

Naming Genes for Dystonia: DYT-z or Ditzzy?

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Abstract

Dystonias are a clinically and etiologically diverse group of disorders. Numerous genes have now been associated with different dystonia syndromes, and multiple strategies have been proposed for how these genes should be lumped and split into meaningful categories. The traditional approach has been based on the Human Genome Organization's plan for naming genetic loci for all disorders. For dystonia this involves a DYT prefix followed by a number (e.g., DYT1, DYT2, DYT3, etc.). A more recently proposed approach involves assigning multiple prefixes according to the main elements of the phenotype (e.g., DYT, PARK, CHOR, TREM, etc.) followed by the name of the responsible gene. This article describes these nomenclature systems and summarizes some of their limitations. We focus on dystonia as an example, although the concepts may be applied to all movement disorders.

Keywords: Dystonia, nomenclature, gene, locus, mutation, genetic variant

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Brief history of gene nomenclature

Historically, most disease-associated genes were discovered by a process known as “linkage analysis.” In brief, large families with multiple individuals affected by a specific disorder were collected, and genetic “markers” with known locations spread across all chromosomes were examined for family members with and without the disorder. Then, large stretches of DNA were sequenced in the chromosomal locations closest to the markers that correlated best with the disease phenotype. Having multiple large and unrelated families greatly aided this process by increasing the statistical power to detect correlations between the disease phenotype and the genetic marker. Therefore, identifying multiple unrelated families with the same condition was historically essential for the identification of novel disease genes.

To aid the process of identifying families with similar disorders, the Human Genome Organization (HUGO) developed a convention for acknowledging potential new genes for families in which linkage studies pointed to a specific chromosomal location or “locus.” HUGO intended

that the locus name should be dropped after the gene was discovered because knowing the gene is more important than linkage-based statistical estimates of its location in the genome. Therefore, the original intention of the HUGO locus nomenclature system was to provide a temporary label to aid in the identification of families for linkage analyses.

The HUGO convention was applied for naming loci for candidate genes to all human disorders. Movement disorders were grouped according to the main aspects of the clinical phenotype and given a specific prefix such as Parkinson's disease (PARK), spinocerebellar ataxia (SCA), hereditary spastic paraplegia (HSP), or dystonia (DYT). When linkage studies for a new family pointed to a novel locus different from previously identified loci, the prefix was appended with a distinct number (e.g., DYT1, DYT2, DYT3, etc.). In this way, multiple unrelated families that might share defects in the same gene could be identified and analyzed together to improve the chances of finding the relevant gene.

Prefix assignments were never generated for certain disorders where linkage studies had not yet identified meaningful targets, including tremor,

myoclonus, paroxysmal dyskinesias, and others. This simple nomenclature system has been in use for many years, but it has also led to numerous problems.¹ The problems are illustrated here using dystonia as an example, although similar problems have been described for other movement disorders.

The DYT prefix is misleading

The DYT prefix was intended for disorders where dystonia is an important aspect of the phenotype. This is not always the case. For example, the myoclonus–dystonia syndrome was assigned to the DYT11 locus, and at least one causative gene has been identified (*SGCE*). However, the most consistent feature of this disorder is myoclonus, not dystonia.^{2,3} Many patients with this disorder also have dystonia, and dystonia may sometimes be severe. However, dystonia is often quite subtle, with a slight tilting of the head, or slightly scalloped posture of a hand. Sometimes there is myoclonus without any dystonia, and the disorder is then called essential myoclonus. Similarly, the paroxysmal dyskinesias were assigned to DYT8 (*MR-I*), DYT10 or DYT19 (*PRRT2*), and DYT9 or DYT18 (*SLC2A1*). However, in these disorders, the movement disorder is quite varied and reflects various combinations of dystonia, chorea, ataxia, and sometimes other abnormalities.⁴ Dystonia is not always a prominent feature of these conditions. In other words, lists of genes with the DYT label misleadingly imply that they all designate disorders where dystonia is an important aspect of the phenotype.

In other cases, the DYT prefix was applied appropriately, but subsequent identification of the gene led to recognition of alternative phenotypes where dystonia was a minor component or even lacking. For example, DYT9 and DYT18 were assigned to paroxysmal exertional dyskinesia, where the most prominent movement abnormality is dystonic posturing following exercise.⁵ Identification of the associated gene (*SLC2A1*) led to the appreciation that the same gene was already linked with several other phenotypes, including infantile encephalopathy with seizures and ataxia, several different types of epilepsy, and hemiplegic migraine.⁶ In fact, paroxysmal exertional dyskinesia is a relatively uncommon phenotype for pathological genetic variants in *SLC2A1*. Similarly, DYT12 was assigned to the syndrome of rapid-onset dystonia-parkinsonism, where dystonia is a frequent and prominent problem.⁷ However, the responsible gene (*ATP1A3*) was again linked with other phenotypes, including alternating hemiplegia of childhood and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss).⁸ In these other disorders, dystonia may be minor or absent. In other words, discovery of a gene associated with some DYT loci led to the realization that dystonia was a relatively minor phenotype of a more complex group of clinical syndromes.

In addition to having several DYT labels assigned to disorders where dystonia is sometimes minor, the converse is also true; there are multiple disorders where dystonia is a consistent or major aspect of the clinical phenotype, yet they lack DYT labels. In some cases, the reason is that the gene was identified before the DYT naming convention was established. For example, dystonia is universal in classic Lesch–Nyhan disease,⁹ and may be the presenting or main problem in the Lesch–Nyhan variants.¹⁰ The responsible gene, *HPRT1*, was found

in 1985 before the DYT convention started. Similarly, dystonia occurs in the majority of individuals with neurological Wilson’s disease (*ATP7B*).¹¹ In some cases, dystonia is the presenting problem, or the most disabling problem. Despite the prevalence and severity of dystonia in Lesch–Nyhan disease and Wilson’s disease, neither has been assigned a DYT label. In fact, there are more than 100 disorders without DYT labels where dystonia may be an important feature of the phenotype.¹²

More recently, several new genes have been discovered where dystonia is a prominent feature of the phenotype. An example involves defects in manganese transporters linked to the *SLC39A14* or *SLC30A10* genes, where dystonia is a consistent and prominent problem.^{13–15} In both cases, a DYT prefix was not assigned because dystonia was only one feature of a more complex phenotype, and assigning a DYT prefix neglected other important aspects of the phenotype. The methods for gene discovery in these more recent studies were less dependent on traditional linkage methods; therefore, there was no value in assigning a DYT locus label. Nowadays, more genes are being found using methods where linkage analysis plays a minor role.

Clinicians need access to complete and accurate lists of dystonia genes for diagnostic purposes. Basic scientists need access to complete and accurate lists to elucidate biological pathways. The traditional lists of disorders with the DYT prefix misleadingly imply that dystonia is a consistent or major aspect of the disorders listed. These lists also are misleadingly incomplete because they neglect a large number of disorders where dystonia is relevant.

The numbering convention has become inconsistent

In addition to the DYT prefix being misleading, the numbering system has become confusing because of inconsistent use and multiple errors. If a locus aims to guide investigations for a unique dystonia gene, then there should be a one-to-one correspondence between one locus name and one gene. This is not the case. DYT5 (dopa-responsive dystonia) includes at least two genes (*GCHI* and *TH*).¹⁶ Genetic variants in *SPR* were later found to cause the dopa-responsive dystonia phenotype by a candidate gene approach, and not by linkage analysis; therefore, a locus was never assigned. However, some investigators have begun to include *SPR* under the DYT5 umbrella because of a shared phenotype.^{17,18} Therefore, DYT5 has become synonymous with the dopa-responsive dystonia phenotype, not a label for a unique genetic locus.

The DYT2 label has evolved in a similarly confusing way. This label was originally reserved for a family with autosomal recessive dystonia. Multiple unrelated families with autosomal recessive dystonia were later described as DYT2.^{19–21} Occasionally, the term “DYT2-like” was used when the dystonic phenotype did not precisely match the original family. The *HPCA* gene was later identified for one of these families,²² and has now taken the DYT2 label. However, no linkage studies were conducted for any of these families, and therefore it is impossible to know if any shared the same locus or gene. Like DYT5 for dopa-responsive dystonia, the DYT2 label has transformed from a locus into a phenotype, which is caused by multiple different genes.

Just as some DYT labels may have multiple genes, several genes have multiple DYT labels. For example, the *SLC2A1* gene accounts for both

DYT9 and DYT18 and the *PRRT2* gene accounts for DYT10 and DYT19. These discrepancies were caused by errors in the original assignments of a DYT number to what was thought to be a unique locus for a unique gene.

In other cases, DYT loci were erroneously assigned because the original linkage analysis was wrong. For example, classical linkage studies designated DYT14 as a novel locus for dopa-responsive dystonia unrelated to the previously designated locus (DYT5) for dopa-responsive dystonia caused by pathological genetic variants in *GCH1*. However, the gene responsible for DYT14 proved to be the same gene (*GCH1*) because incorrect phenotypic assessments led to a misleading linkage analysis result.²³ The existence of a dystonia gene for cervical dystonia at the DYT7 locus in one large family has similarly been questioned because of uncertainties in assigning the phenotypic status for affected versus unaffected family members.²⁴ These errors emphasize that loci defined by linkage studies are statistical estimates of the locations of presumed genes that are based on phenotypes that may be mild or may evolve with age; therefore, there will always be some chance that they are wrong.

Finally, there is at least one example where the DYT label did not follow the standard naming convention. The term “DYT-CA” was coined to describe a phenotype of cervical dystonia combined with progressive cerebellar ataxia.²⁵ This label seems quite sensible because of the combination of dystonia and ataxia, but its position in lists relative to other DYT loci causes confusion, and this disorder is therefore often omitted from gene lists that follow the HUGO tradition.

Recently proposed nomenclature plan

To address the many problems with HUGO’s original nomenclature system, a new system was proposed by a task force for genetic nomenclature in the Movement Disorders Society (MDS).²⁶ The new proposal called for several major changes: (1) Multiple prefixes would be combined to better recognize the phenotype, (2) new phenotype prefixes would be established where they were previously lacking, (3) the numbering system would be replaced by the actual gene name, (4) all disorders would be given a label under the new system, including those that did not have labels under the HUGO plan, and (5) only confirmed disease-causing genetic variants would be included in the list (i.e., pathogenic variants in a gene need to be reported by at least two independent groups). The newly proposed nomenclature system solves several of the problems with the HUGO nomenclature system. However, as further described below, the new system also creates new problems.²⁷

Permitting multiple prefixes and establishing new prefixes as proposed by the MDS task force address the problem of forcing complex phenotypes into HUGO’s oversimplified single prefix plan. For example, pure dystonia is designated with DYT only, while dystonia combined with parkinsonism would be designated as DYT/PARK, and dystonia combined with ataxia would be designated as DYT/SCA. New prefixes would include tremor (TREM), paroxysmal dyskinesias (PxD), myoclonus (MYOC), and others. The MDS task force further recommended that phenotypic prefixes should be assigned only when the phenotype is observed as a prominent feature in the majority of cases and should be confirmed by at least two independent groups. Together, these changes would more accurately reflect the phenotype, including

mixed phenotypes, and even changing phenotypes resulting from the growth of knowledge as new cases are described.

A major challenge in implementing the proposed changes is that assigning prefixes requires some arbitrary decisions. For example, the MDS task force recommended that DYT11 (*SGCE*) should be labeled as DYT-*SGCE*. However, myoclonus is often a more prominent aspect of the phenotype than dystonia.²³ Hence, it could be argued that the proper prefix should be MYOC, or MYOC/DYT. The task force also recommended that DYT1 should be labeled as DYT-*TOR1A* to emphasize the importance of dystonia. However, the majority of dystonia patients also have tremor, which can sometimes be the most prominent feature. Here again, it could be argued that a more accurate prefix would be DYT/TREM-*TOR1A*. These examples highlight the arbitrary nature of prefix assignment under the proposed system and raise an even more difficult question regarding who has the authority to declare the most prominent phenotype(s), and who will arbitrate when there are disagreements among experts. Furthermore, the label will change when alternative phenotypes are discovered, a phenomenon that is nearly universal in human genetics.

Lesch–Nyhan disease provides another example. The MDS task force recommended that this disease should be designated as DYT/CHOR-*HPRT1*. However, chorea is not a prominent feature in the majority of either classic⁹ or atypical variant phenotypes¹⁰ associated with pathogenic genetic variants in *HPRT1*. The reasons for including CHOR therefore could be disputed, and a somewhat arbitrary decision would have to be made. Who arbitrates the disagreement? On the other hand, there are some other very important aspects of the phenotype that are nearly universal, such as intellectual disability, overproduction of uric acid, and macrocytic erythrocytes.²⁸ Should all of these phenotypic elements be acknowledged too? If the answer is “no,” then the proposed nomenclature system is relevant only for the movement disorder, and it is not likely to be adopted by colleagues in genetics outside of the movement disorders field. If the answer is “yes,” then it is easy to see how the proposed nomenclature system rapidly becomes unwieldy for complex phenotypes.

Under the new plan, a DYT label would be assigned for all genes associated with dystonia, including those that never had a DYT name before. This proposal means that genes discovered before the HUGO system started would be recognized. It also means that new genes that bypassed the need to name a locus would be recognized. This proposal corrects the weakness of the traditional nomenclature plan that led to lists neglecting a large number of genes associated with dystonia. Aside from providing a system to catalog dystonia-related genes, this plan has limited value. For example, under the new system, Wilson’s disease is caused by pathogenic variants in the *ATP7B* gene and might be assigned DYT/PARK/TREM-*ATP7B*. It seems very unlikely that clinicians or geneticists will adopt this designation over “Wilson’s disease” or the “*ATP7B*” gene. If this is the case, the value of the new label is limited.

Also under the new plan, the DYT number would be replaced by the actual gene. DYT1 in HUGO nomenclature system is replaced by DYT-*TOR1A* in the MDS task force nomenclature system. Similarly,

DYT5 (dopa-responsive dystonia) becomes DYT/PARK-*GCH1* or DYT/PARK-*TH* to acknowledge the frequent occurrence of parkinsonism in this disorder, as well as potentially different causal genes. This proposal means that a name cannot be assigned until a gene is identified, preventing confusion associated with incorrect assignment of loci names that occurred with the old nomenclature system. However, the requirement for gene identification defeats the original purpose of this nomenclature system: to aid the identification of families with similar phenotypes to find these genes in the first place. This limitation would require a new nomenclature plan to identify families in which a suspected gene needs to be confirmed.

Synopsis

In summary, the HUGO-based locus naming system is fraught with problems. The new nomenclature system proposed by the MDS task force solves some of these problems but creates new ones. The new plan reduces the likelihood of inappropriate or incomplete phenotypic prefixes, intends to be more inclusive and complete, and limits errors in the numbering system. At the same time, the new system brings limitations of arbitrary phenotypic prefixes, complex and unwieldy names, and a loss of the original value of naming potential novel loci for linkage studies. The nomenclature system proposed by the MDS task force also requires a high degree of expertise in neurogenetics, and it is still under development, because many disorders have not yet been given names. Even if all relevant disorders can be given labels, these labels will

continue to evolve as new phenotypes and potential new disease-associated genes are described. This means that the proposed nomenclature will be constantly changing. Without stable names, it is likely that this system will be difficult to learn and will contribute to ongoing confusion.

The fundamental problem is that both gene nomenclature systems are trying to be something they are not. The original purpose was to identify families with similar phenotypes to aid linkage studies (Table 1). Although HUGO intended that the DYT labels should be dropped once the responsible gene was found, the labels were adopted for naming disorders and cataloging them. A relatively simple goal therefore has been distorted into a tool for organizing genetic disorders. The distortion of the original intent has produced many unintended consequences. For example, the HUGO-based DYT list has been reproduced numerous times in reviews on dystonia and referred to as a classification system for genetics. This convention is not a classification system, rather it is a list.

Another unintended consequence is that the DYT labels are now being translated for other uses as if they are abbreviations. There are now multiple published articles in the literature with “Dystonia-1” in the title line rather than the more commonly accepted name of “DYT1 dystonia.”^{29,30} The same is true for DYT6 dystonia and “Dystonia-6.”^{31,32} The International Classification of Diseases and Related Health Problems medical classification system of the World Health Organization has similarly translated these DYT labels as if they are abbreviations, and terms such as “Dystonia-1” and “Dystonia-6” are

Table 1. Comparison of Traditional and New Nomenclature Plans

Characteristic	Traditional HUGO Plan	MDS Task Force Plan
Useful for linkage studies	Yes	No; it requires identification of gene before a label is assigned
Inclusive of all dystonias	Poor; large numbers of dystonias are missing and will never be added	Modest; large numbers of dystonias are still not assigned labels
Identifies a single unique disorder	No	Yes
Label is stable over time	Yes; except for errors	No, prefix will evolve as new information expands the phenotype
Clear process for assigning labels	Yes; assigned by HUGO	No; unclear authority for assignment
Simple and easy to use	Yes	No; requires substantial expertise in neurogenetics
Accommodates multiple movement phenotypes	No	Yes
Accommodates non-movement phenotypes	No	No
Likely to be adopted by non-movement fields	Yes; already in use across all of medicine	No; relevant only for movement field
Accurately reflects the dominant movement disorder phenotype	No; not all DYT labels correspond to disorders where dystonia is the dominant feature	Partly; based on order of prefix listing
Useful clinical system for classifying dystonias into meaningful groups	No; this is a list, not a classification system	Partly; depending on prefix
Useful biological system for classifying dystonias into meaningful groups	No; this is a list, not a classification system	No; provides gene name only

Abbreviations: HUGO, the Human Genome Organization; MDS, Movement Disorders Society.

now being used to identify diagnoses for clinical billing and insurance coverage. The proliferation of multiple names for a single disorder is not useful.

Finally, it should be noted that neither the traditional nor the more recently proposed nomenclature strategies are compatible with oligo-inheritance, where one disorder may be the result of combined defects in multiple genes. None of the proposed nomenclature plans strategies is compatible with disorders associated with genomic deletions, which may span several genes.

Recommendations for the future

For clinical neurologists, memorizing the HUGO-based DYT numbers is not useful because there is limited practical value in a label that estimates a chromosomal locus (e.g., DYT24). Similarly, using labels that attempt to provide a synopsis of the phenotype as a prefix to the gene (e.g., DYT/PARK-*ATP1A3*) presents an oversimplified view for many disease phenotypes, and it is a cumbersome task to learn and apply. These nomenclature systems are not appropriate for application in the clinic.

For clinical neurologists, genetic disorders can be described by the name of the syndrome or disease (e.g., Wilson's disease) and/or the responsible gene (e.g., *ATP7B*). An additional label is not needed. In fact, this approach has been adopted already for several genetic disorders. For example, the many varied phenotypes associated with pathogenic variants in *GLUT1* have been called "GLUT1 deficiency syndromes."³³ If a clinician wants to refer to a more specific phenotype, then wordings such as "*GLUT1*-associated paroxysmal dyskinesia" can be used. Similarly, the many phenotypes associated with pathogenic variants in *ATP1A3* have collectively been called "*ATP1A3*-related disorders."⁸ For this approach to nomenclature, there is no need or value in an additional "DYT" label.

For basic scientists interested in the genetics of dystonia or its biological pathways, the HUGO-based list is limited because it is largely incomplete and has numerous errors. The new system provided by the MDS task force also bears several limitations because it is still incomplete, it relies on arbitrary decisions by individuals with uncertain authority to define the most relevant phenotypes, and it will always be in flux and lagging behind knowledge created by constant identification of novel disease-associated genes and gene-related phenotypes. Furthermore, the pathway for arbitrating disagreements for labels is not clear; therefore, this approach will inevitably lead to experts using different labels for the same disorder.

The recognition that multiple dystonia-associated genes are part of independent but convergent biological pathways is one of the most important conceptual advances made possible by the remarkable growth in the number of relevant genes.^{34,35} In the near future, classifying genes based on patterns of inheritance or shared biological pathways will have more relevance for understanding their biology and directing treatment strategies than classifying them according to varied and changing clinical phenotypes. Such classification systems may serve to better identify individuals with different genotypes who may respond to similar mechanism-based treatments.

New disorders and new genes are being found regularly. Of course, when they are first described, those describing them will have to recommend appropriate names. These recommendations should not be bound by complex nomenclature plans that have limited clinical or scientific value.

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