkinson disease due to mutations in the parkin gene, Huntington disease and cranial, cervical and/or limb dystonia in some forms of spino-cerebellar ataxia. Of special note, neuropsychiatric Wilson disease may present with isolated dystonia, especially cranial, oropharyngeal and other cranial, limb or other dystonia (Machado 2006), and should be considered in younger persons with dystonia (Soltanzadeh 2007).

Always consider the disease which are highly treatable or for which delay in diagnosis could result in irreversible decline: consider l-dopa trial for possible dopa-responsive-dystonia, consider Wilson disease which may present with classic wing-better tremor, but may also present with dystonia and other movements, and may mimic rapid-onset dystonia-parkinsonism, and now also consider GLUT1 deficiency.

Parkinsonism: While differing from isolated dystonia in that the syndromes (except autosomal dominant DRD and RDP as mentioned above) are usually associated with nigral degeneration, a portion of individuals with genetic parkinsonism may also exhibit dystonia. If it occurs early in life, it may be attributable to mutations in parkin, PINK1, DJ1, ATP13A2 (Kufor Rakeb), PLA2G6, and PRKRA (DYT16, which may occur with parkinsonism). Parkin-related disease may present solely as dystonia in some family members. The metabolic autosomal recessive dopa-responsive-dystonia (DRD) syndromes, such as that due to sepiapterin reductase deficiency or Tyrosine Hydroxylase (DYT5b), are rare, and likely not associated with neurodegeneration, but may have parkinsonism as early features with the dystonia. Finally, dystonia involving the legs and trunk may be an early feature of parkinsonism. While differing from isolated dystonia in that the syndrome is associated with nigral degeneration, a portion of individuals with genetic parkinsonism, particularly the autosomal recessive forms, including parkin, (PINK1, DJ1) and Kufor Rakeb may have initial presentation with early onset dystonia.

Ataxia: Ataxia may be present together with dystonia in ataxia-telangiectasia (AT) and variant AT (where dystonia may be a primary feature with little or no ataxia in most family members), spinocerebellar ataxias, Wilson, Vitamin E deficiency, Niemann-Pick type C (NPC), ataxia with oculomotor apraxia, GM2, and Fahr disease.

Neuropathy: is classically present with the dystonia in metachromatic leukodystrophy, neuroacanthocytosis, and the spinocerebellar ataxias.

Myoclonus: (in addition to the myoclonus-dystonia syndromes) is present in juvenile Huntington Disease (HD), AT, tardive dystonia, corticobasal syndrome, and neuronal ceroid lipofuscinosis (NCL).

Dementia travels with dystonia in Pantothenate kinase-associated neurodegeneration (PKAN), juvenile HD, GM2 gangliosidosis, NCL, NPC, Neuroacanthocytosis, and fronto-temporal dementia. For many of these the dystonia is more classically cranial, although there is a range.

Oculogyric crisis When oculogyric crisis is noted, Aromatic amino acid decarboxylase deficiency should be considered. Acute dystonic reaction from neuroleptics is probably the most common cause of oculogyric crises. It has also been reported in a single case with rapid-onset-dystonia parkinsonism (Termsarasab 15).

Vertical gaze paresis raises suspicion for Niemann-Pick type C, Kufor Rakeb and Progressive-supranuclear-palsy

Visual loss or an abnormal optic exam may indicate NBIA disorders, especially PKAN, mitochondrial cytopathies, gangliosidoses and NCL

Pathophysiology of dystonias:
There are several major approaches to pathophysiologic mechanisms. These include focus on dystonia as a disorder of inhibition and plasticity, as well as consideration of dystonia as a network and circuit disorder, and finally, due to cellular and molecular abnormalities (for reviews see Breakefield *et al*, 2008). Finally, there may be a developmental role in the pathophysiology of dystonia as well. These are not mutually exclusive, *pathophysiologic mechanisms overlap, but categories are separated to improve clarity. It is presumed that i*n combination dysfunction of these mechanisms lead to the abnormality of motor control that leads to involuntary muscle activity causing twisting movements and abnormal postures (Albanese *et al*, 2013).

1) Disorder of Inhibition and Plasticity:
The involuntary movements of dystonia are postulated to be caused fundamentally by three pathophysiological mechanisms: a) loss of inhibition at multiple levels of nervous system (Hallett, 2006), b) exaggeration of normal mechanisms of brain plasticity with reorganization of cortical regions (Quartarone *et al*, 2013), and c) dysfunctional sensory input, sensory processing and abnormal sensorimotor integration (Molloy *et al*, 2003).

The loss of inhibition responsible for the excessive movement in dystonia patients is characterized electromyographically by abnormally long bursts of muscle activity, co-contraction of antagonists, overflow of activity into unintended muscles (Hallett, 2004), and the classic irregular amplitude variable frequency 3-7 Hz muscle bursts of dystonic tremors (Deuschl *et al*, 2001). Spinal and brainstem reflexes are also abnormal in the regions affected by focal or segmental dystonia. For example, in focal hand dystonia there is loss of reciprocal inhibition in the arm, and in blepharospasm the blink reflex recovery test shows abnormal loss of inhibition after the second stimulus (for review see Hallett, 2006).

Loss of inhibition is also demonstrated at the motor cortical level with tests that reveal abnormal short intracortical inhibition, long intracortical inhibition, as well as abnormal cortical silent periods (Ikoma *et al*, 1996). These failures of inhibition may arise from a breakdown of ‘‘surround inhibition’’ in which the brain is not properly suppressing unwanted movements to allow the intended movement to take place (Mink 1996, Sohn *et al*, 2004).

Abnormal brain plasticity is thought to be integral to the pathogenesis of dystonia (Quartarone *et al*, 2006). This has been demonstrated using the technique of paired associative stimulation (PAS), which reveals an increase in synaptic long-term potentiation (LTP)-like plasticity in dystonia. With this technique, a median nerve shock is paired with a precisely timed transcranial magnetic stimulation (TMS) to the sensorimotor cortex. This results in increased amplitudes of the motor evoked potentials produced by TMS (Hallett, 2006).

A clinically relatable animal model of aberrant plasticity has been revealed by studies showing repetitive activity resulted in augmented cortical activity. Monkeys could no longer perform a repetitive act after being trained to for long periods of time, analogous to focal task-specific dystonia (Byl, 2007). The sensory cortex revealed larger than normal receptive fields suggesting that the prolonged synchronous sensory input caused the receptive field enlargement, and that the abnormal sensory function led to dystonia (Bara-Jimenez *et al*, 1998). Though sensory function in patients with cervical dystonia, blepharospasm and hand dystonia is clinically normal, detailed testing of spatial and temporal discrimination has revealed subtle impairments supporting this concept.

Sensory dysfunction and abnormal sensorimotor integration can also be demonstrated by a variety of clinical methods. The somatosensory evoked potential (SEP) from the hands in focal dystonia shows abnormal N20 responses, and disordered representation in the primary sensory cortex, both from the affected hand as well as from the clinically normal contralateral hand. This bilateral SEP abnormality may be more innate than a consequence of repetitive activity (Meunier *et al*, 2001). Other SEP studies linked to reaction time tasks also revealed abnormal sensorimotor integration where the N30 peak is not normally gated to the go stimulus in patients with focal hand dystonia. Finally, fMRI studies have shown abnormally high activity in the sensory cortex with specific tasks when patients are experiencing dystonia (Blood *et al*, 2004).

2) Network and Circuit abnormalities:
Abnormal circuitry in the striatum is also thought to be associated with the development of dystonia.

This may be apparent on the gross level with pathology or structural MRI, or on the less obvious level of functional imaging, very high resolution MRI or the effects of deep brain stimulation. Lesions of the basal ganglia and thalamus are found in neuropathology and structural imaging in some etiologies of dystonia, particularly stroke, and dystonia due to some metabolic causes. In contrast, there is no neuroanatomical abnormality and no apparent neurodegeneration in isolated inherited dystonia, however, the metabolic topography in some forms shows excessive activity in inhibitory pathways (Eidelberg, 1998) and volumetric enlargement of the basal ganglia and microstructural brain changes may also be found (Vo *et al*, 2015). Further support for the pivotal role of basal ganglia dysfunction in DBS is that most effective surgical intervention is deep brain stimulation in Globus pallidus internus (GPi) or subthalamic nucleus (STN), the main output nuclei of the basal ganglia (Alterman *et al*, 2007).

See Table 2 for a listing of some of the different genetic forms of dystonia—more detail of forms in addition to DYT1 and DYT6 will be discussed in the course. The list includes ANO3, which has now been replicated in additional families (Zech 2016, Blackburn 2016), as well as a new gene, lysine specific methyltransferase 2B (KMT2B) that has been implicated in early-onset generalized dystonia, although may also be syndromic with a broader phenotype, and regulates transcription (Zech 2016, Meyer 2017).

Functional neuroimaging has demonstrated network abnormalities for different genetic forms of dystonia (please see reviewed by Asanuma 2005 and Niethammer 2011), including DYT1, DYT5 and DYT6 dystonia. The cerebellar basis of dystonia is based on evidence that some forms of acquired dystonia have cerebellar lesions (LeDoux *et al*, 2003, Prudente *et al*, 2014) and the finding that cerebellar connectivity with the thalamus may relate to penetrance in carriers of DYT1 dystonia (Argyelan *et al*, 2009). Taken together with the plasticity and disordered sensorimotor integration, these suggest that basal ganglia and cerebellar dysfunction forms the core of the network (Reviewed by Prudente et al 2014).

3) Cellular and Molecular abnormalities, with specific focus on DYT1 dystonia

Dysfunction of cholinergic and dopaminergic neural elements in the basal ganglia and cerebellum have been proposed to provide unified pathophysiology of genetic etiologies of dystonia. These are reviewed in detail by Eskow Jaunarajs (2015), and Dauer (2014). These explain not only cholinergic associations in DYT1 dystonia, but also why anticholinergic and dopaminergic medications are main pharmacological therapies (Jankovic, 2013). The major genes which where dopamine signaling plays a role are the dopa-responsive dystonias (GTP-cyclohydrolase1 *GCH1*, tyrosine hydroxylase deficiency, and sepiapterin reductase deficiency, and GNAL (DYT25). (Fuchs 2012). GNAL encodes the Stimulatory alpha g-protein discovered in olfactory epithelial neurons (MSNs, Gαolf couples D1R of the direct pathway and A2AR of the indirect pathway to the activation of adenylate cyclase type 5, ADCY5). Mutations in ADCY5 are responsible for an expanding phenotype of childhood onset dystonia and chorea (Carapito 15). Of interest, while GNAL is considered a AD disorder, a homozygous case was recently reported in two siblings with early childhood hypertonia, then intellectual disability and more significant dystonia (Masuho 16).

a) DYT1 **(Tor1A) dystonia**: The majority of early onset isolated dystonia is attributable to mutations in the *DYT1* (Tor1A) gene. It occurs in Jewish AND non-Jewish families, and is found worldwide. The average age of onset is 13 years (range 3-64 years), and almost all cases start by age 26 or less. In 90% of cases, a limb is the first affected site, and one or more limbs are almost always affected (Bressman 2000). In 50% of cases there is a pattern of generalization involving both legs or one leg and the trunk, and dystonia in these sites often results in disability. Spread to cranial and cervical muscles is less common, and occurs in approximately 15-20% of cases. While the sites and ages of onset are relatively homogeneous, there may be tremendous clinical heterogeneity in severity and spread of dystonia, even among family members, (i.e. varied expressivity) with some family members having only undiagnosed writer's cramp, and others demonstrating severe life-threatening dystonic storm (Opal 2002). DYT1 dystonia occurs due to a three-base pair (GAG) deletion in exon 5 of the *DYT1* gene on chromosome 9q34 (Ozelius 1998) This common deletion is found in all patients with this disease regardless of ethnic background. While other mutations have been suggested, their relevance is not yet clear (Calakos 2010). Therefore genetic screening is limited to screening for the GAG deletion.

Despite that the gene was determined in 1998 (Ozelius 1998), the pathophysiology of DYT1 dystonia is still poorly understood (reviewed by Dauer, 2014). *DYT1* encodes a nuclear envelope heat shock protein in the AAA+ family of ATPases known as torsinA. The protein is widely expressed in the brain, including in the basal ganglia, cerebral cortex, hippocampus, and cerebellum. Mutation in torsinA changes its intracellular localization, with animal and cell culture models supporting redistribution of the protein to the nuclear envelope from the endoplasmic reticulum. Torsin A is thus a resident in the lumen of the endoplasmic reticular/nuclear envelope. Additionally mutant human torsin A shows decreased ATPase activity when expressed in bacterial cultures. It is considered a dominant negative effect as the disorder is autosomal dominant, and only a single mutated gene (with a normal second gene) causes the cellular redistribution.

While the role of torsinA in normal cell function is still largely not known, it has been postulated to effect the interactions between the nucleus and the cytoskeleton, the endoplasmic reticulum associated degradation (ERAD) system stress pathways, vesicular trafficking along the microtubular components of the cytoskeleton, neurite growth, and/or regulation of the exocytosis of synaptic vesicles. A potential link to the network approach is

that transgenic mice expressing mutant human DYT1 show increased striatal dopamine turnover, which could be attributable to exocytosis. Additionally, transgenic mice have dopamine D2 receptor abnormalities associated with altered GABAergic neurotransmission, and in response to dopaminergic afferent activity, show abnormal responses of cholinergic interneurons. An overarching approach to link the cellular and circuit approach is that the loss of torsinA function causes activation of ERAD stress pathways and neurodegeneration in a set of discrete set of sensorimotor brain regions linked previously to the pathophysiology of DYT1 dystonia (Liang 2014, Dauer 2014), and there is a strong role for both cholinergic and dopaminergic pathways (Eskow Jaunarajs 29015, Furukawa 2000). Additional support for dopaminergic role in dystonia is the occurrence of dystonias after exposure to D2 receptor blocking agents (e.g. metaclopramide, haloperidol), and the emergence of dystonia as a result of a number of mutations in the biosynthetic pathway for dopamine, such as in dopa-responsive-dystonia. Most recently, impaired eIF2alpha signaling has been identified as linked to DYT1 dystonia using a genome-wide interference RNA screen (Rittiner et al, 2016). This was also suggested to play a role in DYT16 dystonia, and because EIF2lpha is part of a pathway involved in cellular stress response and synaptic plasticity, an overall role for this in dystonia was postulated.

Of paramount importance is the limited penetrance of DYT1 dystonia, with only approximately 30% of gene carriers manifesting symptoms. Late onset cases (up to the age of 64 with oromandibular dystonia) are rare (Klein 2004). Thus there is a temporal window of vulnerability whereby if carriers exceed the age of 26, they are extraordinarily unlikely to develop new onset symptoms. Dauer et al have shown a murine correlate to this human phenomenon whereby a conditional knock-out causes perinuclear accumulation of ubiquitin and the E3 ubiquitin ligase in discrete group of sensorimotor regions including cortex, GP, and DCN (Liang 2014) followed by neurodegeneration. These effects become fixed during murine maturation. The sensorimotor regions parallel those with demonstrated abnormalities on FDG-PET imaging (Argyelan 2009). However this model appears to be most applicable to onset of dystonia, as despite the window of vulnerability to developing dystonia, individuals with DYT1 mutations may show dramatic improvement of dystonia both in early and late disease with oral medications and with deep brain stimulation therapy.

Factors that affect this penetrance in humans are not well known. There is a histidine polymorphism at residue 216 of the codon has been associated with decreased penetrance of the mutation; however, because it is an uncommon polymorphism overall, it only accounts for a small fraction of the reduced penetrance, and other factors must be at play (Risch 2007). Therefore the question emerges as to whether carriers who do not manifest dystonia have sequellae attributable to the DYT1 mutation separate from manifesting frank dystonia. Among carriers of the DYT1 mutation who have not developed dystonia, there may be an endophenotype with functional imaging abnormalities, with cerebellothamocortical connectivity regulating penetrance (Argyelan 2009). Further carriers may have slowness in motor learning tests (Carbon 2011) and a higher prevalence of affective disorders than control subjects without the mutation (Heiman 2004). Transcranial magnetic stimulation (TMS) of the cortex in manifesting and non-manifesting carriers of DYT1 reveals abnormal cortical electrical activity; specifically intracortical inhibition is decreased in carriers of the DYT1 deletion. Transgenic mouse models of DYT1 dystonia show abnormal inhibition in the globus pallidus externa (GPE) and interna (GPI) after stimulation of the cortex. Taken together, these suggest that there are brain changes attributable to harboring the DYT1 mutation, and that there may be patterns separate from the development of dystonia.

b) Other common mechanisms are also proposed for the genetic dystonias, and focus on THAP1:
***DYT6* (THAP1) dystonia** occurs relatively early but has a broad age at onset (mean 16 years, with range 2 to 53 years). The body regions first affected included the cranial muscles (larynx, tongue and facial muscles in approximately 25%), neck (about 25%), arm (approximately 50%) and in contrast to *DYT1*, rarely the leg (4%). There is variable but frequent progression, and while the leg may be affected in 50%, the need for assistive devices for mobility is much less than in *DYT1* dystonia. For most, disability stemmed from cranial and cervical dystonia, including significant speech difficulties.

DYT6 is inherited in an autosomal dominant manner with reduced penetrance (~60%) and variable expressivity. Although more cases of DYT6 mutations in women are reported, initial penetrance studies have not demonstrated that female gender is associated with increased penetrance.

The founder mutation found in the three initial families of Amish-Mennonite origin and the subsequent one represented a 5 bp insertion/3 bp deletion (indel) resulting in premature termination of the THAP1 protein. Subsequently multiple other mutations in THAP1 have been identified worldwide, and are catalogued at the curated website: http://www.umd.be/THAP1/Blanchard.

The molecular/cellular mechanism for which mutations in *THAP1* result in primary dystonia is not clear. THAP1 regulates endothelial cell proliferation through its DNA binding domain. Both known mutations are likely to be sufficient to abolish its DNA binding activity and, hypothetically, to potentially cause transcriptional dysregulation affecting downstream targets. An alternative pathway involving programmed cell death has also been proposed as a possible etiologic mechanism, as THAP1 is known to function also as a proapoptotic factor.

From a circuit standpoint, functional imaging has shown both similarities and differences with DYT1 dystonia.

Regional metabolic patterns are distinct between manifesting and nonmanifesting carriers of DYT1 and DYT6 mutations.

Unifying theories are described in detail by Lohmann and Klein 2013, and include models describing disorders of cytoskeleton and intracellular transport that include not only DYT1 (as described above), but also TUBB4 (DYT4), myoclonus-dystonia due to mutations in *SGCE* (DYT11). Genetic etiologies of dystonia associated with abnormalities of ion channels include not only the channelopathies and rapid-onset-dystonia parkinsonism (*ATP1A3*, DYT12) (discussed below), but also ANO3 (DYT24), an isolated dystonia with cervical dystonia and sometimes tremor as the primary manifestation. Disorders of transcriptional regulation include (TAF, DYT3) and THAP1 (DYT6). Disorders of cell cycle control include (*THAP1* and possibly *CIZ* (DYT23). Mutations in GNAL are an infrequent cause of cervical dystonia

4) Additional evidence for a developmental role in the pathophysiology of dystonia. In addition to functional imaging changes (Niethammer 2011), and a window of vulnerability in DYT1 dystonia, this window is also seen in other dystonias, such as glutaric aciduria type 1 (Strauss 2003), including the differential expression of dystonia at different ages with early onset disease tending to involve the leg and spread rostrally, whereas late-adult onset is likely to start in the cranial regions and not spread (Greene 1995). Other examples of an age dependent phenotype include dopa-responsive-dystonia and rapid onset dystonia parkinsonism.

a)**Dopa-responsive-dystonia** (DRD, Please also see syllabus from Dr. Tarsy): DRD is highly treatable, usually childhood onset disorder usually with leg dystonia and excellent response to levo-dopa. (As noted above, DRD may also respond to anti-cholinergics, but l-dopa is the preferred medication). Autosomal dominant DRD is due to an incompletely penetrant mutation in (GCH1). GCH1 promotes the synthesis of tetrahydrobiopterin, an aromatic amino acid hydroxylase that is necessary for the hydroxylation of phenylalanine to tyrosine and tyrosine to l-dopa. Of great interest is that mutation carriers typically present in childhood or adolescence with leg dystonia, and while parkinsonism may be present, it is not usually a prominent feature. In contrast, individuals who harbor GCH1 mutations may not develop disease until the 50s to 70s, at which point parkinsonism, which may closely mimic IPD, is the predominant finding. It is not clear why this metabolic disorder causes predominant generalized dystonia in childhood and parkinsonism in later life, and suggests that the brain response to the metabolic stress varies throughout life, and that the same deficit results in varied pathophysiology.

b)**Rapid-onset dystonia parkinsonism**: RDP is a rare disorder, with prominent bulbar and tonic dystonia spasticity and postural instability (Brashear 2007). The bulbar features may mimic Wilson disease, and as Wilson disease is treatable neurodegenerative disorder, should be considered in the differential of RDP, RDP is attributable to mutations in the gene for the Na+/K+ ATPase alpha3 subunit (ATP1A3) (De Carvalho Aguilar 2004). Since identification of the gene it has now become apparent that mutations in this gene are responsible not only for classic RDP, but alternating hemiplegia of childhood, and the phenotype is likely both age and genotype dependent (Rosewich 2014).

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Recent reviews summarizing themes highlighted in this syllabus are bolded.

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