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Genetics in dystonia

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SUMMARY

While Hermann Oppenheim probably described the first cases of genetic (DYT1) dystonia in 1911, the 'modern history' of dystonia genetics dates back to 1994 when mutations in the *GTP cyclohydrolase I* gene were discovered to cause dopa-responsive dystonia. Due to the advent of next-generation sequencing, the field of dystonia genetics has been evolving very rapidly over the past two years, resulting in the reporting of 'DYT1-25' and, for the first time, in the identification of genes associated with adult-onset focal/segmental dystonia. However, three of these putative new genes still await independent confirmation (*TUBB4/DYT4*; *CIZ1/DYT23*; *ANO3/DYT24*) and only 11 'DYT' genes have been unequivocally demonstrated to cause different forms of dystonia. Based on a recent consensus approach, dystonias are subdivided on clinical grounds into isolated (with or without tremor) and combined (with other movement disorders) forms. Confirmed genes for isolated dystonias include *TOR1A/DYT1*; *THAP1/DYT6*; *GNAL/DYT25*. In the combined forms, dystonia is accompanied by parkinsonism (*GCH1/DYT5a*; *TH/DYT5b*; *ATP1A3/DYT12*; *TAF1/DYT3*) or myoclonus (*SGCE/DYT11*). Persistent and paroxysmal forms are distinguished according to their temporal pattern. The paroxysmal forms of dystonia/dyskinesias present with a mixed pattern of hyperkinetic movement disorders (*PRRT2/DYT10*; *MR-1/DYT8*; *SLC2A1/DYT18*).

1. Introduction

It may have been Hermann Oppenheim who described the first case of genetic (DYT1) dystonia as early as 102 years ago in his landmark paper from 1911 entitled "Über eine eigenartige Krampfkrankheit des kindlichen und jugendlichen Alters [About a peculiar cramping sickness in children and adolescents] (Dysbasia lordotica progressiva, Dystonia musculorum deformans" [1,2]. This article is remarkable not only for its insightful clinical description and for the coining of the term 'dystonia', but also for the fact that Oppenheim clearly recognized dystonia as an organic disorder, as opposed to 'hysteria'. Notably, he even pointed to a possible hereditary influence, as well as to the uniform ethnic (Ashkenazi Jewish) and geographic (Eastern European) origin of his patients [1,2].

The 'modern history' of dystonia genetics (Fig. 1) dates back to 1994 when the first 'DYT' gene was discovered, i.e. *GTP cyclohydrolase I*, mutations in which cause dopa-responsive dystonia [3]. This was followed by the identification of an additional eight dystonia genes over the next 15 years. Due to the advent of next-generation sequencing technology, the field of dystonia genetics has been evolving very rapidly over the past two years, leading to the reporting of another five genes since 2011. Importantly, however, three of these putative new genes still await independent confirmation (Figs. 1 and 2).

Following an introductory paragraph on the recently revised definition and classification of dystonia, confirmed genetic forms will be reviewed in detail below.

2. Definition and classification of dystonia

From 2011 to 2013, an international panel of dystonia experts developed a consensus update of the definition and classification of dystonia suggesting the following revised definition: Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation [4].

Several classification schemes have been employed to categorize the various forms of dystonia and are useful when trying to establish the diagnosis of a specific form of dystonia. The two main axes of classification currently considered most relevant are clinical and etiological [4]. On clinical grounds, the updated dystonia classification proposes characterization by age of onset (infancy, childhood, adolescence, early and late adulthood), body distribution (focal, segmental, multifocal and generalized), temporal pattern (static or progressive disease course; persistent, action-specific, diurnal or paroxysmal presentation), and association with

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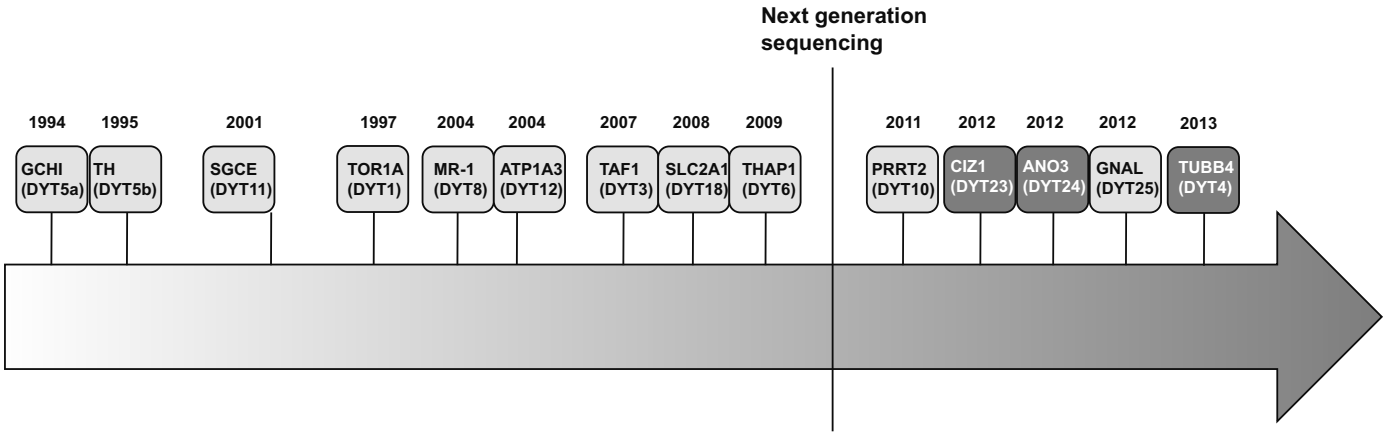

Fig. 1. Time line of gene discoveries for isolated and combined forms of dystonia. While the advent of next-generation sequencing has led to rapid advances in gene identification, three of these five novel genes (shaded in gray) have not yet been independently confirmed.

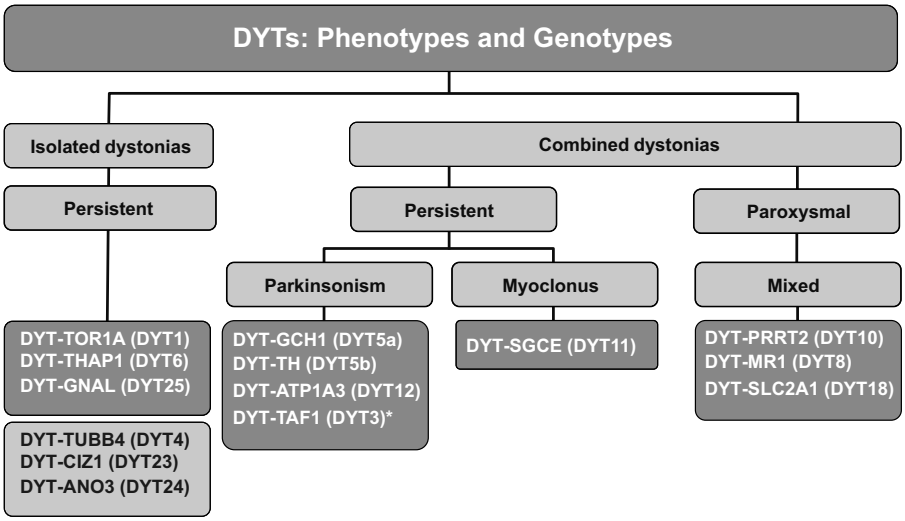

Fig. 2. Overview of phenotypes and corresponding genotypes of hereditary forms of isolated and combined dystonia. Based on distribution of symptoms, dystonias can be further subdivided into isolated and combined (with other movement disorders) forms. According to the temporal pattern of the dystonia/dyskinesia, the latter are further grouped into persistent and paroxysmal. In most of the persistent forms, dystonia is combined with parkinsonism. Another well-recognized form of dystonia is myoclonus-dystonia, in which dystonia and myoclonus coexist. The paroxysmal forms of dystonia/dyskinesias present with a mixed pattern of hyperkinetic movement disorders. Forms of dystonia with confirmed genes are shaded in dark gray; three recently reported new dystonia genes awaiting independent confirmation are shaded in light gray. *The genetic basis of DYT-TAF1 (DYT3) has not been unequivocally determined. However, it is linked to the X chromosome and can be tested for on the basis of a clearly established founder haplotype, and is thus included in the scheme.

additional features (isolated or combined with other movement disorders [4]. Formerly, isolated dystonia was referred to as 'primary dystonia' and combined dystonia (e.g. with parkinsonism or myoclonus) as 'dystonia-plus'. Clinical description along these lines enables formulating dystonia syndromes, e.g. early-onset generalized isolated dystonia or focal isolated dystonia with onset in adulthood.

Genetic features used for classification include mode of inheritance and molecular genetic data, such as linkage to a known gene locus or identification of a specific genetic defect. This list of currently 25 'DYTs' (Table 1) represents an assortment of clinically and genetically heterogeneous disorders, which names monogenic forms of dystonia in chronologic order based on their first appearance in the literature. In response to the increasing number of inconsistencies of the 'DYT' designations, a new nomenclature system for genetic forms of movement disorders, including dystonia, has been proposed [5]. According to the new system, only confirmed genes are included in the list of 'DYTs' and are no longer numbered. Rather, the 'DYT' prefix is followed by the gene name or gene locus, for example, 'DYT-TOR1A' (previously known as DYT1) [5] (Table 2). In the present article, the revised definition and categorization as well as the new nomenclature will be employed.

An accurate description of the dystonia phenotype is the first step when evaluating a patient for dystonia. Important hints for classification can also be derived from the disease course. For example, a sudden-onset dystonia disorder is compatible with rapid-onset dystonia-parkinsonism. While many dystonias can be triggered or exacerbated by non-specific factors, such as stress, fatigue, action or certain postures, other forms of dystonia/dyskinesia may be elicited by specific triggering factors, such as sudden movement in paroxysmal kinesigenic dyskinesia. Response to treatment may also aid in the confirmation of a diagnosis, as a 'therapeutic' response to alcohol is characteristic of myoclonus-dystonia, and improvement with L-dopa supports a diagnosis of dopa-responsive dystonia.

Finally, dystonia may occur in conjunction with a wide variety of other neurological and non-neurological symptoms and signs, which is then labeled 'complex dystonia'. Complex dystonia has previously often been referred to as 'secondary dystonia'; also, the term 'secondary dystonia' has been used to indicate a known cause