

## INVITED REVIEW

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# The genetics of primary dystonias and related disorders

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### Summary

Dystonias are a heterogeneous group of disorders which are known to have a strong inherited basis. This review details recent advances in our understanding of the genetic basis of dystonias, including the primary dystonias, the ‘dystonia-plus’ syndromes and hereditodegenerative disorders. The review focuses particularly on clinical and genetic features and molecular mechanisms. Conditions discussed in detail include idiopathic torsion

dystonia (*DYT1*), focal dystonias (*DYT7*) and mixed dystonias (*DYT6* and *DYT13*), dopa-responsive dystonia, myoclonus dystonia, rapid-onset dystonia parkinsonism, Fahr disease, Aicardi–Goutieres syndrome, Hallervorden–Spatz syndrome, X-linked dystonia parkinsonism, deafness–dystonia syndrome, mitochondrial dystonias, neuroacanthocytosis and the paroxysmal dystonias/dyskinesias.

**Keywords:** dystonia; L-dopa; parkinsonism; myoclonus; mitochondria

**Abbreviations:** DRD = dopa-responsive dystonia; ITD = idiopathic torsion dystonia; PDJ = juvenile onset Parkinson’s disease; PKC = paroxysmal kinesigenic choreoathetosis; PNKD = paroxysmal non-kinesigenic dyskinesia; TH = tyrosine hydroxylase

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### Introduction

Dystonia is a disorder of movement caused by ‘involuntary, sustained muscle contractions affecting one or more sites of the body, frequently causing twisting and repetitive movements, or abnormal postures’ (Fahn *et al.*, 1987, 1998). The genetic contribution to the development of dystonia has been recognized for many years, but it is only recently that some of the chromosomal loci and genes involved in dystonia have been identified, so that the molecular mechanisms involved can begin to be elucidated. There have been several reviews on the genetics of dystonia (e.g. Muller *et al.*, 1998; Warner and Jarman, 1998; Thyagarajan, 1999) but in the past few years there has been further progress in understanding the genetic and molecular mechanisms underlying the various dystonias. The aim of this review is to consider this recent progress with particular reference to clinical diagnosis, genetic counselling, functional data and future research directions.

Dystonia may be classified in several ways. One way is according to the distribution of affected body parts (Table 1)

(Fahn *et al.*, 1998). Clinically, this is useful because onset of dystonia in the limbs, particularly the legs, is more likely to be associated with spread to other body parts and has important implications for treatment, management and prognosis, since generalized dystonia is usually much more disabling. Furthermore, the genetic basis of generalized dystonias tends to differ from that of purely focal types.

Dystonias may also be classified according to the age of onset and this also has important prognostic implications, since those dystonias with an earlier age of onset are also more likely to generalize and to have a more severe course. This means that conditions that have their onset in childhood tend to be generalized (or are likely become generalized), whereas the adult-onset dystonias tend to be focal and to remain so.

Another method of classification is by aetiology. Primary torsion dystonia [also known as ‘idiopathic torsion dystonia’ (ITD)] is that in which dystonia is the sole symptom. Most patients with primary dystonia do not have a family history,

**Table 1** Classification of dystonias by affected body part

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Focal dystonia: a single body part affected
Eyelids (blepharospasm)
Mouth (oromandibular dystonia, musician's cramp)
Larynx (dystonic adductor dysphonia or whispering dysphonia)
Neck (cervical dystonia, previously known as spasmodic torticollis)
Hand and arm (writer's cramp)
Segmental dystonia
Cranial: two or more parts of cranial and neck musculature affected
Axial: neck and trunk affected
Brachial: one arm and axial; both arms, with or without neck, with or without trunk
Crural: one leg and trunk; both legs, with or without trunk
Generalized dystonia
Combination of segmental crural and any other segment
Multifocal dystonia
Two or more non-contiguous parts affected
Hemidystonia
Ipsilateral arm and leg affected

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but families with multiple affected individuals are well described. The term 'dystonia-plus' refers to conditions in which dystonia is one of only two neurological conditions present, the other usually being myoclonus or parkinsonism. Heredodegenerative dystonias are those in which the dystonia is part of a more widespread neurodegenerative syndrome, often with a known inheritance pattern. Secondary ('symptomatic') dystonias are caused by environmental insults such as strokes, tumours, infections, drugs and toxins (Fahn *et al.*, 1987). Except for tardive dystonias (for which no predisposing genes have been identified), the secondary group do not obviously have genetic causes and will not be considered further here. The classification by aetiology is particularly useful, because the presence of neurological features other than dystonia immediately suggests that dystonia-plus, a heredodegenerative syndrome or a secondary dystonia is present. However, it should be noted that the converse is not always true, since some secondary dystonias can present with pure dystonia

Most recently, dystonias have been classified by genetic criteria, such as the pattern of inheritance or the disease locus, and this is likely to be increasingly the case as our knowledge of the genetic basis of dystonias increases (Fig. 1 and Tables 2 and 3).

The paroxysmal dyskinesias constitute a group that is clinically rather separate from both the primary and secondary dystonias because the patients are clinically well between episodes and may have other neurological features, such as epilepsy or chorea. They are included in a separate section in this review.

The prevalence of dystonia is unknown, although it is probably more common than is generally appreciated. Total prevalence rates vary from 127 per million to 329 per million (Nutt *et al.*, 1988; Duffey *et al.*, 1998). Focal dystonia is by far the most common type, accounting for between 61 per million and 300 per million depending on the study and method of ascertainment [Nutt *et al.*, 1988; Nakashima *et al.*,

1995; Duarte *et al.*, 1999; Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group, 2000]. There are anecdotal accounts that home visits of patients may identify other, previously undiagnosed, affected family members (Waddy *et al.*, 1991; Németh *et al.*, 1999a), suggesting that published prevalence figures are likely to be underestimates.

All patients with generalized dystonia and occasionally those with focal or segmental dystonia require prompt investigation to exclude secondary causes and to look for treatable conditions, such as Wilson disease and dopa-responsive dystonia (DRD). Genetic investigations may be appropriate in some patients and are detailed below. If no specific treatable cause is found, treatment is symptomatic and usually consists of pharmacological intervention, injection of affected muscles with botulinum toxin or occasionally peripheral or stereotactic central surgery (Dauer *et al.*, 1998; Adler, 2000; Adler and Kumar, 2000; Bressman, 2000). A major recent advance has been the treatment of generalized dystonia by deep-brain stimulation (Coubes *et al.*, 2000).

In the following sections, the genetic aspects of primary dystonias and related conditions will be addressed in turn, with particular reference to how genetic advances might aid clinical diagnosis and management. This will include a review of key clinical features, inheritance patterns, linkage and gene isolation (where the information is available) and any molecular information. Finally, the future prospects for diagnosis, understanding the molecular mechanisms and developing novel treatment strategies will be considered.

### Primary dystonias

The primary dystonias are those with no other neurological abnormalities. They were originally described as 'idiopathic' as there were no neurophysiological, neurochemical or pathological clues to the underlying aetiology, but many are now known to have a genetic basis. The familial primary

dystonias can be subdivided into predominantly generalized and predominantly focal groups. Sometimes, different patients in the same family have different subtypes and in such cases the term 'mixed dystonia' may be used. Although there is no absolute distinction between the subtypes, the published literature frequently uses this terminology and it will be adhered to in the following sections.

***Predominantly generalized dystonia***  
*Autosomal dominant, early-onset dystonia*  
*(idiopathic torsion dystonia, dystonia 1; gene locus DYT1)*

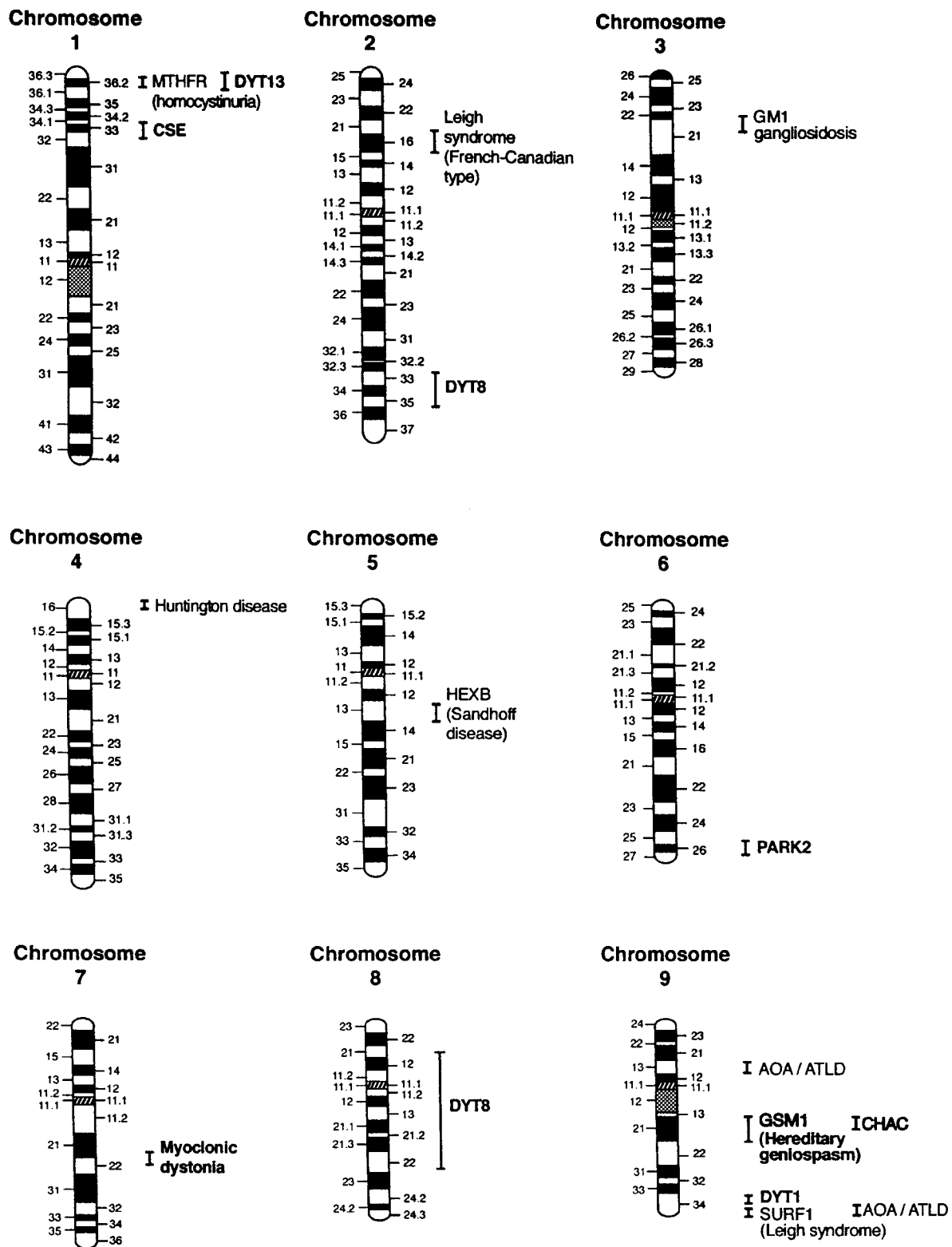
In 'typical' idiopathic torsion dystonia (ITD), symptoms develop first in the arm or leg in middle to late childhood and progress to generalized dystonia within about 5 years. Patients may be severely handicapped by the dystonia but are intellectually normal and have no other neurological abnormalities. Although onset is usually in childhood or early adulthood, it has been described in middle life (Bressman *et al.*, 2000). There is marked clinical variability, ranging from children who are profoundly disabled to adults who are obligate carriers of the disease gene and have few or no symptoms of the condition. An early age of onset and site of onset in the legs indicate a poor prognosis (Burke *et al.*, 1986; Marsden, 1988). There is considerable evidence that the disorder is caused by a malfunction of the basal ganglia. For example, striatal [<sup>18</sup>F]dopa uptake is reduced and metabolic activity increased in the lentiform nucleus and premotor cortices, measured using [<sup>18</sup>F]fluorodeoxyglucose and PET scanning (Playford *et al.*, 1993; Eidelberg, 1998; Eidelberg *et al.*, 1998). However, striatal dopamine was found to be essentially normal in the post-mortem brain of one patient carrying the *DYT1* mutation (Furukawa *et al.*, 2000a), suggesting that there is a functional disturbance within the nigrostriatal dopaminergic system rather than a structural or degenerative abnormality.

The prevalence of ITD has been reported to be five to 10 times higher in Ashkenazi Jews than in the non-Jewish population (Zeman and Dyken, 1967; Zilber *et al.*, 1984), and this high prevalence has been attributed to a founder mutation which appears to have occurred ~350 years ago in Lithuania or Byelorussia (Risch *et al.*, 1995). Segregation analysis has shown that ITD is an autosomal dominant trait with a penetrance of 30–40% in both Jewish and non-Jewish populations (Bressman *et al.*, 1989; Risch *et al.*, 1990; Kramer *et al.*, 1994). Linkage analysis assigned *DYT1*, the disease locus for ITD, to chromosome 9q32–q34 in both Jewish and non-Jewish families (Ozelius *et al.*, 1989, 1992, 1997a; Kramer *et al.*, 1990) (see also Figs 1 and 2). When the mutated gene (also known as torsin A) was identified, the majority of typical early-onset ITD cases from all ethnic origins, whether inherited, sporadic or caused by a *de novo* mutation, were found to be caused by the deletion of an in-frame GAG trinucleotide with subsequent loss of a single

glutamic acid (Ozelius *et al.*, 1997b, 1998; Gasser *et al.*, 1998; Klein *et al.*, 1998a; Valente *et al.*, 1998; Kamm *et al.*, 1999; Lebre *et al.*, 1999; Leube *et al.*, 1999; Slominsky *et al.*, 1999; Brassat *et al.*, 2000; Matsumoto *et al.*, 2001). The GAG deletion (referred to as the *DYT1* mutation) accounts for almost all mutations in torsin A, suggesting that the glutamic acid residue which is lost plays a crucial role in the function of the protein. A single patient has also been described who has a maternally inherited 18-bp deletion in exon 5 (966–983del, Phe323–Tyr328del). The patient had early-onset dystonia (age 5 years), starting in the legs, and also had myoclonus. There was a maternal family history of dystonia, but no myoclonus. However, the index patient's father had myoclonus (but not the deletion), and this may have accounted for the unusual phenotype (Leung *et al.*, 2001).

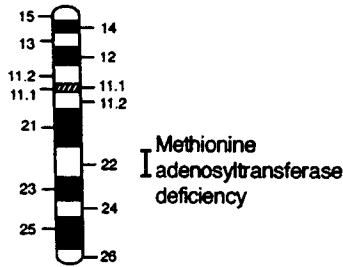
Despite the importance of the GAG deletion in ITD, a minority of patients with 'typical' torsion dystonia do not have this or any other mutation in torsin A, suggesting the presence of other loci (Ozelius *et al.*, 1997b, 1999; Valente *et al.*, 1998). Conversely, a minority of patients with atypical phenotypes (e.g. focal dystonia in the arms) have the GAG deletion, whereas the majority of patients with atypical torsion dystonia do not have mutations in the torsin A gene, again confirming the presence of other dystonia loci (Gasser *et al.*, 1998; Valente *et al.*, 1998; Kamm *et al.*, 1999; Lebre *et al.*, 1999; Leube *et al.*, 1999; Jarman *et al.*, 1999a, b). One of these loci is designated *DYT4* and is discussed later.

The torsin A gene is composed of 5 exons and the GAG deletion is in exon 5 at nucleotide 946 (Fig. 2 and Table 2). Expression analysis has revealed that torsin A is expressed at high levels in the pars compacta of the substantia nigra, a significant finding in view of the importance of this structure in the dopaminergic system and its degeneration in idiopathic Parkinson's disease (Augood *et al.*, 1998, 1999). The torsin A protein is a member of an evolutionarily highly conserved group of proteins with homology to the adenosine triphosphatases (ATPases) and heat-shock proteins. Wild-type torsin A protein has been expressed in neural cells and is located in a punctate pattern throughout the cell body and neurites; it co-localizes with endoplasmic reticulum markers and vesicular markers such as VAMP-2 (synaptobrevin). In contrast, mutant torsin A (with an in-frame GAG deletion) forms large inclusions around the cell nucleus with whorls that appear to derive from the endoplasmic reticulum (Hewett *et al.*, 2000). The authors suggest that mutant torsin A protein interferes with the integrity of the endoplasmic reticulum, membrane trafficking and downstream vesicular release from neurones. In another study, wild-type torsin A was localized to a network of membranes displaying significant co-immunoreactivity with the endoplasmic reticulum protein binding protein (BiP), but mutant torsin A was found in large spheroidal structures lacking BiP immunoreactivity (Kustedjo *et al.*, 2000). These authors also suggest that torsin A acts as a molecular chaperone assisting in the correct folding of secreted and/or membrane proteins. Further work is required to determine how mutant torsin A causes neuronal

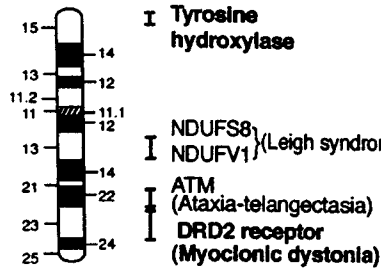


**Fig. 1** Known chromosomal locations of primary dystonias and related conditions. Conditions that are discussed in the text are shown in bold type. AOA/ATLD = ataxia with oculomotor apraxia/ataxia-telangiectasia-like disorder (Németh *et al.*, 2000; do Ceu Moreira *et al.*, 2001); HPRT1 = hypoxanthine guanine phosphoribosyltransferase 1; MAPT = microtubule-associated protein tau; MECP2 = methyl-CpG-binding protein 2; MTHFR = methyltetrahydrofolate reductase; NDUFS7 = NADH-ubiquinone oxidoreductase Fe-S protein 7; NDUFS8 = NADH-ubiquinone oxidoreductase Fe-S protein 8; NDUFV1 = NADH-ubiquinone oxidoreductase flavoprotein 1; NPC2 = Niemann-Pick disease type C2; SCA3 = spinocerebellar ataxia type 3; PDHA1 = pyruvate dehydrogenase complex, e1- $\alpha$  polypeptide 1 (pyruvate dehydrogenase deficiency).

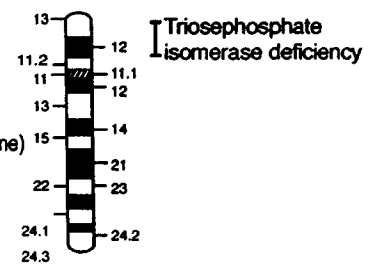
**Chromosome 10**



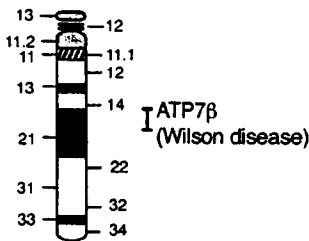
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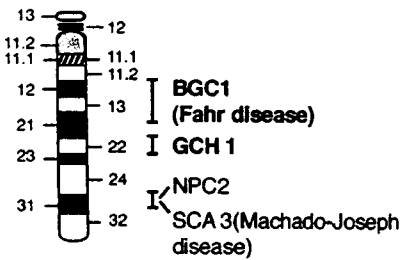
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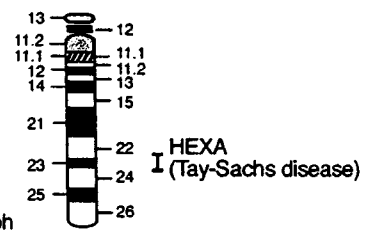
**Chromosome 13**



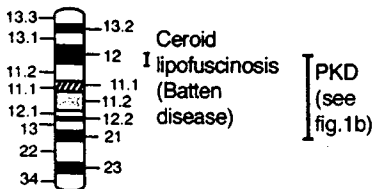
**Chromosome 14**



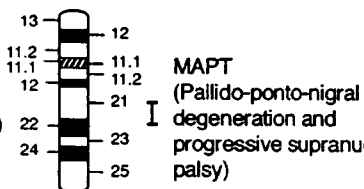
**Chromosome 15**



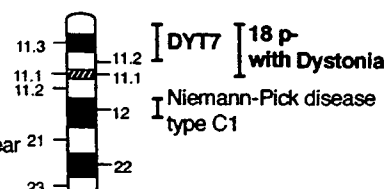
**Chromosome 16**



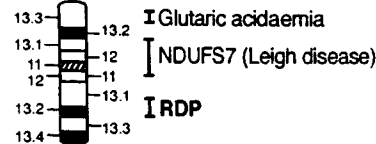
**Chromosome 17**



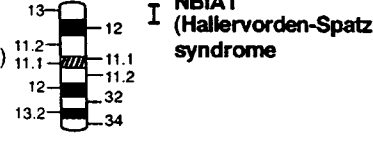
**Chromosome 18**



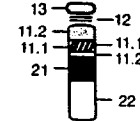
**Chromosome 19**



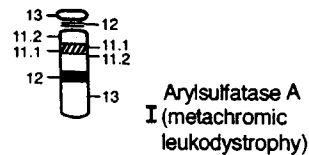
**Chromosome 20**



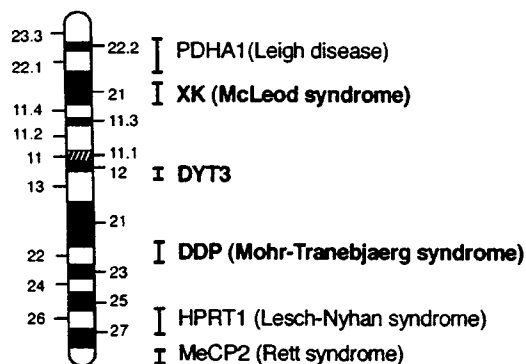
**Chromosome 21**

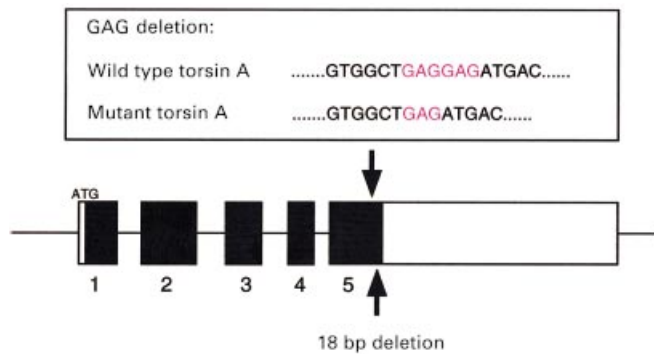


**Chromosome 22**



**Chromosome X**





**Fig. 2** Genomic structure of *DYT1* and location of the GAG deletion and 18 bp deletion in idiopathic torsion dystonia. The filled boxes indicate translated regions of the torsin A gene. The GAG deletion is found in the majority of typical early-onset torsion dystonia cases, the 18 bp deletion only in one patient.

dysfunction and why this results in dominant inheritance with incomplete penetrance. Further work is also required to determine whether the primary site of action is within the dopaminergic system.

Who should be tested for the *DYT1* mutation? The 'typical' phenotype associated with the *DYT1* mutation is of early-onset dystonia in a limb, particularly the leg, with frequent spread to other limbs, which contrasts with 'non-*DYT1*' patients, who often have later-onset dystonia and more frequently have prominent cervical or cranial involvement. A clinical algorithm has been devised which suggests that testing should be restricted to patients with age of onset under 26 years and any site of onset, as this predicts *DYT1* carrier status with the highest sensitivity and specificity (Bressman *et al.*, 2000). In addition, those patients with older onset who have a relative with early-onset disease should also be tested. However, using these guidelines may result in a small number of *DYT1* carriers being missed and referral for genetic counselling is therefore recommended (Bressman *et al.*, 2000). The main difficulties in counselling are the low penetrance of the disease and the marked variability in clinical severity. Empirical recurrence risks were calculated prior to the availability of *DYT1* testing (Fletcher *et al.*, 1990). The theoretical recurrence risk in a familial case for a child or sibling (using a penetrance of 42%) was 21% and in an isolated case it was about 14%. However, in both familial and isolated cases the observed risk was rather lower. Unfortunately, no data are available on the risk of having a severely affected child. *DYT1* carriers, therefore, may face very difficult reproductive issues and in these circumstances preimplantation genetic diagnosis (when available) may be a solution.

#### *Autosomal dominant type dystonia (dystonia 4; gene locus DYT4)*

Although there are patients with non-*DYT1* generalized dystonia, few large families have been documented in the

literature. An Australian family was described by Parker *et al.* (1985) and Ahmad *et al.* (1993), in which linkage to 9q34 was excluded and it was given the locus designation *DYT4*. The dystonia was inherited as an autosomal dominant trait with complete penetrance in all examined obligate carriers and the age of onset ranged from 13 to 37 years. Many of the patients presented with 'whispering dysphonia', the others with torticollis. Most eventually developed generalized dystonia. A confusing feature of the family was that two patients had Wilson disease. Linkage analysis also excluded the Wilson disease locus (Ahmad *et al.*, 1993) and the *DYT6* and *DYT7* loci (see below) (Jarman *et al.*, 1999a, b).

#### *Autosomal recessive dystonia (dystonia 2; gene locus DYT2)*

This pattern of inheritance was proposed for many Ashkenazi families with dystonia, but was later excluded (Risch *et al.*, 1990). Some cases have been reported in which the parents were consanguineous, suggesting autosomal recessive inheritance (Gimenez-Roldan *et al.*, 1988), but this interpretation has been disputed (Fletcher, 1990; Fletcher *et al.*, 1990). Dopa-responsive dystonia due to autosomal recessive mutations of tyrosine hydroxylase have been described and are discussed in the section on dystonia-plus syndromes.

#### *Predominantly focal or segmental dystonias*

##### *Adult-onset idiopathic torsion dystonia*

Adult-onset ITD, also known as adult-onset focal dystonia, differs in two important ways from early-onset ITD. First, the condition frequently presents in mid-adult life (although this can vary from adolescence to late in life); secondly, the symptoms usually affect one body part and do not generalize, although they occasionally spread to adjacent regions (segmental dystonia). The most frequently affected regions are the craniocervical region, the hands or lower limbs and, less commonly, the oromandibular region or larynx. Rarely, the dystonia may affect the pharynx or other regions (Table 1). The clinical features of cervical dystonia, the commonest type seen in clinical practice, include twisting or jerking of the head, head tremor, neck pain and considerable social and psychological disability (Dauer *et al.*, 1998). Focal dystonias (except for task-specific dystonias, such as writer's cramp and musician's cramp) are present most of the time, although certain positions or situations (stress, fatigue, etc.) may aggravate the condition. Some of the focal dystonias, particularly cervical dystonia, respond well to local injections of botulinum toxin. For most subtypes of focal dystonia, there is an excess of females, although some authors have reported an excess of males with writer's cramp [Soland *et al.*, 1996a; Epidemiological Study Group of Dystonia in Europe (ESDE) Collaborative Group, 1999, 2000]. Some patients (~10%), particularly those with cervical dystonia, may experience one or more periods of remission which may last for many years,

hence the description 'spasmodic torticollis'. This term should not be confused with 'paroxysmal dystonia', in which the patient has periodic recurrences of the condition but is well between recurrences (see later).

As discussed above, patients who present with lower-limb focal dystonia are more likely to develop more widespread disease, as are those with a family history or early-onset disease. These patients may warrant testing for the *DYT1* mutation, but in patients with typical late-onset focal dystonia and no family history of early-onset dystonia (onset <26 years), testing is likely to be negative.

Focal dystonia is well recognized to be associated with specific neurological conditions, such as myoclonus and parkinsonism (see below), but is rarely associated with other neurological disorders. The only apparent exception to this is the co-existence of dystonia and Tourette syndrome/tics in individual patients or in different members of the same family (Tolosa, 1981; Lees *et al.*, 1984; Jankovic and Nutt, 1988; Elston *et al.*, 1989; Jankovic and Stone, 1991; Stone and Jankovic, 1991; Németh *et al.*, 1999a). The relationship is interesting because both are thought to be disorders of the basal ganglia, suggesting that the same genetic factors may predispose to both of them. However, tics are quite common in the general population and the association could be coincidental. Resolving this problem is likely to require the identification of the genes involved in each disorder.

Numerous studies have suggested that focal dystonia has a genetic basis, although the proportions of inherited and sporadic cases are not yet known and very little is known about the specific genetic loci. On the basis of surveys and home visits, Waddy *et al.* (1991) suggested that ~25% of individuals have a significant family history. Also, several autosomal dominant families with focal and/or segmental dystonia, mainly of the craniocervical, adult-onset type, have been reported (Thompson, 1986; Uitti and Maraganore, 1993; Bressman *et al.*, 1994, 1996; Leube *et al.*, 1996; Cassetta *et al.*, 1999; Munchau *et al.*, 2000a). These families may provide clues to the genetic basis of focal dystonia.

Occasional patients affected with late-onset, purely focal dystonia seek genetic counselling, concerned that a child might be severely handicapped, as might occur with the *DYT1* mutation. Provided the onset is late and there is no family history of early-onset dystonia (<26 years) the patient can be reassured as the likelihood of being a *DYT1* carrier is low. However, there is little accurate information on recurrence risks for focal dystonia. They have not been calculated empirically in sporadic cases and there are few studies of penetrance in familial focal dystonias, although the penetrance was estimated to be between 42 and 84% in a single large family (Leube *et al.*, 1996; see below).

To date only one locus for pure focal dystonia, *DYT7*, and two loci for the mixed dystonias, *DYT6* and *DYT13*, have been identified, no gene mutations have been identified. Many other families are not linked to these loci, indicating further genetic heterogeneity (Holmgren *et al.*, 1995; Almasy *et al.*, 1997; Bentivoglio *et al.*, 1997; Klein *et al.*, 1998b;

Jarman *et al.*, 1999a, b; Kamm *et al.*, 1999, 2000; Friedman *et al.*, 2000; Valente *et al.*, 2001a). In the following sections, the clinical features associated with the chromosomal loci *DYT7*, *DYT6* and *DYT13* are outlined.

### *Autosomal dominant focal dystonia (dystonia 7; gene locus DYT7)*

A large German family was reported with autosomal dominant focal dystonia with incomplete penetrance (Leube *et al.*, 1996). Most patients had spasmodic torticollis, one had spasmodic dysphonia and several had postural hand tremor. The mean age of disease onset in this family was 43 years (range 28–70 years). The disease gene was localized to the short arm of chromosome 18 (Leube *et al.*, 1996). Analysis of other patients with adult-onset focal dystonia from north-western Germany and Central Europe revealed similar haplotypes to the original family, suggesting a founder effect (Leube *et al.*, 1997a, b) but these data have not been confirmed (Klein *et al.*, 1998c).

Three patients with developmental delay and dystonia have been reported with distal interstitial deletions of 18p. The age of onset was between 12 and 15 years and was associated with multifocal increased white matter signal on T<sub>2</sub>-weighted MRI (Klein *et al.*, 1999a). The deletions overlap with that of the *DYT7* locus (Figs 1 and 2).

### *Mixed dystonias*

#### *Adult-onset idiopathic torsion dystonia of mixed type (dystonia 6; gene locus DYT6)*

Clinical and genetic analysis has been performed on two Mennonite families with idiopathic torsion dystonia (Almasy *et al.*, 1997). The inheritance pattern was autosomal dominant with incomplete penetrance. Some affected individuals had a phenotype indistinguishable from that found with the *DYT1* mutation. However, the site of onset was cranial or cervical in about half of the patients and those who presented with limb symptoms later developed cranial or cervical symptoms. The age of onset was also later (average 18.9 years in *DYT6* versus 13.6 years in *DYT1*). In two of the cases with *DYT6*, the symptoms remained focal. Linkage analysis mapped the gene in both families to chromosome 8p21-8q22.

#### *Primary torsion dystonia with predominant craniocervical or upper limb onset (dystonia 13; gene locus DYT13)*

An Italian family has been reported in which there is focal or segmental dystonia, usually of adult onset and affecting the craniocervical region (Bentivoglio *et al.*, 1997). In this respect, the clinical features resemble those of idiopathic late-onset focal dystonia. However, some patients had early-onset dystonia (age 5 years) and a few developed generalized dystonia, suggesting that the dystonia in this family should be

**Table 2** Genetic classification of primary dystonias

Designation	OMIM ref. no.	Clinical features	Age of onset	Inheritance pattern	Locus	Chromosome location	Gene	Gene test available*
Dystonia 1 AD early-onset dystonia, IDT, Oppenheim's dystonia	128100	Dystonia, may present as focal, usually in the limbs, often generalizes, especially if early onset	Usually childhood, may be later (<26 years in most cases)	AD, incomplete penetrance	<i>DYT1</i>	9q34	Torsin A; 5 exons, ORF 998 bp	Yes, usually in specialist laboratories
Dystonia 2 AR dystonia (unconfirmed)	224500	–	–	AR	–	–	–	No
Dystonia 3 X-linked dystonia parkinsonism (XP); also known as lubag	314250	Only described in individuals from the Philippines; usually males; usually generalized dystonia; parkinsonism unresponsive to L-dopa; progressive neurodegenerative syndrome	Adults (average 35 years)	XR	<i>DYT3</i>	Xq13.1	–	No, haplotyping in Filipino males on research basis
Dystonia 4 Torsion dystonia 4	128101	Single large Australian family; laryngeal and cervical dystonia	13–37 years	AD	–	–	–	No
Dystonia 5 Hereditary progressive dystonia with marked diurnal fluctuation (HPD); Segawa syndrome; dopa-responsive dystonia (DRD); (DYT5 symbol now withdrawn)	128230	Usually dystonia; may be 'atypical cerebral palsy'; gait disturbance or other; treatable with low-dose L-dopa	Variable, often childhood	AD, incomplete penetrance	<i>GCHI</i>	14q22.1-q22.2	<i>GCHI</i> ; 6 exons covering 30 kb, ~3 kb transcript	Yes, on research basis
Dystonia 6 Adult-onset ITD of mixed type	602629	Two Mennonite families; focal or generalized; cranial, cervical or limb dystonia	Average 19 years	AD	<i>DYT6</i>	8p21-p22	–	No
Dystonia 7 Adult-onset ITD; idiopathic focal dystonia; (IFD) AD late-onset dystonia	602124	Single German family; focal dystonia (cervical and laryngeal dystonia) and postural tremor	28–70 years	AD, incomplete penetrance	<i>DYT7</i>	18p	–	No
Dystonia 8 Paroxysmal non-kinesigenic dyskinesia (PNKD); paroxysmal dystonic choreoathetosis (PDC); familial paroxysmal dyskinesia; Mount–Reback syndrome	118800	Attacks of dystonia, chorea and athetosis lasting 5 min to 4 h, precipitated by alcohol, caffeine, hunger, fatigue, nicotine and emotional stress	Variable: early childhood, adolescence or early adulthood	AD, incomplete penetrance	<i>PNKD</i>	2q33-q35	–	No
Dystonia 9 Choreoathetosis, spasticity and episodic ataxia	601042	Involuntary movements and dystonia; precipitated by alcohol, fatigue, emotional stress and spastic paraplegia during and between episodes	2–15 years	AD	<i>CSE</i>	1p	–	No



Table 2 Continued

Designation	OMIM ref. no.	Clinical features	Age of onset	Inheritance pattern	Locus	Chromosome location	Gene	Gene test available*
Dystonia 10 Paroxysmal kinesigenic choreoathetosis	128200	Choreoathetosis precipitated by sudden unexpected movements; respond to anticonvulsant therapy	6–16 years	AD, incomplete penetrance	<i>PKC</i>	16p11.2-q12.1	-	No
Dystonia 11 Myoclonic dystonia; alcohol-responsive dystonia	159900	Myoclonus and/or dystonia; alcohol-responsive in some patients	Variable but may be in early childhood	AD, incomplete penetrance	<i>SGCE</i>	7q21	$\epsilon$ -Sarcoglycan; 11 exons	No, possibly on research basis
Dystonia 12 Rapid-onset dystonia with parkinsonism (RDP)	128235	Dystonia or parkinsonism developing over hours or weeks	Childhood, adolescence or adulthood	AD, incomplete penetrance	-	19q13	-	No
Dystonia 13 Focal dystonia with cranio-cervical features	-	Single Italian family, cranial or cervical dystonia; some focal, some generalized	5 years to adult	AD, incomplete penetrance	<i>DYT13</i>	1p36.13-36.32	-	No

AD = autosomal dominant; AR = autosomal recessive; XR = X-linked recessive; OMIM = Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>); ORF = open reading frame. \*<http://www.genetests.org> is a directory of up-to-date genetic testing laboratories; individual research laboratories can be contacted for research-based tests.

classified as the mixed type. Inheritance was autosomal dominant with incomplete penetrance, estimated to be <60%. Recently, the chromosomal locus in this family, *DYT13*, has been localized to a 22 cM (centimorgan) interval on 1p36.13-36.32 (Valente *et al.*, 2001a) (Fig. 1 and Table 2).

### Hereditary geniospasm (gene locus GSM1)

Hereditary geniospasm (also known as hereditary chin-trembling, hereditary chin myoclonus, familial trembling of the chin) is an unusual movement disorder in which there are episodes of involuntary tremor of the chin and lower lip. Episodes usually start in childhood and may be precipitated by stress, concentration and emotion. It may be present during sleep and is not suppressible. There are no associated neurological abnormalities and the condition may improve with age. The male : female ratio is 1.3 : 1. Electrophysiology suggests that the movement disorder resembles myoclonus more than tremor (Destee *et al.*, 1997). Inheritance is autosomal dominant but may be with complete or incomplete penetrance (Danek, 1993; Soland *et al.*, 1996b; Destee *et al.*, 1997). A locus has been identified at 9q13-q21 in a single British family and genetic heterogeneity was found (Jarman *et al.*, 1997a).

### Dystonia-plus syndromes

#### *Dopa-responsive dystonia [dystonia 5 and DYT5 now withdrawn; gene locus GTP cyclohydrolase I (GCH1)]*

Dopa-responsive dystonia (DRD) is characterized by dystonia, concurrent or subsequent parkinsonism, diurnal worsening of symptoms in ~75% of cases (Nygaard *et al.*, 1991) and a dramatic therapeutic response to L-dopa in most patients. The prevalence of DRD is thought to be 0.5–1.0 per million (Nygaard, 1993), but may well be higher as cases are still consistently missed or misdiagnosed. Women are affected two to four times more frequently than men (Nygaard *et al.*, 1988; Nygaard, 1993; Ichinose *et al.*, 1994). Symptoms and age of onset vary considerably between patients (Table 4). Although onset is usually during childhood or adolescence, adult onset does occur. Dystonia is the most common presentation and may be the only feature. In childhood, DRD may present with a phenotype resembling atypical cerebral palsy (Nygaard *et al.*, 1994; Bandmann *et al.*, 1996), whereas in adulthood DRD can present with parkinsonian tremor and rigidity as well as brisk tendon reflexes and extensor plantars (Harwood *et al.*, 1994). Some patients have focal dystonias, including oromandibular dystonia, or minor symptoms, such as abnormal positioning of one foot or difficulty with writing, while others have generalized dystonia and are wheelchair-bound if untreated (Nygaard *et al.*, 1988; Steinberger *et al.*, 1999). Because of this wide spectrum of symptoms and age of onset, the diagnosis of DRD may be missed and it is widely recommended that all

**Table 3** Genetic classification of hereditary degenerative dystonias

Designation	OMIM ref. no.	Clinical features	Age of onset	Inheritance pattern	Locus	Chromosome location	Gene	Gene test available*
Fahr disease (idiopathic basal ganglia calcification; BGC1; IBGC; bilateral striopallidodentate calcinosis)	213600	Progressive dystonia, parkinsonism, dysphagia, neuropsychiatric disturbances, ataxia	30–60 years	AD	<i>BGC1</i>	14q	Unknown	No
Aicardi–Goutieres syndrome (familial, early-onset encephalopathy with calcifications of basal ganglia and chronic cerebrospinal fluid lymphocytosis)	225750	Microcephaly with intracerebral calcification and white matter disease, spasticity, dystonia, visual inattention and abnormal eye movements, persistent vegetative state	Usually diagnosed shortly after birth or during early childhood	AR	<i>AGS1</i>	3p21	Unknown	No
Hallervorden–Spatz syndrome (neurodegeneration with brain iron accumulation 1 NBIA1; pantothenate kinase-associated neurodegeneration; PKAN)	234200	Extrapyramidal features, dementia and ocular abnormalities	Usually 1st or 2nd decade, death by 30 years	AR	<i>PANK2</i>	20p12.3-p13	<i>PANK2</i> , 1.85 kb transcript; ubiquitous expression including brain; 6 exons	Possibly on research basis
Autosomal recessive juvenile-onset Parkinson's disease with dystonia (AR-JP; PDJ)	602544	Parkinsonism and mild dystonia (usually in the foot). Sleep benefit; good response to L-dopa but early development of tardive dyskinesias	Usually <40 years	AR	<i>PARK2</i>	6q25.2-q27	Parkin 4.5 kb transcript 465 amino acids; ubiquitous expression including brain; 12 exons covering >1 Mb	Possibly on research basis
McLeod syndrome (Kell blood groups precursor)	314850	Areflexia, dystonia and chorea, orofacial dyskinesias, facial and generalized tics, epilepsy, psychiatric disturbances and dementia, late-onset muscular dystrophy and cardiomyopathy	4th decade	XR	<i>XK</i>	Xp21	<i>XK</i> 4.5 and 5.2 kb transcripts, 444 amino acids; 3 exons	Possibly on research basis

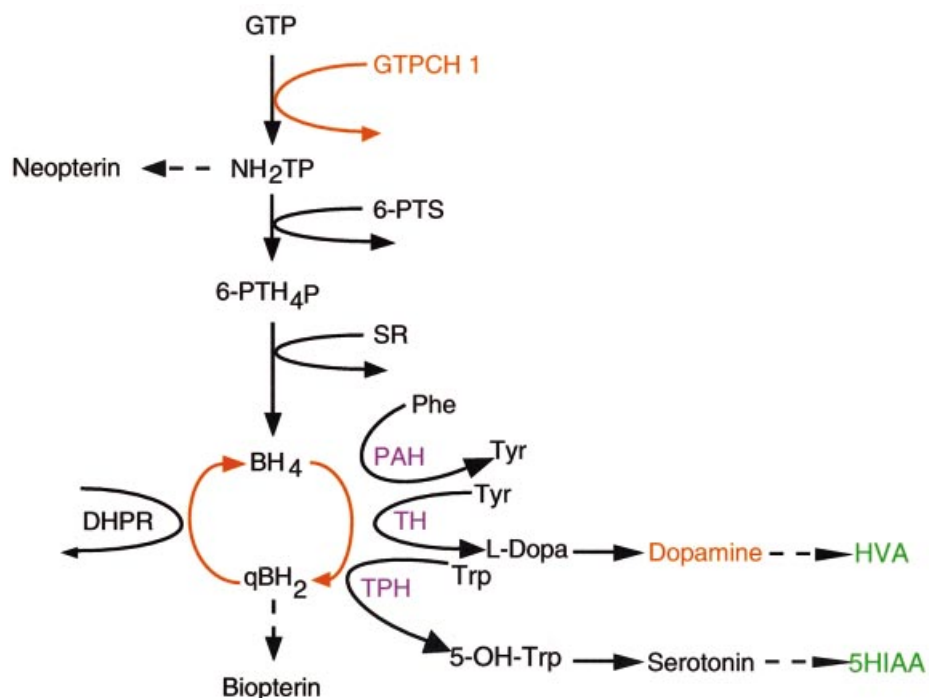
**Table 3** *Continued*

Designation	OMIM ref. no.	Clinical features	Age of onset	Inheritance pattern	Locus	Chromosome location	Gene	Gene test available*
Chorea–acanthocytosis (CHAC) (Levine-Critchley syndrome; amyotrophic chorea with acanthocytosis)	200150	Mutilating orofacial dyskinesia, involuntary vocalizations and other tics, limb chorea, dysarthria, hyporeflexia or areflexia, amyotrophy, dysphagia, muscle weakness, seizures, limb dystonia, parkinsonism and dementia, cardiomyopathies	3rd and 4th decade	AR	<i>CHAC</i>	9q21	<i>CHAC</i> /chorein 10 and 11 kb transcripts; ubiquitous expression; predicted 3174 amino acids; 73 exons covering 250 kb	Possibly on research basis
X-linked deafness–dystonia–optic atrophy (Mohr–Tranebjaerg syndrome)	304700	Sensorineural hearing loss, dystonia, dementia, psychotic features, optic atrophy, mental retardation, hip fractures, peripheral neuropathy, progressive neurodegenerative syndrome	Childhood	XR	<i>DFN-1/MTS</i>	Xq21.3-Xq22	DDP 1.167 kb transcript; various tissue expression, including foetal and adult brain; 97 amino acids; 2 exons	Possibly on research basis

AD = autosomal dominant; AR = autosomal recessive; XR = X-linked recessive; OMIM = Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db=OMIM>).

**Table 4** Clinical features that may occur in dopa-responsive dystonia

Dystonic features	Other features
Limb dystonia	Responsive to low dose L-dopa
Generalized dystonia	Responsive to low dose anticholinergics
Blepharospasm	Developmental delay
Oromandibular dystonia	Abnormal gait (may be dystonic, walking on toes or non-specific)
Cervical dystonia	Parkinsonism
Writer's cramp	Diurnal fluctuation
Hand tremor	Fatigue
Truncal dystonia	Spastic paraparesis (pseudopyramidal signs)
	Scoliosis
	Tremulous limbs
	Stiffness



**Fig. 3** The aromatic amino acid hydroxylases and the function of tetrahydrobiopterin. BH<sub>4</sub> = tetrahydrobiopterin; DHPR = dihydropteridine reductase; GTP = guanosine triphosphate; GTPCH I = guanosine triphosphate cyclohydrolase 1; 5HIAA = 5-hydroxyindoleacetic acid; HVA = homovanillic acid; NH<sub>2</sub>TP = dihydroneopterin triphosphate; 5-OH-Trp = 5-hydroxy tryptophan; PAH = phenylalanine hydroxylase; 6-PTH<sub>4</sub>P = 6-pyruvoyl-tetrahydropterin; 6-PTS = 6-pyruvoyl-tetrahydropterin synthase; qBH<sub>2</sub> = q-dihydrobiopterin; SR = sepiapterin reductase; TH = tyrosine hydroxylase; TPH = tryptophan hydroxylase.

children with an extrapyramidal motor disorder that is not attributable to hypoxic ischaemic encephalopathy and all individuals with symptoms within the spectrum of DRD (including an unexplained gait disorder) be given a trial of L-dopa.

DRD is usually inherited as an autosomal dominant trait. There is incomplete penetrance (~30%) (Nygaard *et al.*, 1990), but if subtle signs and atypical symptoms are taken into account the penetrance can range from 40 to 100% (Steinberger *et al.*, 1998). Autosomal recessive inheritance has been reported but is very rare and has been associated with mutations in the tyrosine hydroxylase (*TH*) gene on

11p15.5 (Knappskog *et al.*, 1995; Luedecke *et al.*, 1995; van den Heuvel *et al.*, 1998; Furukawa *et al.*, 2001). In one patient with a *TH* gene mutation the presentation simulated spastic paraplegia which dramatically responded to treatment with L-dopa (Furukawa *et al.*, 2001).

Linkage analyses in dominant DRD families assigned the disease locus, *DYT5*, to chromosome arm 14q11-q24.3 (Figs 1 and 2) and heterozygous mutations were identified in the *GCHI* gene, which codes for guanosine triphosphate cyclohydrolase I (GTPCH I) (Nygaard *et al.*, 1993; Ichinose *et al.*, 1994). GTPCH I is the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin (BH<sub>4</sub>) and BH<sub>4</sub> is an

essential cofactor for the amino acid monooxygenases phenylalanine, tyrosine and tryptophan hydroxylase (Fig. 3). Reduced activity of GTPCH I in DRD patients is thought to cause symptoms by the depletion of dopamine and this assumption is consistent with the pronounced therapeutic effect of L-dopa, even in patients who have been severely incapacitated for several years.

*GCHI* is composed of six exons and mutations have been found in all exons in DRD patients (documented by Blau *et al.*, 2000 in the Tetrahydrobiopterin home page, <http://www.bh4.org/biomdb1.html>). However, only ~40–50% of patients with DRD (including sporadic cases) have detectable mutations in *GCHI* (Bandmann *et al.*, 1996, 1998; Tassin *et al.*, 2000). The other families may have mutations in its regulatory region or in other genes such as the *TH* gene. Interestingly, the majority of mutations result in truncation of the enzyme, whereas amino acid changes are comparatively rare. A large deletion (~1.2 kb) across exon 3 has been reported; this was only detected by Southern blotting and RT-PCR (reverse transcription–polymerase chain reaction) (Furukawa *et al.*, 2000b).

The clinical syndrome of DRD is usually caused by heterozygous mutations in *GCHI*. Very rare patients are described who are homozygous for mutations in *GCHI* and, if untreated, have a progressive neurological syndrome that includes mental retardation, convulsions, disturbance of tone and posture, abnormal movements, hypersalivation and swallowing difficulties ('atypical phenylketonuria') (Thony and Blau, 1997; Blau *et al.*, 2001). Compound *GCHI* heterozygotes are also described. The phenotype is intermediate in severity between DRD and 'atypical phenylketonuria' with hyperphenylalaninaemia requiring treatment with BH4 in addition to L-dopa (Furukawa *et al.*, 1998).

The difference in clinical phenotype between *GCHI* heterozygotes and homozygotes might indicate that autosomal dominant DRD is a haploinsufficiency condition of GTPCH I. However, patients with DRD have GTPCH I levels which are ~20% of normal, rather than the expected 50%, suggesting that other factors are also involved in its regulation. For example, the dominant mutation G201E reduces the level of wild-type protein, suggesting that the mutant protein interferes with or inhibits the wild-type protein (a dominant negative effect) (Hirano *et al.*, 1998; Hwu *et al.*, 2000). However, events at the transcriptional level may also be important (Ichinose *et al.*, 2000).

Although the diagnosis of DRD is a clinical one, further investigations may be necessary since the differential diagnosis includes ITD, autosomal recessive juvenile onset Parkinson's disease (PDJ), and autosomal recessive TH deficiency (Tanaka *et al.*, 1987; Fink *et al.*, 1988). A precise diagnosis is particularly necessary for genetic counselling since the risk of having affected offspring is 20–50% in GTPCH I deficiency (depending on the level of penetrance), whereas the risk to offspring of patients with autosomal recessive conditions is likely to be low unless consanguinity is present.

Ideally, the diagnosis could be confirmed by mutation testing of *GCHI*, but this is not usually routinely available and other methods may be required. A diagnosis of ITD may be excluded by testing for the *DYT1* mutation. Some patients with DRD respond particularly well to low-dose anticholinergics, which may distinguish them from patients with ITD or PDJ (Jarman *et al.*, 1997). Metabolic testing may also be necessary (Wevers *et al.*, 1999; Blau *et al.*, 2001). In *GCHI* heterozygotes, CSF examination reveals low concentrations of homovanillic acid (HVA), 5-hydroxyindoleacetic acid (HIAA) (metabolites of dopamine and serotonin, respectively), neopterin, biopterin and GTPCH I activity (Williams *et al.*, 1979; Fink *et al.*, 1988; Nygaard *et al.*, 1993; Blau *et al.*, 2001). The phenylalanine loading test in dominant DRD is also abnormal (Hyland *et al.*, 1997; Blau *et al.*, 2001). In PDJ, the levels of neopterin and HVA in CSF are moderately decreased but the phenylalanine loading test is normal, whereas in TH deficiency the CSF levels of HVA are decreased, but neopterin, biopterin, tyrosine and HIAA are all normal (Brautigam *et al.*, 1999).

Recent research shows that *GCHI* heterozygotes also have low levels of GTPCH I activity in peripheral blood mononuclear cells (Ichinose *et al.*, 2000) and low neopterin, biopterin and GTPCH I activity in cytokine-stimulated cultured skin fibroblasts (Bonafe *et al.*, 2001), suggesting that these tests may also be useful in the future.

Although genetic analysis is not routinely available, one study has compared the clinical and genetic features of 22 families with dopa-responsive dystonia (Tassin *et al.*, 2000). Eleven families were shown to have mutations in *GCHI* and three were found to have mutations in parkin (*PARK2*), one of the genes responsible for autosomal recessive PDJ (Kitada *et al.*, 1998; Mizuno *et al.*, 2001). This condition is characterized by early-onset (<40 years) Parkinson's disease and there is frequently concurrent development of mild foot dystonia. Diurnal fluctuation of symptoms (sleep benefit) is well described. The genetic study revealed that there was considerable clinical overlap between patients with DRD and PDJ. Age of onset was from early childhood onwards; dystonia tended to be in the lower limbs, or generalized but included writer's cramp and other focal dystonias; reflexes ranged from normal to brisk; and the response to low-dose L-dopa was good. Tardive dyskinesias, which are not thought to be present in DRD, were found in two families with *GCHI* mutations. The major distinguishing clinical features were the presence of extensor plantars in some cases of DRD but in no cases of PDJ, and parkinsonian features, which were more consistently found in PDJ. The distinguishing genetic feature was that autosomal recessive inheritance was suspected in some of the families who turned out to have PDJ. The study illustrates the difficulty in making an accurate clinical diagnosis in these conditions and strengthens the case for metabolic and genetic testing in families in whom recurrence risks are an issue.

### **Myoclonic dystonia (dystonia 11; gene locus DYT11)**

Dystonia can occur in combination with myoclonus (brisk, shock-like jerks of the limbs) and may be sporadic or hereditary. Two varieties of myoclonus with dystonia have been described (Quinn, 1996). 'Essential myoclonus' is a relatively mild condition starting in the first or second decade, and is inherited as an autosomal dominant trait with incomplete penetrance. Some patients with essential myoclonus also have dystonia affecting the hands, neck, trunk or legs (Quinn *et al.*, 1988). There are no seizures, dementia or ataxia, the EEG is normal and there may be a dramatic response to alcohol. Essential myoclonus has been distinguished from 'myoclonic dystonia' or 'myoclonus-dystonia', in which dystonia is the core feature but tremor and rapid jerky movements that resemble myoclonus may also be present. The age of onset, pattern of body involvement, presence of myoclonus and response to alcohol are all variable.

Recent genetic studies suggest that essential myoclonus and myoclonus-dystonia may be allelic disorders. A locus on chromosome 7q21 has been identified in numerous families from several ethnic backgrounds. The age of onset varies from 6 months to 38 years and inheritance is autosomal dominant with incomplete penetrance. Some patients have essential myoclonus whilst others have myoclonic dystonia affecting the neck, arms, trunk or face. The response to alcohol varies from excellent to negligible and appears to be independent of the type of dystonia (Nygaard *et al.*, 1999; Klein *et al.*, 2000; Asmus *et al.*, 2001; Vidailhet *et al.*, 2001). The gene causing myoclonus-dystonia linked to chromosome 7 turns out to be  $\epsilon$ -sarcoglycan (*SGCE*), which is part of the dystrophin-glycoprotein complex (Zimprich *et al.*, 2001). It is highly expressed in the CNS and expression of the disease shows a strong parental origin effect with greatly reduced penetrance in the offspring of affected females, suggesting that the gene may be imprinted. The identification of mutations in this gene is an exciting new development in dystonia genetics.

Another locus for myoclonic dystonia has also been found on chromosome 11q in a large Welsh-Scottish-German family (Klein *et al.*, 1999b). There was autosomal dominant inheritance with incomplete penetrance and age of onset between 2 and 16 years of age. Some individuals had predominant myoclonus, one had dystonia and others had both features. They also reported affective disorders, including depression, manic depression, anxiety, panic attacks and obsessive-compulsive disorder. Three patients reported less severe myoclonus after ingestion of alcohol. Mutation analysis in this family revealed a missense change in the D<sub>2</sub> dopamine receptor gene (G→A transition, Val154Ile) in the first base of codon 154, a highly conserved region of the gene. The change was not found in any controls. This finding has not been replicated in several other myoclonus-dystonia families (Klein *et al.*, 2000) and the 11q form does not currently have a dystonia locus designation.

### **Rapid-onset dystonia parkinsonism (dystonia 12; gene locus DYT12)**

Rapid-onset dystonia parkinsonism (RDP) is a very rare condition in which dystonic spasms, bradykinesia, postural instability, dysarthria and dysphagia develop over a period ranging from several hours to weeks (Dobyns *et al.*, 1993). Inheritance is autosomal dominant with incomplete penetrance. A less rapid clinical course has also been described, with a gradual progression of dystonia and parkinsonism over 6–18 months (Brashear *et al.*, 1996). Onset can occur during childhood, adolescence or adulthood (Dobyns *et al.*, 1993; Brashear *et al.*, 1996, 1997; Webb *et al.*, 1999). In contrast to DRD, RPD is not effectively treated with L-dopa. There are low levels of HVA in the CSF and neuroimaging studies indicate that there is no degeneration of dopaminergic nerve terminals in RDP, suggesting that RDP results from a functional deficit, as in primary dystonia, rather than neuronal loss, as in Parkinson's disease (Brashear *et al.*, 1998a, b, 1999). A locus for RDP has now been localized to chromosome 19q13 in two American families (Kramer *et al.*, 1999) and in one Irish family (Pittock *et al.*, 2000).

### **Heredodegenerative dystonia**

The heredodegenerative dystonias are the most heterogeneous group of dystonias and include autosomal dominant, autosomal recessive, X-linked and mitochondrial disorders. Patients typically present with a dystonia-plus syndrome and often have other neurological features, such as dementia, dysarthria, ataxia and a variety of other movement disorders, such as choreoathetosis and parkinsonism. Extensive investigations may be required in patients presenting with this group of conditions to exclude causes such as Wilson disease, Niemann-Pick disease type C or ataxia-telangiectasia. In the following sections, some of the heredodegenerative disorders are discussed, considering particularly conditions in which dystonia may be a presenting or prominent feature and in which particular progress in molecular characterization has been made in the past few years. The reader is referred to Fahn *et al.* (1987) and Figs 1 and 2 for a comprehensive list of the causes of heredodegenerative dystonias.

### **Fahr disease (gene locus IBGC1)**

Fahr disease or idiopathic basal ganglia calcification is a rare disorder characterized by progressive dystonia, parkinsonism, dysphagia and neuropsychiatric disturbances. Ataxia may also occur. Despite the presence of intracerebral calcification, there are no detectable abnormalities of calcium or phosphate metabolism and no known infectious metabolic or other genetic aetiologies. The age of onset is usually between 30 and 60 years. Imaging reveals calcification predominantly in the globus pallidus, but other regions, including the putamen, caudate, dentate, thalamus and cerebral white matter, can also be affected. An autosomal dominant mode of inheritance has

been reported in a few families (Manyam *et al.*, 1992; Kobari *et al.*, 1997; Geschwind *et al.*, 1999). In one of the families, more than half of the patients suffered from dystonia, usually a focal dystonia affecting the upper or lower limbs, jaw dystonia or writer's cramp. Linkage analysis performed on 24 members of this family revealed a locus on chromosome 14q. Interestingly, the authors report an age of onset that decreases on average every 20 years, in subsequent generations which would be consistent with genetic anticipation (Geschwind *et al.*, 1999).

### ***Aicardi–Goutieres syndrome (gene locus AGS1)***

Aicardi–Goutieres syndrome is a severe familial encephalopathy which is usually diagnosed shortly after birth and is fatal or causes a persistent vegetative state in early childhood. The neurological features include microcephaly with intracerebral calcification and white matter disease, spasticity, dystonia, visual inattention and abnormal eye movements (reviewed in Tolmie *et al.*, 1995). It is often associated with a sterile CSF lymphocytosis and elevated levels of interferon  $\alpha$  in both serum and CSF (Goutieres *et al.*, 1998). Inheritance is autosomal recessive with genetic heterogeneity and one locus has been found on chromosome 3p21 (Crow *et al.*, 2000).

### ***Hallervorden–Spatz syndrome (pantothenate kinase-associated neurodegeneration gene locus PKAN)***

Hallervorden–Spatz syndrome is a rare autosomal recessive condition, characterized by extrapyramidal features, dementia and ocular abnormalities. Usually, the condition presents in childhood or adolescence, but adult-onset cases have been described and death occurs on average 11 years after onset. There is usually progressive rigidity, first in the lower and later in the upper extremities, and an equinovarus deformity of the foot has been the first sign in several cases. Involuntary movements of choreic or athetoid type sometimes precede or accompany the rigidity. Both involuntary movements and rigidity may involve muscles supplied by the cranial nerves, resulting in difficulty in articulation and swallowing. Mental deterioration and epilepsy occur in some patients. Ocular abnormalities include optic atrophy, gaze palsies and nystagmus. A pigmentary retinopathy is also described occasionally. The varied clinical features make diagnosis difficult during life. There are inconsistent reports of acanthocytosis, but if these are present the diagnosis should be reviewed carefully (Hardie, 1989). The pathological hallmark of Hallervorden–Spatz syndrome is a rust-brown discoloration of the medial part of the globus pallidus bilaterally, with some discoloration of the zona reticularis of the substantia nigra. This discoloration is a result of deposition of iron and other pigments and in some patients leads to low attenuation signals on T<sub>2</sub>-weighted MRI, with a region of hyperintensity in the internal segment of the globus

pallidus (the 'eye of the tiger' sign). The gene involved in Hallervorden–Spatz syndrome has been localized to chromosome 20p12.3-p13 and has been identified recently as a novel pantothenate kinase gene (*PANK2*) (Taylor *et al.*, 1996; Zhou *et al.*, 2001). The enzyme is expressed at high levels in the brain and is an essential regulatory enzyme in the biosynthesis of coenzyme A, which is important in intermediary and fatty acid metabolism. Further work will determine how mutations in *PANK2* are associated with neurodegeneration.

Julius Hallervorden and Hugo Spatz, whose names are attached to the disorder, participated in euthanasia programmes during World War II, and it has been suggested that the eponym Hallervorden–Spatz be removed and replaced with the functional alternative, 'pantothenate kinase-associated neurodegeneration' (PKAN). This term is now used in OMIM (On-line Mendelian Inheritance in Man).

### ***X-linked dystonia–parkinsonism syndrome (dystonia 3; gene locus DYT3)***

The X-linked dystonia–parkinsonism syndrome (XDP) is a very rare condition, characterized by dystonia and frequently by concurrent parkinsonism (Fahn and Moskowitz, 1988). It was first identified on the island of Panay in the Philippines (Lee *et al.*, 1976, 1991) and is sometimes known locally as 'lubag', which refers to the twisting movements (Wilhelmsen *et al.*, 1991). The disease has a prevalence on Panay of ~1 in 4000 males and it originated from a single mutation (founder effect). XDP has also been reported in Filipino immigrants in North America and may occur elsewhere, although it has been diagnosed beyond doubt only in people of Filipino extraction. There are two reports of Caucasians with symptoms and neuropathological features which are similar to those of XDP (Gibb *et al.*, 1992; Factor and Barron, 1997) but their relationship to XDP is unknown.

The inheritance of XDP is X-linked recessive and penetrance appears to be complete in male gene carriers by the end of the fifth decade. Although almost all patients are males, there are reports of three females with XDP who apparently carried two copies of the defective gene (Kupke *et al.*, 1990; Waters *et al.*, 1993a). The mean age of onset is 35 years and the initial presentation is usually a focal dystonia which generalizes after a median duration of 5 years (Lee *et al.*, 1991). Unlike other forms of dystonia, the site of onset is very variable (lower limbs, axial musculature, upper limbs or head) and the site of onset does not affect the course of the disease, which is progressive and severely disabling in most cases. Parkinsonian features include bradykinesia, tremor, rigidity and loss of postural reflexes (Lee *et al.*, 1991; Muller *et al.*, 1998). The duration of illness can exceed 40 years but shorter courses of the disorder are more common. Death usually occurs due to dysphagia and aspiration pneumonia. CT and MRI examinations of patients are normal. PET analysis in three XDP patients revealed 'selective reduction in normalized striatal glucose metabolism' (Eidelberg *et al.*,

1993). Neuropathological investigations of the brains of XDP patients revealed neuronal loss and astrocytosis in the caudate nucleus and lateral putamen (Altrocchi and Forno, 1983; Waters *et al.*, 1993b).

The disease locus, *DYT3*, was assigned to the proximal long arm of the X chromosome (Kupke *et al.*, 1990; Wilhelmsen *et al.*, 1991) and the critical interval narrowed down to a small region in Xq13.1 (Haberhausen *et al.*, 1995; Németh *et al.*, 1999b). Several candidate genes have been excluded by mutation analysis (Peters *et al.*, 1997; Németh *et al.*, 1999b). Indirect genetic diagnosis is possible in Filipino patients using haplotype analysis but detailed molecular analyses (especially in non-Filipino patients with symptoms suggestive of XDP) will rely on the isolation of *DYT3*.

### ***X-linked deafness–dystonia–optic atrophy syndrome (gene locus DFN1/MTS)***

X-linked deafness–dystonia–optic atrophy syndrome, or Mohr–Tranebjaerg syndrome (MTS), is characterized by X-linked recessive sensorineural hearing loss, dystonia, dementia, psychotic features and optic atrophy. Other features include mental retardation, hip fractures and peripheral neuropathy. The condition usually starts in childhood and is progressive. Some patients die in adolescence but others have survived into their 50s. In carrier females there may be mild hearing loss and a mild peripheral neuropathy. Autopsy in one patient revealed neuronal loss and gliosis in both caudate nuclei, putamen and globus pallidus (Hayes *et al.*, 1998). The *DFN1/MTS* locus was assigned to Xq21.3–Xq22 by linkage analysis (Tranebjaerg *et al.*, 1995) and a mutation identified subsequently in a novel gene, *DDP* (deafness–dystonia peptide) (Jin *et al.*, 1996). The original mutations described were deletions or frameshift/nonsense mutations, but more recently a *de novo* missense mutation has also been described (Tranebjaerg *et al.*, 2000).

The *DDP* gene product turns out to be a nuclear-encoded mitochondrial protein. Mitochondria contain their own genome, which encodes components of oxidative phosphorylation. However, mitochondria contain hundreds of other proteins that are involved in their structure and function. These proteins are all nuclear-encoded and are imported from the cytosol into the mitochondria. *DDP* is homologous to a family of proteins in yeast known as the ‘Tiny Tims’, which are part of a complex of proteins called inner membrane translocases or TIMs. These translocases are involved in transporting nuclear-encoded proteins into mitochondria for insertion into the inner mitochondrial membrane or transport into the matrix (Koehler *et al.*, 1998a, b, 1999; Leuenberger *et al.*, 1999; Koehler, 2000; Paschen *et al.*, 2000). Future work will be required to unravel the role of *DDP* in humans and the mechanisms by which mutations lead to the clinical features of the Mohr–Tranebjaerg syndrome.

### ***Mitochondrial function in dystonia***

Apart from MTS, there is further evidence that disturbances of mitochondrial function are present in other forms of dystonia. The best example of this is dystonia associated with Leber’s hereditary optic neuropathy (LHON). LHON is characterized by acute or subacute loss of vision with onset between 18 and 30 years of age and marked male preponderance, and in some families dystonia is also present. Two families have been described in which LHON and dystonia segregate, sometimes separately and sometimes in combination. All individuals were related through the maternal line. The dystonia was of the early-onset generalized type (age 5 years onwards) and the neurological disorder progressed to include corticospinal tract dysfunction, dysarthria and abnormal extraocular movements. In one family, of Hispanic origin, there was also intellectual impairment and in this family CT examination showed bilateral basal ganglia lucencies (Novotny *et al.*, 1986). A mitochondrial DNA mutation at nucleotide 14 559 was identified subsequently (Jun *et al.*, 1994). In the second family, of Dutch origin, intelligence was normal but there was also bradykinesia, athetosis and amyotrophy. Two mutations, at nucleotides 11 696 and 14 596, were identified; they caused severe deficiency of complex I (De Vries *et al.*, 1996). These cases support the idea that mitochondrial dysfunction may be associated with dystonia, but other mechanisms may also be at work since some genetic defects in the respiratory chain are not associated with dystonia (Truong *et al.*, 1990; Lera *et al.*, 1994; DiMauro and DeVivo, 1996; Dahl, 1998; Zhu *et al.*, 1998).

### ***Neuroacanthocytosis***

The term ‘neuroacanthocytosis’ is used to describe the association of peripheral blood acanthocytosis (a term derived from the Greek to describe ‘thorny’ red blood cells) with a neurological disorder. There are two main groups of patients: those with lipid abnormalities, in whom a spinocerebellar ataxia is the major neurological problem (e.g. abetalipoproteinaemia), and those in whom lipid profiles are normal and movement disorders, seizures and dementia predominate. Only the latter group are considered here.

### ***McLeod syndrome (gene locus XK)***

McLeod syndrome is a distinct form of neuroacanthocytosis defined on the basis of a specific blood group phenotype with weak expression of all Kell antigens in the Kell blood group system.

The McLeod phenotype is characterized by abnormalities in the haematopoietic and neuromuscular systems and is inherited as an X-linked recessive trait (reviewed in Hardie, 1989). The condition usually develops in the fourth or fifth decade of life and the vast majority of patients are male.



Female carriers show mosaicism in the Kell blood group system and erythrocyte morphology.

After the ABO and rhesus blood groups, the Kell system is the most important (reviewed in Redman *et al.*, 1999). Most healthy individuals have normal levels of Kell antigens. A few people are  $K_{null}$ , with undetectable Kell antigens, but are otherwise healthy. The *XK* gene codes for the Kx antigen, which is covalently linked to Kell through a disulphide bond (Russo *et al.*, 1998). In most healthy individuals, the level of Kx is normal, whereas in  $K_{null}$  individuals there are increased levels of Kx. In contrast, patients with the McLeod phenotype and mutations in *XK* have markedly reduced Kell antigenicity associated with the absence of Kx. They also have haematological abnormalities which include acanthocytes in peripheral blood films, a permanent haemolytic state with a reduced level of haptoglobin, reticulocytosis, bone marrow hyperplasia and splenomegaly (Wimer *et al.*, 1977). The red cells do not appear to have any other biochemical abnormalities, such as altered composition of phospholipid or cholesterol/phospholipid ratios.

The clinical features of McLeod syndrome include the insidious onset of areflexia, dystonia and chorea (Hardie, 1989). There may also be orofacial dyskinesias, facial and generalized tics, epilepsy, psychiatric disturbances, dementia (Jung *et al.*, 2001) and late-onset muscular dystrophy and cardiomyopathy with an elevated creatinine kinase concentration, in the range 1000–3000 IU/l. The cardiomyopathy is occasionally clinically significant and patients should have cardiac evaluation (Malandrini *et al.*, 1994). The electrical and histological evidence of a neurogenic myopathy is present early in life but there is little clinical evidence for this until at least the fourth decade. Neuroimaging studies of McLeod patients reveal atrophy of the caudate nucleus with generalized cerebral atrophy and PET scanning reveals a reduction in the binding of striatal dopamine  $D_2$  receptors and reduced striatal 2-fluoro-2-deoxyglucose uptake (Jung *et al.*, 2001; Oechsner *et al.*, 2001).

The *XK* locus is located in Xp21, close to the genes for Duchenne muscular dystrophy (*DMD*), chronic granulomatous disease and X-linked retinitis pigmentosa type 3 (*RP3*). Rare patients have been described who have contiguous gene deletion syndromes involving all four loci, and the DNA from these patients was instrumental in locating and cloning the gene (Ho *et al.*, 1994). However, in most patients the myopathy associated with *XK* mutations is distinct from that of Duchenne muscular dystrophy.

*XK* encodes a 444-amino acid protein, which is homologous to a *Caenorhabditis elegans* protein known as ced-8, with 19% identity and 37% overall similarity (Stanfield and Horvitz, 2000). Both ced-8 and the *XK* protein contain 10 hydrophobic predicted transmembrane-spanning segments and most of the sequence similarity is between these regions. The ced-8 protein is involved in programmed cell death in *C. elegans*, possibly by playing a role in the initiation of cell death during embryogenesis. The homology with *XK* has led to the suggestion that mutated forms of *XK* protein, like ced-

8, may cause neurodegeneration because of abnormalities in these developmental pathways of programmed cell death.

### **Chorea–acanthocytosis (gene locus CHAC)**

The neurological features of chorea–acanthocytosis (CHAC) overlap significantly with those of McLeod syndrome, but the condition tends to develop slightly earlier than McLeod syndrome and many patients present in their 20s and 30s. There are approximately equal numbers of males and females affected. One of the most characteristic presenting features is a mutilating orofacial dyskinesia with involuntary vocalizations and other tics, which can be misdiagnosed as Tourette syndrome. Other characteristic features include limb chorea, dysarthria, hyporeflexia or areflexia, amyotrophy and dysphagia. There may also be muscle weakness, seizures, limb dystonia, parkinsonism and dementia (Hardie, 1989; Hardie *et al.*, 1991). Cardiomyopathies are reported and warrant cardiac investigation (Cavalli *et al.*, 1995; Kageyama *et al.*, 2000). As in the McLeod syndrome, motor conduction velocities are usually normal but muscle denervation is detectable on electromyography. Lipid profiles are normal and there is imaging evidence of caudate and cerebral atrophy. Pathological examination reveals consistent neuronal loss and gliosis in the caudate and putamen with frequent neuronal loss in the globus pallidus and occasional abnormalities of the thalamus (reviewed in Rinne *et al.*, 1994).

The pattern of inheritance of CHAC was controversial but recent linkage analysis has clearly demonstrated that it is an autosomal recessive disorder mapping to chromosome 9q21 (Rubio *et al.*, 1997). Mutations in the *CHAC* gene have recently been identified (Rampoldi *et al.*, 2001; Ueno *et al.*, 2001). It is a large gene containing 73 exons, which are alternatively spliced. The gene covers 250 kb of genomic DNA, making it one of the largest genes identified. The *CHAC* protein is predicted to contain 3174 amino acids and shows homology to the  $NH_2$  and  $COOH$  terminals of several proteins in yeast, *C. elegans*, *Drosophila melanogaster*, *Arabidopsis* and *Dictyostelium*. Some of these proteins are involved in the localization of proteins within the trans-Golgi network, suggesting that the *CHAC* protein may have a similar function, but further work is required to determine how mutations in *CHAC* cause neurodegeneration.

Because McLeod syndrome and CHAC have similar clinical features, the precise diagnosis can be difficult in an isolated male with neuroacanthocytosis and a normal lipid profile. However, there is some practical importance in obtaining an accurate genetic diagnosis because of the big difference in recurrence risk. For example, the sister of an isolated patient has less than a 1% chance of having an affected child if the condition is autosomal recessive (provided there is no consanguinity), whereas if the condition is X-linked there is a 50% chance of a boy being affected. Since both causative genes have been identified, one might expect the genetic diagnosis to be easier. Unfortunately, the size of the *CHAC* gene is likely to preclude mutation analysis

in diagnostic laboratories and the genetic diagnosis is likely to rest on the exclusion of the McLeod syndrome if Kell antigen profiles are normal and no mutation is found in *XK*. However, mutation analysis of the *CHAC* gene might be available on a research basis and might be particularly useful in populations in which a common mutation exists (i.e. a founder mutation), since the recurrence risk would be 25% if two carriers had children.

### Paroxysmal dyskinesias

This is a distinct group of conditions which can be distinguished from other forms of dystonia by their periodic occurrence, the patient being free of symptoms the majority of the time. The conditions are clinically and genetically heterogeneous and the genetic varieties are documented below.

#### *Paroxysmal non-kinesigenic dyskinesia*

Paroxysmal non-kinesigenic dyskinesia (PNKD), previously known as paroxysmal dystonic choreoathetosis or Mount-Reback syndrome, was first described in a large family with many affected members (Mount and Reback, 1940). PNKD is characterized by attacks of dystonia, chorea and athetosis that can last from 5 min to 4 h, may occur several times a day and can be precipitated by alcohol and caffeine and, to a lesser extent, by hunger, fatigue, nicotine and emotional stress but not by movement, exertion or sleep (Lance, 1977; Goodenough *et al.*, 1978; Fink *et al.*, 1997). Age of disease onset varies widely and can be in early childhood, adolescence or early adulthood. The majority of cases are familial, with only rare reports of sporadic cases. The disease can be quite disabling due to interference of the involuntary movements with walking, coordinated use of the arms and hands, speaking, chewing and swallowing. Neurological examination between episodes is normal.

PNKD is inherited as an autosomal dominant trait, with incomplete penetrance in some families (Fink *et al.*, 1996). Linkage analysis has identified a locus in distal 2q (Fink *et al.*, 1996; Fouad *et al.*, 1996; Rashkind *et al.*, 1998; Matsuo *et al.*, 1999), but the gene has not yet been identified.

#### *Paroxysmal kinesigenic choreoathetosis*

Paroxysmal kinesigenic choreoathetosis (PKC) may be inherited as an autosomal dominant trait with incomplete penetrance although most cases are sporadic (Marsden, 1996). Attacks usually start between age 6 and 16 years, are precipitated by sudden unexpected movements (i.e. they are kinesigenic) and are of shorter duration (seconds to minutes) and more frequent than attacks of PNKD, occurring up to 100 times per day. They usually respond to anticonvulsant therapy. Some PKC patients or their family members have a history of epilepsy (Jung *et al.*, 1973; Goodenough *et al.*, 1978; Tan *et al.*, 1998), although a causal relationship

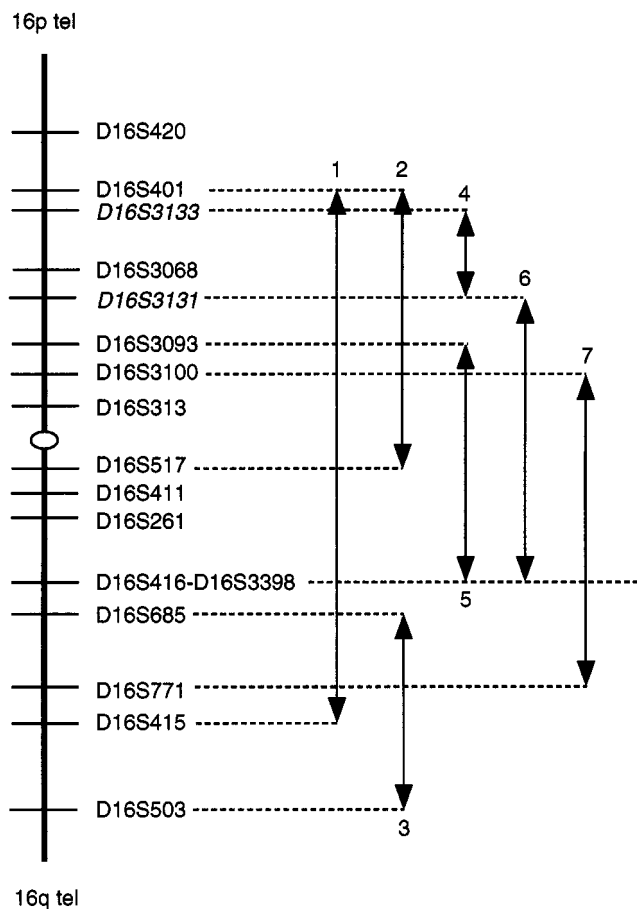
between the two abnormalities remains controversial. However, the occurrence of afebrile infantile convulsions in some patients with PKC or in their relatives has been well recognized in previous reports (Hudgins and Corbin, 1966; Hamada *et al.*, 1998; Nagamitsu *et al.*, 1999; Sadamatsu *et al.*, 1999). Recently, PKC has been mapped to chromosome 16p11.2-q12.1 in families from varied ethnic backgrounds (Tomita *et al.*, 1999; Bennett *et al.*, 2000; Swoboda *et al.*, 2000; Valente *et al.*, 2000). The clinical features in all the families were typical and in some of them infantile convulsions also occurred (Tomita *et al.*, 1999; Swoboda *et al.*, 2000). The disease loci identified by the different research groups and in different families do not overlap (Fig. 4) and Valente *et al.* (2000) suggested this might be explained by the existence of a gene family in the pericentromeric region of chromosome 16, resulting from gene duplication events.

Interestingly, the chromosomal loci in some families overlap with the locus for infantile convulsions with paroxysmal choreoathetosis (*ICCA*). This has been described in patients from France and China and is an autosomal dominant trait with variably expressed paroxysmal choreoathetosis (Szepetowski *et al.*, 1997; Lee *et al.*, 1998). There were non-febrile partial or generalized convulsions between the ages of 3 and 12 months and later choreoathetosis developed, which occurred at rest or was induced by exertion or anxiety. *ICCA* also maps to 16p12-q12 and partially overlaps with the other loci (Fig. 4). In addition, some cases of autosomal dominant benign familial infantile convulsions map to the same region (Caraballo *et al.*, 2001).

Autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp has also been mapped to 16p12-q11.2 in three individuals from a consanguineous Sardinian family (Guerrini *et al.*, 1999) (Fig. 4). The clinical features included partial seizures starting between the ages of 12 months and 3 years. In early childhood, dystonic episodes occurred which were triggered after prolonged exercise (usually >20 min) and recovered after the same period of time. The dystonic episodes greatly improved with age. In late adolescence, writer's cramp developed in all three patients.

#### *Paroxysmal exercise-induced dyskinesias (PED)*

This is an extremely rare condition and in total only 22 cases have been reported, 15 of them sporadic (Lance, 1977; Bhatia *et al.*, 1997; Kluge *et al.*, 1998). Munchau *et al.* (2000) have also reported a family with PED and migraine and Margari *et al.* (2000) reported a family with PED and benign epilepsy. PED can be distinguished from other paroxysmal disorders on clinical grounds. The attacks are mainly dystonic, affecting primarily the leg, and are precipitated by exercise as opposed to the onset of movement. Age of onset can range from 2 to 30 years. The attacks can last for a few minutes to hours and are not generally responsive to medication. Although the genetic loci have not been identified, Munchau and colleagues excluded linkage to chromosomes 2q (*PNKD*), 19



**Fig. 4** Location of PKC loci on chromosome 16. 1 = BFIC (benign familial infantile convulsions) (Caraballo *et al.*, 2001); 2 = ICCA syndrome (Szepetowski *et al.*, 1997); 3 = PKC (Valente *et al.*, 2000); 4 = RE-PED-WC syndrome; 5 = PKC and BFIC (Tomita *et al.*, 1999); 6 = PKC and BFIC (Swoboda *et al.*, 2000); 7 = PKC (Bennett *et al.*, 2000). Reproduced from the paper by Caraballo *et al.* (2001) in the *American Journal of Human Genetics* with permission from The University of Chicago Press.

(familial hemiplegic migraine) and 16 (*PKC*, rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp, *ICCA*)

### ***Paroxysmal choreoathetosis and episodic ataxia and spasticity (MIM 601042)***

Paroxysmal choreoathetosis and episodic ataxia and spasticity (CSE) is an autosomal dominant condition in which the involuntary movements and dystonia are similar to those in PNKD (Auburger *et al.*, 1996). Age of onset ranged from 2 to 15 years. Episodes of involuntary movements, dystonic postures of toes, legs and arms, dysarthria, paraesthesias and double vision lasted for ~20 min and occurred at a frequency ranging from twice a day to twice a year. Episodes could be induced by alcohol, fatigue and emotional stress. However, unlike PNKD, episodes could be precipitated by

physical exercise and five of the 18 patients had spastic paraplegia both during and between episodes of dyskinesia. The disease gene in this family was mapped to a 12 cM interval on chromosome 1p (1p21-p13.3).

### **Conclusions**

The dystonias are clinically and genetically heterogeneous and it is essential that a precise diagnosis is made in all cases, including a genetic one if at all possible, since this will provide important information for prognosis, optimal treatment regimes and potential recurrence risks for family members. At present, the only genetic mutation testing which is available on a routine basis (in some countries) is for the GAG deletion of *DYT1*. Testing for mutations in other genes causing dystonia, such as *GCH1*, parkin, *XK/CHAC*, *DDP*, Cu-ATPase (Wilson disease) and *NPC1* (Niemann-Pick disease type C), is usually only available on a research basis.

Despite the diversity of the dystonias, there are some common themes emerging from recent molecular analyses of these conditions which may have important implications for understanding their genesis and for devising treatment strategies. First, the expression pattern of torsin A in the substantia nigra, the occurrence of both parkinsonism and dystonia in several syndromes and the mutation in the dopamine receptor in myoclonic dystonia all suggest that there is functional and anatomical linkage between dystonia and the dopaminergic system. The nature of this association is under active investigation. Secondly, there is some evidence that mitochondrial defects can also cause dystonia, although it is unclear whether this is a primary or a secondary effect (Shoffner, 1995; Wallace and Murdock, 1999). Thirdly, there is good evidence that the paroxysmal dyskinesias are clinically and genetically distinct from the primary dystonias. The available data suggest that there is overlap between the paroxysmal movement disorders, epilepsy and the episodic ataxias and that all of these conditions may be caused by mutations in CNS ion channels, as has been shown already for the episodic ataxias and other paroxysmal disorders (Gordon, 1998; Bhatia, 1999; Moxley, 2000). Finally, the primary dystonias and dystonia-plus syndromes tend to be inherited as autosomal dominant traits, whereas the degenerative dystonias are often inherited as autosomal recessive traits. Identifying the genetic mechanisms and modifying genes underlying these patterns of inheritance will be crucial for the development of novel treatment strategies, which are likely to be very varied and disease or mechanism specific. For all types of dystonia, pharmacological treatment may be used to circumvent abnormal cellular pathways or wild-type genes might be introduced and expressed using various vectors. Stereotactic surgery is regaining popularity following its success in Parkinson disease and preliminary results have been encouraging, particularly in generalized dystonias (Krack and Vercueil, 2001). Other approaches for the autosomal dominant dystonias might include molecular

techniques (using ribozymes, antisense oligonucleotides etc.) to suppress mutant gene expression, leaving the wild-type allele intact (Millington-Ward *et al.*, 1997). Treatments for the degenerative dystonias are likely to be more of a challenge and could follow the path of Huntington disease, in which foetal transplantation and neuroprotective agents are currently being tested (Ferrante *et al.*, 2000; Beal and Hantraye, 2001).

Is genetic testing likely to increase? Although only testing for *DYT1* is currently available, this may change if there is sufficient demand. This is likely if patients wish to have accurate recurrence risks or pursue preimplantation genetic diagnosis. Increased demand is also likely if gene therapies become a reality, since a precise diagnosis will be necessary before embarking on any clinical trials. Although gene therapies are not yet available, the explosion in the molecular understanding of some dystonias suggests that they will be in the future. Hopefully, this knowledge will ultimately improve the quality of life for patients and their families.

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