Presently, 17 distinct monogenic primary dystonias referred to as dystonias 1–4, 5a,b, 6–8, 10–13 and 15–18 (loci DYT 1–4, 5a,b, 6–8, 10–13, 15–18) have been recognized. Twelve forms are inherited as autosomal dominant, four as autosomal recessive and one as an X-linked recessive trait. Three additional autosomal dominant forms (DYT9, DYT19 and DYT20) might exist based on linkage mapping to regions apparently different from, yet in close proximity to or overlapping with the known loci DYT18, DYT10 and DYT8. Clinically, this group of movement disorders includes pure dystonias and dystonia plus syndromes. In addition, dyskinesias (paroxysmal dystonias), although phenotypically distinct from classical dystonias, are discussed within this group. In pure dystonias, dystonia is occasionally accompanied by tremor. In dystonia plus syndromes, dystonia as the prominent sign concurs with other movement abnormalities such as myoclonus and parkinsonism. In the dyskinesias, dystonia occurs as a paroxysmal sign in association with other movement anomalies and sometimes seizures. While gross neuropathological changes are absent in most primary dystonias, including the paroxysmal forms, striking morphological alterations are found in some, such as in the X-linked dystonia–parkinsonism syndrome (DYT3). Neuropathological findings at the microscopic level have also been reported in several cases of dystonia 1 and 5, both of which were previously thought to be morphologically normal. One locus, DYT14 had been erroneously assigned, by linkage mapping, in a family with dystonia 5. There are two forms of dystonia 5, one autosomal dominant and one autosomal recessive. These forms are designated here as dystonia 5a and dystonia 5b (DYT5a, DYT5b), respectively. The disease gene has been identified in 10 primary dystonias, seven autosomal dominant (TOR1A/DYT1, GCH1/DYT5a, THAP1/DYT6, PNKD1/MR-1/DYT8, SGCE/DYT11, ATP1A3/DYT12 and SLC2A1/DYT18), two autosomal recessive (TH/DYT5b and PRKRA/DYT16) and one X-chromosomal recessive (TAF1/DYT3). This article summarizes all known aspects on each of the monogenic primary dystonias, including phenotype, neuropathology, imaging, inheritance, mapping, molecular genetics, molecular pathology, animal models and treatment. Suggestions for the diagnostic procedure in primary dystonias are given. Although much is now known about the molecular basis of primary dystonias, treatment of patients is still mainly symptomatic. The only exceptions are dystonias 5a and 5b with their excellent long-term response to L-dopa substitution.

**Abbreviations:**

- CT = computed tomography
- DA = dopamine
- DRD = dopa-responsive dystonia
- ER = endoplasmic reticulum
- MRI = magnetic resonance imaging
- M-D = myoclonus dystonia
- NE = nuclear envelope
- PKC = paroxysmal kinesigenic choreoathetosis
- PKD = paroxysmal kinesigenic dyskinesia
- PTS = 6-pyruvoyltetrahydropterin synthase
- SR = sepiapterine reductase
- THAP = thanatos-associated protein
- TH = tyrosine hydroxylase
- XDP = X-chromosomal dystonia parkinsonism syndrome

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Introduction

Dystonias are characterized by involuntary muscle contractions which result in twisting and repetitive movements and abnormal postures (Fahn et al., 1987). Primary dystonias can be distinguished from secondary ones (Fahn et al., 1998; Geyer and Bressman, 2006). Primary forms solely or mainly present with dystonia. They are frequently inherited as monogenic traits and usually lack gross neuropathological changes. Dystonia plus syndromes are monogenic dystonias without detectable neurological abnormalities but with additional neurological manifestations such as myoclonus and parkinsonism (Albanese et al., 2006). A third group includes paroxysmal dyskinesias with episodes of dystonic involvement and no gross neuropathological anomalies. In contrast, secondary dystonia occurs as one of the several signs and symptoms within another, frequently neurological, oncological or metabolic disorder, after intoxication or after trauma. In these forms, neuropathological findings are common and dystonia is thought to occur ‘secondary’ to another disorder or an external insult. Heredodenerative diseases associated with dystonia including various autosomal dominant (e.g. Huntington’s disease, some spinocerebellar ataxias) and autosomal recessive (e.g. juvenile parkinsonism, Wilson’s disease, pantothenate kinase associated neuro-degeneration) disorders should be considered a subgroup of secondary dystonias (e.g. Geyer and Bressman, 2006).

Our knowledge and understanding of monogenic forms of primary dystonias has grown dramatically during the last two decades. In 1990, only eight monogenic forms were recognized and only one disease gene (DYT1) had been mapped by linkage analysis (Müller and Kupke, 1990). The number of distinct primary dystonias and dystonia plus syndromes had increased to 13 by 1999 (Müller et al., 1999). The disorders were designated as dystonias 1–12, the disease loci as DYT1-12 (the autosomal dominant and recessive forms of dopa-responsive dystonia (DRD) were both listed under Dystonia 5/DYT5). Although eight variants had been chromosomally mapped, only three disease genes had been identified at this time. Gene discovery and recognition of additional variants has further accelerated during the last 10 years (e.g. de Carvalho Aguiar and Ozelius, 2002; Nemeth, 2002; Geyer and Bressman, 2006; Tarsy and Simon, 2006; Breakefield et al., 2008) and was greatly propelled by the completion of the human genome project.

This article gives a comprehensive update on the monogenic primary dystonias. It aims at providing the reader with a fast overview of this group of disorders. The primary dystonias are divided into three subgroups, all of which present with dystonia as a major sign. These subgroups are referred to as ‘pure dystonias’ (classified as ‘primary dystonias’ by some, e.g. Albanese et al., 2006), ‘dystonias plus’ and ‘paroxysmal dystonias’. This classification system is in line with the original and widely accepted proposal by Fahn et al. (1987) to divide the dystonias into two groups: the primary and the secondary forms. It avoids the introduction of additional dystonias independent of primary and secondary forms. The known findings are discussed for each of the currently recognized forms including phenotype, neuropathology, imaging, prevalence, molecular genetics, molecular pathology, animal models and treatment. First, the autosomal dominant pure dystonias are discussed, followed by dystonia plus syndromes and the paroxysmal dystonias. The autosomal recessive pure dystonias and dystonia plus syndromes and the only X-linked recessive dystonia plus syndrome are reviewed thereafter. Although there are no specific treatments in most dystonias, aspects on therapy are discussed for various forms of dystonia separately if therapeutic approaches have been described that appear to be particularly beneficial in a given dystonia.

Autosomal Dominant Primary Dystonias (Table 1)

Pure dystonias

Dystonia 1 (early-onset dystonia, idiopathic torsion dystonia, dystonia musculorum deformans); DYT1, TOR1A; OMIM 128 100

Phenotype

Onset of dystonia 1 is most commonly during childhood. Usually first symptoms occur in the limbs and dystonia generalizes within a few years of onset. However, clinical presentation can vary remarkably with respect to age and site of onset and progression. Onset can be during adolescence and early adulthood, and in some cases dystonia does not generalize but remains focal or segmental (e.g. Bressman et al., 2002; Grundmann et al., 2003).

Neuropathology

Several studies failed to detect neuropathological changes in dystonia 1. In particular, immunohistochemistry of the basal ganglia did not reveal morphological abnormalities (Walker et al., 2002). More recently however, brainstem abnormalities were observed in four typical dystonia 1 patients. McNaught et al. (2004) reported the detection of neuronal perinuclear inclusion bodies in the mid-brain reticular formation and in the periaqueductal grey matter. These inclusions were immunoreactive for ubiquitin, torsinA and nuclear envelope (NE) protein lamin A/C. In brains from patients with adult-onset dystonia thought to be dystonia 1, Holton et al. (2008) did not find such inclusions. These findings suggest that the underlying molecular pathological mechanisms might differ in early- and adult-onset dystonia 1. However, the diagnosis of dystonia 1 had not been confirmed molecularly in three of the cases described by Holton et al. (2008). In another three cases, no mutation had been detected. Therefore, it is not clear whether these cases could be classified as ‘dystonia 1’. Another study described enlarged dopaminergic cell bodies in the substantia nigra (Rostasy et al., 2003).

Imaging

Magnetic resonance imaging (MRI) and computed tomography (CT) scans are normal in early-onset dystonia. [18F]-fluorodeoxyglucose positron emission tomography (PET) scans of patients with dystonia 1 revealed increased metabolic activity in mid-brain, cerebellum and thalamus. Non-manifesting carriers of a mutation in TOR1A (see below) showed an increased
metabolic activity in the lentiform nuclei, cerebellum and supplementary motor areas (Eidelberg et al., 1998). In contrast, PET studies in dystonia 1 patients of a Chinese family did not reveal hypermetabolism in cerebellum or basal ganglia (Ching et al., 2007). Brain scans of mutation carriers with H2 15O PET during sequence learning showed increased cerebellar activation (Carbon et al., 2008). Furthermore, D2 receptor binding in caudate and putamen was decreased in individuals with TOR1A mutations (Asanuma et al., 2005).

Prevalence, inheritance and mapping

The disorder is most common in the Ashkenazi Jewish population with a prevalence estimated at 1/16,000–1/20,000. In the non-Jewish population, prevalence is about 1/200,000 (summarized in Müller and Kupke, 1990).

Dystonia 1 is inherited as an autosomal dominant trait with a reduced penetrance of ~30% (Bressman et al., 1989; Risch et al., 1990). The disease locus, DYT1, has been assigned to the long arm of chromosome 9 (9q34) by linkage analysis (Ozelius et al., 1990).

Molecular genetics

The disease gene, TOR1A was identified in 1997 (Ozelius et al., 1997). It is composed of five exons and is widely expressed. Expression of TOR1A is regulated by transcription factors of the Ets family. These bind to two Ets binding cores in the upstream region (within _78 and _69 bp) of the gene (Armata et al., 2008).

A three-nucleotide deletion (‘GAG deletion’) of one of two adjacent GAG trinucleotides in exon 5 (904_906delGAG/907_909delGAG) is the most common mutation and found in almost all dystonia 1 patients (summarized in Geyer and Bressman, 2006). This mutation has arisen independently in several populations (Klein et al., 1998a). In the Ashkenazi Jewish population, the GAG deletion originated from a founder who lived in Byelorussia or Lithuania about 350 years ago (Risch et al., 1995). Today the frequency in this population is 1/3,000–1/9,000 (Risch et al., 1990).

The GAG deletion results in the loss of a glutamic acid within the gene product torsinA (Δ302/303). In addition to the GAG deletion, a few other mutations have been described in TOR1A. A G>A transition was detected in exon 5 (c.863G>A) in a female patient with generalized dystonia and in her unaffected mother. The mutation causes the exchange of an arginine for a glutamine (pArg288Gln) in torsinA (Zirn et al., 2008a). A pathogenic role of this mutation is likely: (i) an arginine at position 288 has been evolutionarily highly conserved in all vertebrates including fish (fugu), thus indicating an important function and (ii) functional studies in a cell system indicate the same morphological changes in the nuclear membrane (enlargement of the perinuclear space) that are also found in the common ΔGAG mutation. Pathogenicity of two additional mutations remains unclear. One, an 18 bp deletion within exon 5 (966_983del Phe328_Tyr328del) was detected in patients with myoclonus dystonia (M-D), and a mutation within the gene SGCE commonly mutated in M-D (dystonia 11) was observed in the same patients (Leung et al., 2001; Klein et al., 2002). Another mutation (934_937delAGAG) was detected in healthy blood donor with no known neurological manifestations (Kabacik et al., 2004).

A polymorphism (C/G) within exon 4 of TOR1A results in the exchange of aspartic acid for histidine at position 216 of torsinA (D216H). Aspartic acid (D) is encoded by 88% and histidine (H) by 12% of normal alleles. This polymorphism functions as a modifier of mutant torsinA. In a cellular system, the H216 allele weakens manifestation of the GAG deletion (Kock et al., 2006); and in individuals carrying the GAG deletion, the frequency of H216 alleles is increased in non-manifesting carriers and decreased in carriers with dystonia (Risch et al., 2007; Kamm et al., 2008).

### Table 1 Autosomal dominant primary dystonias

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Designation</th>
<th>OMIM</th>
<th>Chromosomal mapping</th>
<th>Disease gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure dystonia</td>
<td>Dystonia 1</td>
<td>128 100</td>
<td>9q34</td>
<td>TOR1A</td>
</tr>
<tr>
<td></td>
<td>Dystonia 4</td>
<td>128 101</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Dystonia 6</td>
<td>602 629</td>
<td>8p11.21</td>
<td>THAP1</td>
</tr>
<tr>
<td></td>
<td>Dystonia 7</td>
<td>602 124</td>
<td>18p</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Dystonia 13</td>
<td>607 671</td>
<td>1p36.13–p36.32</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Dystonia 2B</td>
<td>607 230</td>
<td>1q22.1–q22.2</td>
<td>GCH1</td>
</tr>
<tr>
<td>Dystonia plus</td>
<td>Dystonia 5a</td>
<td>128 230</td>
<td>14q22.1–q22.2</td>
<td>GCH1</td>
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<td>19q12–q13.2</td>
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<td>607 488</td>
<td>18p11</td>
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<tr>
<td>Paroxysmal dystonia</td>
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<td>118 800</td>
<td>2q35</td>
<td>PNKD1/MR1</td>
</tr>
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<td>1p21–p13.3</td>
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<td>128 200</td>
<td>16p11.2–q12.1</td>
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<td>Dystonia 18</td>
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<td>1p31.3–p35</td>
<td>SLC2A1</td>
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<tr>
<td>(Dystonia 19)</td>
<td>PKD2</td>
<td>611 031</td>
<td>16q13–q22.1</td>
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</tr>
<tr>
<td>(Dystonia 20)</td>
<td>PNKD2</td>
<td>611 147</td>
<td>2q31</td>
<td>–</td>
</tr>
</tbody>
</table>
Molecular pathology

TORT1A encoded torsinA is a member of the AAA+ family of ATPases. AAA+ ATPases (ATPases associated with diverse cellular activities) function as chaperones and mediate conformational changes in target proteins. Affinity for target proteins is high in the ATP-bound but low in the ATP-free state.

TorsinA is mainly located within the NE and the lumen of the endoplasmic reticulum (ER) (Naismith et al., 2004). The NE is composed of an inner (INM) and an outer membrane (ONM), separated by a lumen, the perinuclear space. The ONM is composed of an inner (INM) and an outer membrane (ONM), separated by a lumen, the perinuclear space. The ONM is contiguous with the ER. The location of torsinA within the NE and ER indicates a role in structure and/or function of these cellular membranes. In fact many observations and experimental findings support this notion:

(i) ATP-bound torsinA is associated with the NE, the ATP-free form however, is diffusely distributed throughout the ER. Therefore, torsinA in its active (ATP-bound) state appears to specifically target proteins of the NE (Naismith et al.; 2004; Goodchild et al., 2005);

(ii) torsinA interacts with the luminal domain of lamina-associated polypeptide 1 (LAP1), an integral protein of the inner membrane of the NE (Goodchild and Dauer, 2005);

(iii) a function of torsinA in the NE appears to be neuron specific. While expression of mutated (904_906delGAG/907_909delGAG) TORT1A results in abnormal NE in neurons, it does not affect the NE in non-neuronal cells (Goodchild et al., 2005);

(iv) overexpression of mutant (∆E-) torsinA in cells results in accumulation within the NE and in the formation of ER-derived membrane whorls (Hewett et al., 2000; Kustedjø et al., 2000). TorsinA also interacts with the LAP1-related ER protein LULL1/NET9 (Goodchild and Dauer, 2005);

(v) a potential role of torsinA in processing polypeptides through the ER is suggested by experiments using Gaussia luciferase (Gluc) either alone or fused in-frame to a yellow fluorescent protein (Gluc-YFP). Gluc-YFP co-localizes with ER proteins including torsinA. Fibroblasts from patients with the GAG deletion secreted significantly less Gluc activity than cells from controls (Hewett et al., 2007); and

(vi) torsinA binds to the KASH (klarsicht/ANC-1/syne homology) domain of nesprins (Nery et al., 2008). Nesprins (nesprin-1, -2, -3 including multiple isoforms) span the outer membrane of the NE. They are composed of an N-terminal actin-binding domain, a series of spectrin repeats and a C-terminal KASH domain, which lies within the perinuclear space (Zhen et al., 2002; Padmakumar et al., 2004). By binding to the KASH domains of nesprins -1 and -2, torsinA connects the perinuclear space with cytoplasmic actin. In addition, it binds to nesprin-3s, which interacts with vimentin via plectin. In fibroblasts from torsinA knock-out mice, nesprin-3s is distributed in the ER. Similar findings were obtained with fibroblasts from patients with the GAG deletion.

Taken together, the above findings support a role of torsinA in the NE and ER. In both the NE and ER, torsinA might be involved in maintenance of structural integrity and/or normal function of protein processing and trafficking. Furthermore, in the ER torsinA appears to play a role in the secretory pathway.

Several experimental investigations point to additional functions of torsinA in neurons:

(i) torsinA interacts with kinesin light chain. This interaction is abolished in cells expressing ∆E-torsinA (Kamm et al., 2004a). Kinesin might direct torsinA along microtubules towards the distal end of neuronal processes and become enriched in growth cones. This anterograde transport might be associated with the ER and/or vesicles. TorsinA may thus play a role in neurite outgrowth. In fact, ∆E-torsinA interferes with neurite extension in human neuroblastoma cells (Hewett et al., 2006) and

(ii) another function of torsinA appears to be related to synaptic vesicle recycling (Granata et al., 2008). Experiments in a cell system suggest that torsinA in concert with snapin regulates exocytosis and that ∆E-torsinA abolishes uptake of neurotransmitters such as dopamine (DA). This phenomenon might be one contributing factor to dysregulation of movement in dystonia 1.

Animal models

Expression of human mutant (∆E-torsinA) but not of wild-type torsinA in Drosophila results in locomotor deficiencies. Similar to humans, ∆E- but not wild-type torsinA precipitates protein aggregations in synaptic membranes, nuclei and endosomes of the fly (Koh et al., 2004).

Caldwell et al. (2003) studied the function of torsinA in Caenorhabditis elegans, utilizing a polyglutamine aggregation model. Overexpression of either human torsinA or C. elegans torsin-related protein TOR-2 in these worms caused a dramatic decrease in polyglutamine-induced protein aggregates. A similar effect has been observed with yeast chaperone Hsp104 in this system (Satyal et al., 2000). No such effect was found with ∆E-torsinA. These findings further indicate an important function of torsinA as a chaperone.

Numerous mouse models of dystonia 1 have been developed. Transgenic mice constructed so far express human ∆E-torsinA (hMT1) under the control of either a cytomegalovirus promoter (Sharma et al., 2005), a neuron-specific enolase promoter (Shashidharan et al., 2005) or a murine prion protein promoter (Grundmann et al., 2007). Knock-in mice were constructed by gene targeting with the target vector carrying mouse DNA with only one GAG trinucleotide at the relevant position of tor1a (∆GAG mutation). This generates the mouse orthologue of human ∆E-torsinA (Dang et al., 2005; Goodchild et al., 2005). In addition, tor1a knock-out (Goodchild et al., 2005) and knock-down mice were developed (Dang et al., 2006). There is also a conditional, cerebral cortex-specific knock-out model (Yokoi et al., 2008).

The transgenic mice showed multiple motor deficits, including hyperkinesias and rapid bi-directional circling, dystonic features of the limbs (Shashidharan et al., 2005) and impaired motor learning.
Dystonia 6 is a slowly progressive frequently generalized dystonia. Onset is usually in brachial, cervical or cranial muscles. Occasional onset in limbs is followed by cervical and cranial involvement.

Dysphonia is common. Both frequent cervical and cranial involvement and dysphonia differentiate dystonia 6 from dystonia 1. Age at onset is during childhood and adolescence but adult-onset also occurs. The range of age at onset documented so far is between 9 and 49 years (Bressman et al., 2009; Djarmati et al., 2009; Fuchs et al., 2009). Dystonia 6 was first discovered in Amish–Mennonite families and was referred to as dystonia of ‘mixed’ type (Almasy et al., 1997).

Prevalence, inheritance, mapping and molecular genetics

Presently no data are available on the prevalence of dystonia 6. Recent reports of gene mutations (see below) indicate that dystonia 6 might turn out to be the second most common pure primary monogenic dystonia.

Dystonia 6 is inherited as an autosomal dominant trait with reduced sex-independent penetrance of ~60%. The disease locus, DYT6, was originally assigned to 8p21-q22 by linkage analysis in Amish–Mennonite families (Almasy et al., 1997). Based on the identification of the disease gene, DYT6 is now known to be located in 8p11.21.

Dystonia 6 is caused by mutations in the gene THAP1. THAP1 is composed of three exons and codes for Thanatos-associated protein domain containing apoptosis-associated protein 1 (THAP1). Missense, nonsense and frameshift mutations, including a small insertion/deletion, have been described (Bressman et al., 2009; Djarmati et al., 2009; Fuchs et al., 2009). All three exons can be affected.

Molecular pathology

THAP1 is composed of an N-terminal THAP (thanatos-associated protein) domain. This domain is an atypical zinc-finger and binds to DNA. A proline-rich region, a coiled-coil domain and a nuclear localization signal are located towards the C-terminus of THAP1. The mutations described interfere with THAP1 function, specifically its DNA-binding capacity and its nuclear translocation.

Treatment

Given that deep brain stimulation is a treatment of choice in patients with complex cervical dystonia (Albanese et al., 2006), this surgical procedure should be beneficial in dystonia 6. However, to the best of this author’s knowledge, it has not yet been tried in any of the molecularly diagnosed dystonia 6 patients.

Dystonia 7 (focal, adult-onset dystonia, idiopathic focal dystonia); DYT7; OMIM 602 124

Phenotype

Dystonia 7 was identified in one large family with adult-onset (range 28–70 years) focal dystonia. Definite dystonia was diagnosed in seven family members, of whom six had torticollis and one spasmodic dysphonia. Possible dystonia (signs of torticollis such as muscular hypertrophy and minimal rotation of the head and postural tremor of the hands) was reported in six individuals (Leube et al., 1996).

Inheritance and mapping

In this one family, dystonia 7 was inherited as an autosomal dominant trait. Linkage analysis assigned DYT7 to the short arm of chromosome 18. The maximum LOD score obtained

(Sharma et al., 2005; Grundmann et al., 2007). A decrease in DA release was described in the transgenic mice of Sharma et al. (Balioglu et al., 2007). Motor deficits and hyperactivity were observed in the tor1a knock-down mouse (Dang et al., 2006). Similarly, heterozygous knock-in and knock-out mice (homozygotes are not viable) displayed motor hyperactivity and gait abnormalities (Dang et al., 2005; Goodchild et al., 2005). Morphological changes in knock-in mice included neuronal aggregates and some of the abnormalities of NE and ER described above (Dang et al., 2005; Goodchild et al., 2005). Striatal dopaminergic D2 receptor activation is altered and N-type calcium currents are abnormal in transgenic mice (Pisani et al., 2006). Interestingly, cerebral cortex-specific knock-out mice also exhibit motor anomalies (Yokoi et al., 2008). Therefore, the motor abnormalities observed in the transgenic and knock-in/knock-down mice cannot be entirely ascribed to striatal malfunction.

Dystonia 4 (hereditary whispering dysphonia); DYT4; OMIM 128 101

Phenotype

This form of dystonia was described in one large Australian family including at least 20 established cases (Parker, 1985; Ahmad et al., 1993). In all but three patients dysphonia was the first manifestation and was described as ‘whispering dysphonia’ by the original investigator (Parker, 1985). Ten affected subjects were re-examined by Ahmad et al. (1993), nine had generalized and one had segmental dystonia. Onset in affected family members ranged from 13 to 37 years. In two affected siblings, the diagnosis of Wilson’s disease was established.

Inheritance

Dystonia 4 is inherited as autosomal dominant trait with apparently complete penetrance and variable expressivity. Linkage analyses ruled out known dystonia loci, in particular DYT1 and DYT6 (Ahmad et al., 1993; Djarmati et al., 2009). Furthermore, Wilson’s disease was excluded in all affected family members but in the two clinically and biochemically diagnosed cases. The disease locus, DYT4 has not yet been chromosomally assigned.

Dystonia 6 (idiopathic torsion dystonia of ‘mixed’ type); DYT6, THAP1; OMIM 602 629

Phenotype

Dystonia 6 is caused by mutations in the gene THAP1 (Balcioglu et al., 2007). Currents are abnormal in transgenic mice (Pisani et al., 2006). Dopaminergic D2 receptor activation is altered and N-type calcium release was described in the transgenic mice of Sharma et al., 2005; Grundmann et al., 2005). Motor deficits and hyperactivity were observed in the tor1a knock-down mouse (Dang et al., 2006). Similarly, heterozygous knock-in and knock-out mice (homozygotes are not viable) displayed motor hyperactivity and gait abnormalities (Dang et al., 2005; Goodchild et al., 2005). Morphological changes in knock-in mice included neuronal aggregates and some of the abnormalities of NE and ER described above (Dang et al., 2005; Goodchild et al., 2005). Striatal dopaminergic D2 receptor activation is altered and N-type calcium currents are abnormal in transgenic mice (Pisani et al., 2006). Interestingly, cerebral cortex-specific knock-out mice also exhibit motor anomalies (Yokoi et al., 2008). Therefore, the motor abnormalities observed in the transgenic and knock-in/knock-down mice cannot be entirely ascribed to striatal malfunction.

Dystonia 6 is a slowly progressive frequently generalized dystonia. Onset is usually in brachial, cervical or cranial muscles. Occasional onset in limbs is followed by cervical and cranial involvement.
was 2.68 at θ = 0 for marker D18S452 (Leube et al., 1996). Sporadic cases with focal cervical dystonia from Northwestern Germany were thought to share a common haplotype within the short arm of chromosome 18 (Leube et al., 1997a, b). This was not confirmed in a larger patient sample (Klein et al., 1998b).

**Dystonia 13 (primary dystonia with mixed phenotype); DYT13; OMIM 607671**

**Phenotype**

Dystonia 13 has been reported in one large Italian family. Onset was in the cervical or cranial–cervical region in six (out of eight) patients and the arms in two. Dystonia progressed slowly and became segmental in most cases. In two, a mild generalized dystonia had developed. Average age at onset was 15.6 (SD 12.5) years (Bentivoglio et al., 1997). This form is characterized by a ‘mixed dystonia phenotype’.

**Inheritance and mapping**

Dystonia 13 is inherited as an autosomal dominant trait. Linkage analysis assigned the disease locus to a 22 cM interval in the short arm of chromosome 1 (1p36.13-p36.32) (Valente et al., 2001).

**Dystonia plus syndromes**

**Dystonia 5a (DRD; Segawa syndrome; hereditary progressive dystonia with marked diurnal fluctuation, HPD); DYT5a, GCH1; OMIM 128230**

**Phenotype**

Dystonia 5, also known as Segawa syndrome or DRD, is characterized by diurnal fluctuation of symptoms in ~75% of cases, parkinsonism and a dramatic therapeutic response to L-dopa (Segawa et al., 1976; Nygaard, 1993a, b). I will refer to this form as dystonia 5a to distinguish it from the recessive form, referred to as dystonia 5b. The phenotypic spectrum of dystonia 5a can range from generalized, segmental and focal dystonia via postural anomalies, parkinsonism, abnormal gait and slight tremor to subjective complaints and signs only seen upon induction during clinical examination (Nygaard et al., 1990; Furukawa et al., 1998; Steinberger et al., 1998, 1999; Müller et al., 2002). Age of onset varies widely. While dystonia 5a usually starts during childhood, onset can also occur during adolescence or adulthood.

**Neuropathology**

There are no gross neuropathological anomalies in dystonia 5. Only a few case reports describe minor morphological anomalies and/or depigmentation in substantia nigra and striatum (Raipur et al., 1994; Furukawa et al., 1999; Grötzsch et al., 2002). Although the case reported by Grötzsch et al. (2002) was originally classified as DYT14, subsequent studies demonstrated that the patient actually suffered from dystonia 5a (Wider et al., 2008). Biochemical analyses of the brain of two autopsied cases revealed markedly reduced bipterin levels in the striatum. Tyrosine hydroxylase (TH) levels were reduced to <3% in the putamen of these two DRD patients (Furukawa et al., 1999).

**Imaging**

CT and MRI are normal in DRD. Using PET and [18F]-fluorodeoxyglucose, Asanuma et al. (2005a) found a distinct pattern of regional cerebral metabolic covariation in DRD. Specifically, it was increased metabolic activity in dorsal midbrain, cerebellum and supplementary motor area and reduced activity in basal ganglia and in motor and lateral premotor cortex. DA transporter scans are normal in DRD (Jeon et al., 1998). This is at variance with juvenile parkinsonism, an important differential diagnosis of DRD (see ‘Diagnostic procedure in primary dystonia’ section).

**Prevalence, inheritance and mapping**

Prevalence was reported as 0.5/10^6 but is probably higher owing to under-diagnosis. Females are more frequently affected than males (2.5/1) (Nygaard et al., 1988).

DRD is inherited as an autosomal dominant trait with reduced penetrance. In one large family, penetrance was given as 30% (Nygaard et al., 1990). Once subtle signs and symptoms were taken into account, the sex-average penetrance reached almost 60% in this family. A genotype–phenotype investigation in five DRD families reports a sex-average penetrance of 80%; 55% in males and complete in females (Steinberger et al., 1998). Another study reported a penetrance of 87% for females and 38% for males (Furukawa et al., 1998).

The disease locus, DYT5a, was assigned to the long arm of chromosome 14 (14q22.1-22.2) by linkage analysis (Nygaard et al., 1993a, b).

**Molecular genetics**

The disease gene, GCH1 is composed of six exons and codes for GTP-cyclohydrolase I (Ichinose et al., 1994). Single base changes including nonsense, missense and splice site mutations are detected in 50%–60% of clinically well-characterized DRD cases (Bandmann et al., 1996, 1998; Weber et al., 1997; Steinberger et al., 2000; Furukawa, 2004). In addition, microdeletions are relatively common (Furukawa et al., 2000; Klein et al., 2002, Hagenah et al., 2005, Steinberger et al., 2007; Zirn et al., 2008a). Taken together, mutations in GCH1, including microdeletions, account for 71%–87% of the cases of DRD (Hagenah et al., 2005, Zirn et al., 2008b). In addition, a heterozygous mutation in the 5'untranslated region of the sepiapterine reductase (SR) gene SPR was detected in one case of autosomal dominant DRD (Steinberger et al., 2004).

**Molecular pathology**

Both GCH1 coding for GTP-cyclohydrolase I (GTPCH1) and SPR coding for SR are essential for synthesis of DA. GTPCH1 is the enzyme catalysing the first and rate-limiting step in the synthesis of tetrahydrobiopterin (BH4) (Fig. 1). Similarly, SR is an important enzyme in the BH4 synthetic pathway. BH4 in turn is an essential cofactor of tyrosine, phenylalanine and tryptophan hydroxylases, which catalyse synthesis of L-dopa/DA, tyrosine and 5-hydroxy-tryptophan/serotonin respectively. The clinical phenotype of DRD is the direct result of insufficient synthesis of L-dopa and DA.

GTPCH1 activity can be measured in fibroblasts or lymphoblastoid cells and was found to be reduced by more than 50%
They have reduced BH4 and GTPCH1 levels in the liver. No mutations in some heterozygous mutation carriers (Ichinose et al., 1995). This observation indicated that a dominant-negative effect might be the underlying cause of reduced BH4 synthesis. Accordingly, mutant and wild-type polypeptides would form dys- or non-functional GTPCH1 heterodecamers. Cotransfection experiments using wild-type and mutated GCH1 cDNA appeared to support this notion (Hirano and Ueno, 1999). However, formation of heterodecamers was not found for at least two mutations (R88W, R184H) (Suzuki et al., 1999). This, together with the occurrence of GCH1 deletions, argues against a dominant-negative effect of GCH1 mutations and favours haploinsufficiency. Assuming that both the mechanisms played a role in different individuals, patients with deletions should be affected less severely than those with a point mutation that exerts a dominant-negative effect. This, however, does not appear to be the case. Patients with deletions and point mutations are not clinically distinct.

Animal models

The hph-1 mouse was selected by screening N-ethyl-N-nitrosurea-treated mice for hyperphenylalaninaemia (Bode et al., 1988). Although this mouse strain has slight hyperphenylalaninaemia at birth, the animals normalize during the first few weeks of life. They have reduced BH4 and GTPCH1 levels in the liver. No mutation has been detected in GCH1 but linkage analysis assigned the mutation to a region within 8 cM of the gene. BH4, catecholamines, serotonin and their metabolites are low in the brains of these mice and TH is significantly reduced in the striatum. These biochemical findings are similar to those in humans with DRD. However, hph-1 mice have no obvious motor phenotype (Hyland et al., 2003). Sumi-Ichinose et al. (2001) constructed a 6-pyruvoyl-tetrahydropterin synthase (PTS) knock-out mouse. PTS−/PTS− mice, however, are not viable. By transgenic introduction of human PTS cDNA these mice could be rescued. They have significantly reduced (20% of wild-type) striatal levels of BH4 and TH and display motor deficits similar to human DRD (Sato et al., 2008). A close correlation was observed between the time TH levels decreased in striosomes and the occurrence of motor deficits. TH loss was greater in striosomes than in the surrounding matrix and this distribution may be relevant for the development of dystonic movements.

Treatment

Treatment with low doses (20–300mg) of L-dopa results in complete remission of symptoms in most cases of DRD (Steinberger et al., 2000). No side effects such as ‘ON–OFF phenomena’ or ‘freezing episodes’ are observed in patients with DRD, even after long-term treatment.

Dystonia 11 (M-D; alcohol-responsive dystonia; DYT11, SGCE; OMIM 159900)

Phenotype

Dystonia 11 is characterized by dystonia and myoclonic jerks. Onset is most commonly during childhood and adolescence but can occur as late as during the eighth decade (Foncke et al., 2006). Myoclonic jerks are frequently the first signs and are followed by a relatively mild dystonia, often manifesting as cervical dystonia or writer’s cramp. Myoclonus mainly involves arms and axial musculature. Lower limbs or face (including vocal apparatus) are affected in 25% of the cases each (Asmus and Gasser, 2004; Nardocci et al., 2008; Roze et al., 2008). Myoclonus is responsive to alcohol in most patients. In addition, psychiatric findings are common in dystonia 11. These include depression, obsessive-compulsive behaviour, panic attacks and attention deficit hyperactivity disorder (e.g. Kinugawa et al., 2008).

No neuropathological abnormalities have been described in dystonia 11.

Imaging

CT scans and MRI are normal. In a single patient, single photon emission CT (SPECT) revealed reduced regional cerebral blood flow in both temporal lobes, both frontal lobes and in the right caudate. The authors suggest that these findings might reflect functional/metabolic involvement of these areas in the pathogenesis of dystonia 11 (Papapetropoulos et al., 2008).

Prevalence, inheritance and mapping

Dystonia 11 is very rare. Prevalence data do not exist. Inheritance is autosomal dominant with reduced penetrance owing to maternal imprinting. While paternal transmission of the gene defect always results in disease, maternal origin causes M-D in 10–15% of the cases only. Maternal uniparental disomy can also cause dystonia 11 due to imprinting (inactivation) of both maternal genes (Guettard et al., 2008). DYT11 has been assigned to the long arm of chromosome 7 (7q21) by linkage analysis (Nygaard et al., 1999; Klein et al., 2000).

Molecular genetics

The disease gene SGCE is composed of 12 exons and codes for ε-sarcoglycan (Zimprich et al., 2001). It is widely expressed in both embryonic and adult tissues including muscle and nervous system (Straub et al., 1999; Imamura et al., 2000). Brain regions with particularly high expression levels include olfactory mitral cells, the cerebellar Purkinje cells and mid-brain monoaminergic neurons (Chan et al., 2005). Maternal and paternal alleles of
SGCE are differentially methylated within the CpG island of the promoter region and the first exon of SGCE. Consistent with the imprinting data on DYT11/SGCE, the maternal allele is methylated and therefore inactivated, but the paternal allele is not (Grabowski et al., 2003). Mutations detected in patients include nonsense, missense, splice site, insertions, partial and complete deletions. They result in the synthesis of either aberrant ε-sarcoglycan molecules or of none at all, and are ‘loss of function mutations’ operating via haploinsufficiency (e.g. Hedrich et al., 2004; Asmus et al., 2005; Tezenas du Montcel et al., 2006; summarized by Kinugawa et al., 2009). It was experimentally shown that several missense mutations result in ubiquitination and rapid degradation of the encoded abnormal ε-sarcoglycan molecules (Esapa et al., 2007).

Molecular pathology
ε-sarcoglycan is a transmembrane protein consisting of a signal sequence, a large extracellular domain containing a putative glycosylation site, a transmembrane and a short cytoplasmic domain (McNally et al., 1998). Together with five additional isoforms (α-, β-, γ-, δ- and ζ-sarcoglycans), all transmembrane glycoproteins as well, it is a component of sarcoglycan complexes that form part of the dystrophin–glycoprotein complex in muscles and brain (Lapidos et al., 2004). Except ε-sarcoglycan, mutations in other isoforms such as α-, β-, γ-, and δ-sarcoglycans result in limb-girdle muscular dystrophies. Knock-out mice provide insights into possible pathological mechanisms of loss of ε-sarcoglycan in M-D (see below).

Animal models
Heterozygous paternally inherited SGCE knock-out mice display many features of dystonia 11 including myoclonus, deficient motor coordination and balance, impaired motor learning and psychiatric abnormalities such as anxiety and depression-like behaviour (Yokoi et al., 2006). There are increased levels of DA, 3,4 dihydroxyphenylacetic acid and homovanillic acid in the striatum of knock-out mice. Serotonin (5-hydroxytryptamine) and 5-hydroxyindoleacetic acid levels were not significantly altered. However, increased vertical hyperactivity in individual knock-out mice was positively correlated with 3,4 dihydroxyphenylacetic acid and inversely correlated to 5-hydroxyindoleacetic acid levels. These findings directly implicate the dopaminergic and serotonin system in the pathology of dystonia 11. Currently, it is not known how loss of ε-sarcoglycan mediates the observed changes in striatal DA, serotonin and their metabolites.

Treatment
There are no causal treatments for M-D. Benzodiazepines and anti-epileptic drugs can ameliorate myoclonus. Dystonia may respond to anti-cholinergic treatment. Botulinum toxin injections are beneficial in focal dystonia such as cervical involvement. Some patients were shown to benefit from deep-brain stimulation (Cif et al., 2004).

Dystonia 12 (Rapid-onset dystonia–parkinsonism);
DYT12, ATP1A3; OMIM 128235

Phenotype, neuropathology and imaging
Dystonia 12 is characterized by abrupt onset of dystonia and parkinsonism, which develop within minutes to days of onset. Dystonia typically affects limbs and face (dysarthria, dysphagia). There is a characteristic rostrocaudal (face→arm→leg) gradient (Brashear et al., 2007). Parkinsonian features are bradykinesia and loss of postural reflexes. Occasionally, seizures, paroxysmal dystonia and psychiatric symptoms are observed. Signs and symptoms can be precipitated or worsened by stress (fever, childbirth, emotional agitation and excessive exercise) and alcohol. Age of onset varies widely from childhood (from 4 years onwards) to adulthood (up to 58 years). Most commonly, first attacks occur in late adolescence or early adulthood (Dobyns et al., 1993, Brashear et al., 1997; Pitttock et al., 2000).

Neuropathological examination of one rapid-onset dystonia–parkinsonism brain did not reveal abnormalities (Pittock et al., 2000). CT scans and MRI are normal. Similarly, PET studies did not reveal abnormalities of the DA transporter system (Brashear et al., 1999).

Prevalence, inheritance and mapping
Dystonia 12 is extremely rare. It is inherited as an autosomal dominant trait with reduced penetrance. The exact percentage of reduction cannot be given owing to the small number of families described. The disease locus has been assigned to 19q12-q13.2 by linkage analysis (Kramer et al., 1999; Pitttock et al., 2000; Kamm et al., 2004b).

Molecular genetics
The disease gene ATP1A3 was identified in 2004 (de Carvalho Agular et al., 2004). It is composed of 23 exons (Ovchinnikov et al., 1988) and codes for Na⁺/K⁺-ATPase subunit ε3 (ATP1A3). This subunit is exclusively expressed in neurons. Only missense mutations have been detected so far (de Cavalho Aguiar et al., 2004; Brashear et al., 2007). The mutations are at evolutionarily highly conserved positions of the ATP1A3 polypeptide that are the same in vertebrates, invertebrates and some even in bacteria (de Carvalho Aguiar et al., 2004). The mutations seem to inactivate ATP1A3. The mutated polypeptide is unstable and the mutational mechanism appears to be haploinsufficiency. There is no evidence of a dominant-negative effect since the mutations do not interfere with oligomer formation.

Molecular pathology
Mutations in ATP1A3 render the Na⁺/K⁺-ATPase, encoded by one allele, inactive. Due to haploinsufficiency the ion-transport capacity of neurons is reduced and causes disturbed cellular function. This is especially dramatic when a high ion transport capacity is required, e.g. in situations of stress.

Animal models
Heterozygous Atp1a3 knock-out mice (ε3+/- mice) are hyperactive, display spatial learning and memory deficits, and show an increased locomotor response to methamphetamine. Hippocampal NMDA receptors are reduced by 40%. DA and serotonin levels are unaltered in the striatum. Spatial learning defects are thought to be the direct consequence of reduced NMDA receptor expression in the hippocampus. The increased activity after methamphetamine might be mediated by alteration in the DA and serotonin pathways. DA dysfunction would directly link ATP1A3 deficiency to dystonia. However, such effects have not yet been demonstrated. Interestingly, no abnormal movements have been
observed in α3+/− mice (Moseley et al., 2007). As pointed out by Breakefield et al. (2008), no attempts have yet been made to induce movement abnormalities, e.g. by stress or alcohol.

**Treatment**

There is no causative treatment. Specific symptoms such as anxiety, depression and seizures should be treated with psychiatric drugs and anti-convulsants, respectively. In some cases, L-dopa/ carbidopa results in slight improvement. Physical therapy and relaxation practices can also be beneficial (Brashear and Ozellius, 2008).

**Dystonia 15 (M-D); DYT15; OMIM 607488**

**Phenotype**

Dystonia 15 was observed in one large Canadian family. Affected members presented with jerky movements primarily in upper limbs and axial musculature, in two patients myoclonus was generalized. Four had dystonia of the arms and one of the legs. Symptoms frequently started in the hands as writer’s cramp. Age at onset was between 7 and 15 years (average 9.6 years). Myoclonus was responsive to alcohol (Grimes et al., 2001).

**Inheritance and mapping**

Dystonia 15 is an autosomal dominant disorder and is transmitted with reduced penetrance of 85% in the one family reported. **DYT15** was assigned to a 17cM interval on the short arm of chromosome 18 (18p11) (Grimes et al., 2002).

**Paroxysmal dystonias**

**Dystonia 8 [paroxysmal dystonic choreoathetosis (PDC); paroxysmal non-kinesigenic dyskinesia (PNKD1); non-kinesigenic choreoathetosis; Mount-Reback disease]; DYT8, PNKD1, MR1; OMIM 118800**

**Phenotype**

Dystonia 8 is characterized by attacks of dystonia, chorea, athetosis and ballism occurring at rest. Episodes can last from seconds to several hours and may occur anywhere between several times a day and a few times a year. Symptoms can be precipitated by alcohol or caffeine, and to a lesser extent by nicotine, excitement, fatigue, hunger and emotional stress (Fink et al., 1997). Age at onset varies widely and can be during childhood, adolescence or adulthood. Neurological examination is normal between episodes.

**Neuropathology**

There are usually no neuropathological findings. In some individuals with paroxysmal dyskinesias, lesions of the basal ganglia have been reported (Blakeley and Jankovic, 2002). Since no mutation analyses were performed in these cases, the exact diagnosis remains unknown.

**Imaging**

MRI findings in dystonia 8 are usually normal. In one case with paroxysmal non-kinesigenic dyskinesia, low-intensity signals in globus pallidus and substantia nigra were detected by T2-weighted MRI (Kimura and Nezu, 1999). Mutation analyses, however, have not been performed in this patient and it is not clear whether he suffered from dystonia 8.

**Prevalence, inheritance and mapping**

Dystonia 8 is extremely rare. It is inherited as an autosomal dominant trait with a penetrance >90%. The disease locus, **DYT8**, was assigned to 2q33–35 (Fink et al., 1996) and 2q36 (Fouad et al., 1996) by linkage analysis. **DYT8** is now known to be located in 2q35 based on the identification of the disease gene.

**Molecular genetics**

Dystonia 8 is caused by mutations in the gene **PNKD1** (formerly **MR1**) (Lee et al., 2004; Rainier et al., 2004). **PNKD1/MR1** is composed of 12 exons and codes for PNKD protein (myofibrillo-genesis regulator 1). Alternative splicing of the transcript results in at least three splice variants (Lee et al., 2004). Splice variant **MR-1L**, encoded by exons 3–10 is specifically expressed in the brain. Investigating 14 families with dyskinesias, Bruno et al. (2007) found mutations in eight families. Only affected members from the eight mutation-positive families in fact had PNKD1, once strict diagnostic criteria such as early-onset and precipitation of attacks by caffeine and alcohol were applied. These patients were clinically similar to those originally described by Mount and Reback (1940). Mutations detected include missense mutations at amino acid positions conserved during mammalian evolution (A9V; A7V). These two amino acids appear to be mutation hotspots since they have occurred **de novo** in several unrelated families (Lee et al., 2004; Rainier et al., 2004; Bruno et al., 2007).

**Molecular pathology**

**BRP17**, the mouse orthologue of human MR-1 is expressed in the substantia nigra pars reticulata and pars compacta. It is also expressed in other regions involved in motor control such as the red nucleus and cerebral cortex, cerebellar Purkinje and granule cells. These findings support an important role of MR-1 in normal function (maintenance of excitability?) of these essential areas of the motor system. The polypeptide encoded by splice variant **MR-1L** is localized in the perinuclear region. MR-1 is very similar to hydroxyacylglutathione hydrolase, as deduced by sequence comparison (Lee et al., 2004). Hydroxyacylglutathione hydrolase, a member of the zinc metallohydrolase enzymes with β-lactamase domains, catalyses conversion of methylglyoxal to α-lactate thereby detoxifying this substance. Methylglyoxal is present in coffee, alcoholic beverages and is a by-product of oxidative stress. Impaired function of MR-1 and an increase in methylglyoxal and other upstream compounds of this pathway might therefore explain precipitation of attacks by alcohol, caffeine and stress (Lee et al., 2004).

**Animal models**

Inbred dtz2 hamsters display several features of human idiopathic paroxysmal dystonia, including dystonic attacks induced by stress, twisting movements and abnormal postures. Affected animals are neuropathologically normal but metabolic activity is abnormal in several regions of the brain including basal ganglia and cerebellum (Nobrega et al., 1998; Richter and Löscher, 1998; Hamann et al., 2008). Immunohistochemical investigations revealed a reduced density of striatal GABAergic interneurons in dtz2 hamsters. This results in a decrease in GABA levels and enhanced activity
of GABAergic projection neurons (Gernert et al., 1999). The gene(s) mutated in the dt<sup>e</sup> mutant, however, are yet not known. Presently, no transgenic, knock-out, or knock-in mice have been constructed utilizing BRP17/PNKD1.

**Treatment**

Patients should be encouraged to avoid triggering factors such as alcohol, caffeine and nicotine. Some cases respond to clonazepam, haloperidol or anti-cholinergics.

**Dystonia 9 [PDC with episodic ataxia and spasticity; episodic choreoathetosis/spasticity (CSE)]; DYT9; OMIM 601042**

**Phenotype and treatment**

Dystonia 9 was described in one large family (Auburger et al., 1996). Patients presented with paroxysmal choreoathetosis and dystonia, similar to dystonia 8. In contrast to dystonia 8, however, several affected members of the dystonia 9 family had episodic ataxia. Episodes could be precipitated by alcohol, fatigue, emotional stress and—unlike in dystonia 8—by physical exercise. Furthermore, 5 of 18 patients had spastic paraplegia both during and between episodes of dyskinesia. Episodes occurred between twice a day to twice a week and lasted for ~20 min. Age of onset ranged from 2 to 15 years.

Acetazolamide and phenytoin ameliorated the condition in one, and acetazolamide had a positive effect in a second patient. Other tested patients did not benefit from these medications.

**Inheritance and mapping**

Dystonia 9 is an autosomal dominant condition. The disease gene, DYT9/CSE was assigned to a 12 cM interval on the short arm of chromosome 1 (1p21-p13.3).

Both phenotype and chromosomal location are quite similar to dystonia 18 and both disorders might be the same. This can now be tested by mutation analysis of the disease gene identified in dystonia 18 (see below).

**Dystonia 10 [paroxysmal kinesigenic choreoathetosis (PKC); paroxysmal familial dystonia; paroxysmal kinesigenic dyskinesia (PKD)]; DYT10; OMIM 128200**

**Phenotype and treatment**

Dystonia 10/PKC (Kertesz, 1967; Walker, 1981) is characterized by short attacks of choreiform or dystonic movements that are precipitated by sudden unexpected movements. Episodes last for seconds to minutes and can occur up to 100-times per day. In addition, seizures are observed in some patients (Tan et al., 1998). Age of onset is usually during childhood and adolescence. In one family, signs and symptoms ameliorated or even resolved during adult life (Bennett et al., 2000). Patients respond to anti-convulsant drugs such as phenytoin and carbamazepine.

**Inheritance and mapping**

Inheritance of PKC is autosomal dominant. A disease locus has been assigned to the pericentromeric region of chromosome 16 (16p11.2-q12.1) (Tomita et al., 1999; Bennett et al., 2000).

**Dystonia 18 [paroxysmal exertion-induced dyskinesia; paroxysmal exercise-induced dystonia]; DYT18, SLC2A1; OMIM 612126**

**Phenotype**

Dystonia 18 is characterized by exercise-induced attacks of dystonic, choreatic and ballistic movements primarily affecting the upper and lower limbs (Margari et al., 2000; Münchau et al., 2000; Weber et al., 2008). Attacks can last from a few minutes to close to an hour. Attacks can affect those limbs that were excessively exercised exclusively (Plant et al., 1984; Weber et al., 2008). Accompanying signs and symptoms can include epileptic seizures, migraine, decreased cognitive function, developmental delay and impulsive/aggressive behaviour. Reduced CNS glucose levels and haemolytic anaemia with echinocytosis were described in patients from one family (Weber et al., 2008). Onset of dystonia 18 is during childhood.

**Imaging**

MRI detected hypointense signals in the caudal putamen in two patients and was normal in two additional patients. PET using [³⁸F]fluorodeoxy-glucose indicated decreased glucose metabolism in the right thalamus of three patients investigated (Weber et al., 2008).

**Inheritance, mapping and molecular genetics**

Inheritance of dystonia 18 is autosomal dominant with slightly reduced penetrance. DYT18 is located in the short arm of chromosome 1 (1p31.3–p35).

A candidate gene approach revealed two missense mutations and one 4 bp deletion in the gene SLC2A1 in affected members from three families (Weber et al., 2008). SLC2A1 is composed of 10 exons and codes for glucose transporter 1 (GLUT1).

**Molecular pathology**

Studies in Xenopus oocytes and in human erythrocytes showed that the 4 bp deletion in SLC2A1 causes decreased glucose transport and alters intracellular Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup> levels. The two missense mutations were also shown to affect glucose transport but not the transmembrane transport of cations. These data, in combination with the PET findings (see above), are compatible with the notion that dyskinesias are the result of exertion-induced energy deficit. In addition, some mutations such as the 4 bp deletion can alter cation transport and give rise to haemolysis (which was not seen in affected individuals carrying either one of the missense mutations).

**Treatment**

Carboanhydrase inhibitors such as acetazolamide and diclofenamide can have limited positive effects. Seizures can be controlled by anti-epileptic drugs. L-dopa is not beneficial in dystonia 18. In one patient, a ketogenic diet abolished attacks (Weber et al., 2008).

**Dystonia 19 (PKD 2); DYT19; OMIM 611031**

Designation ‘dystonia 19’ was used for a PKD in which the disease locus was mapped to the long arm of chromosome 16 (16q13-q22.1) (Valente et al., 2000). This region lies in very close proximity to the critical interval of DYT10 and overlaps...
with the *DYT10* critical region delineated in one Afro-American family (Bennett et al., 2000; Valente et al., 2000). Designation of a novel locus based on linkage assignment to an interval in close proximity to an established locus can be problematic as was shown by the initial erroneous assignment of a novel locus *DYT14* in a family that turned out to be affected by dystonia 5a (see above).

**Dystonia 20 PNKD2; DYT20; OMIM 611147**

Designation ‘dystonia 20’ is based on findings in one large Canadian family with PNKD. Linkage analysis in this family assigned the disease locus to an interval in 2q31 slightly proximal to *PNKD1* (Spacey et al., 2006). The authors failed to detect a mutation in *PNKD1/MR1* and postulate a novel locus *DYT20* on chromosome 2p31. This finding needs to be confirmed in other families. The existence of a second PNKD needs to be proven by the detection of mutations in a gene different from *PNKD1/MR1*.

## Autosomal recessive and X-linked primary dystonias (Table 2)

### Pure dystonias

**Dystonia 2 (autosomal recessive torsion dystonia); DYT2; OMIM 224 500**

**Phenotype**

Dystonia 2 is an autosomal recessive dystonia detected in Spanish Gypsy families. In nine affected offspring from four families (three of whom were proven consanguineous), average age of onset was during adolescence (15 years). Affected family members had either generalized (6) or brachial segmental (3) dystonia. Site of onset affected the lower extremities in six and the upper extremities in three (Gime´nez-Rolda´n et al., 1988). Childhood-onset dystonia with a phenotype overlapping with that of dystonia 1 was reported in three affected siblings of a large Iranian Sephardic Jewish pedigree (Khan et al., 2003).

**Inheritance**

Segregation analysis in the three consanguineous Spanish Gypsy families suggests autosomal recessive inheritance of the disorder (Giménez-Roldán et al., 1988). No linkage studies have been performed and no disease locus has been assigned in these families. An additional pedigree with apparent autosomal recessive inheritance was reported in three siblings from a large consanguineous Iranian Sephardic Jewish family (Khan et al., 2003). Mutations at *DYT1* and *DYT11* were not detected. The authors speculate that the affected Sephardic (i.e. ‘Spanish’) Jews might carry the same disease-causing mutation as the Spanish gypsies. Zlotogora (2004), however, points out that a Spanish origin of Iranian Jews is highly unlikely and that the mutation could actually be an autosomal dominant new mutation that has occurred in the germline of one of the parents of the affected sibs (Zlotogora, 2004).

**Dystonia 17 (autosomal recessive torsion dystonia); DYT17; OMIM 612 406**

**Phenotype and imaging**

Dystonia 17 was described in one large consanguineous Lebanese Shiite family with three affected sisters (Chouery et al., 2008). Dystonia had started as torticollis at 19, 17 and 14 years of age, respectively, and spread to other body parts within 3 years of onset. It became segmental in two, and generalized in one patient. All three affected individuals had severe dysarthria and dysphonia. Movement abnormalities other than dystonia were not noted. There is some phenotypic overlap with dystonia 2 patients that can also present with oromandibular dystonia and torticollis. MRI did not reveal specific anomalies.

**Inheritance and mapping**

Inheritance of dystonia 17 is autosomal recessive. The disease locus was assigned to chromosome 20 (20p11.22-q13.12) by autozygosity mapping (Chouery et al., 2008). Since the locus in dystonia 2 has not yet been mapped, it is currently unclear whether dystonia 17 is related or identical to dystonia 2.

### Dystonia plus syndromes

**Dystonia 5b (autosomal recessive DRD; autosomal recessive Segawa syndrome); DYT5b, TH; OMIM 128 230**

**Phenotype**

Phenotype of autosomal recessive DRD (dystonia 5b) is quite similar to that of dystonia 5a but often more severe (Lüdecke et al., 1996; Bartholomé and Lüdecke, 1998). The phenotypic spectrum is quite wide and some cases can present as early-onset parkinsonism (Swaans et al., 1980).

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<td>Autosomal recessive dystonia–parkinsonism</td>
<td>AR</td>
<td>612 067</td>
<td>2q31.3</td>
</tr>
<tr>
<td></td>
<td>Dystonia 3</td>
<td>XDP; &quot;lubag&quot;</td>
<td>XR</td>
<td>314 250</td>
<td>Xq13.1</td>
</tr>
</tbody>
</table>

Table 2 Autosomal and X-chromosomal recessive primary dystonias

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Table 2: Autosomal and X-chromosomal recessive primary dystonias

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Designation</th>
<th>Inheritance</th>
<th>OMIM</th>
<th>Chromosomal mapping</th>
<th>Disease gene</th>
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</thead>
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<tr>
<td>Pure dystonia</td>
<td>Dystonia 2</td>
<td>AR</td>
<td>224 500</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Dystonia 17</td>
<td>AR</td>
<td>612 406</td>
<td>20p11.22-q13.12</td>
<td>–</td>
</tr>
<tr>
<td>Dystonia plus</td>
<td>Dystonia 5b</td>
<td>AR</td>
<td>128 230</td>
<td>11p15.5</td>
<td>TH</td>
</tr>
<tr>
<td></td>
<td>Dystonia 16</td>
<td>AR</td>
<td>612 067</td>
<td>2q31.3</td>
<td>PRKRA</td>
</tr>
<tr>
<td></td>
<td>Dystonia 3</td>
<td>XR</td>
<td>314 250</td>
<td>Xq13.1</td>
<td>TAF1/DYT3</td>
</tr>
</tbody>
</table>
Prevalence, inheritance and mapping
Dystonia 5b is less common than dystonia 5a. Inheritance is autosomal recessive. The disease locus is on the short arm of chromosome 11 (11p15.5).

Molecular genetics
Dystonia 5b is caused by mutations in the gene TH that is composed of 14 exons. It codes for tyrosine hydroxylase TH. There are at least four alternative transcripts of the TH gene. To date, homozygous and compound heterozygous missense and frameshift mutations have been described. In addition a homozygous promoter mutation (-70G-A) was reported in two families (Verbeek et al., 2007). This mutation lies within the cAMP response element and results in decreased synthesis of TH.

Molecular pathology and treatment
Pathological effects are caused by lack of TH and the resulting disturbed conversion from tyrosine to L-dopa (Fig. 1). Long-term treatment with low doses of L-dopa in combination with a decarboxylase inhibitor such as carbidopa abolishes signs and symptoms with no side effects.

Dystonia 16 (autosomal recessive dystonia parkinsonism); DYT16, PRKRA; OMIM 612067
Phenotype and imaging
Dystonia 16 was identified in two consanguineous Brazilian families including six affected members and in one single patient from Brazil (Camargos et al., 2008). All patients had generalized dystonia, which was classified as slight in one, moderate in three and severe in three. Disease onset was during childhood in six (2–12 years) and during adolescence (18 years) in one patient. It started in the lower extremities in four, in the upper limbs in two, and initially presented with dysphonia in one. Site of onset did not affect severity of disease. Concurrent parkinsonism was diagnosed in four patients.

Neither CT scans nor MRI revealed abnormalities in the patients tested.

Inheritance, mapping and molecular genetics
Inheritance of dystonia 16 is autosomal recessive. The disease locus, DYT16 was assigned to 2q31.3 by autozygosity mapping. The same homozygous missense mutation (c.665C>T/P222L) was detected in exon 7 of the gene PRKRA in all seven Brazilian patients. PRKRA is composed of eight exons and codes for protein kinase, interferon-inducible double-stranded RNA-dependent activator. In addition, a heterozygous frameshift mutation (c.266_267delAT; p.H89fsX20) was observed in exon 3 of the gene in one sporadic German patient with early-onset dystonia (Seibler et al., 2008).

Molecular pathology and treatment
PRKRA activates the latent protein kinase PKR in response to stress. PKR plays a role in several cellular processes including signal transduction, cellular differentiation and proliferation, and apoptosis. The p.P222L mutation in the Brazilian patients occurred at a position that is evolutionarily conserved in mammals and is located between the second and third RNA-binding motifs.

It is presently unknown how it changes structure and function of PKR and ultimately causes abnormal movement. L-dopa/carbidopa had a positive effect on bradykinesia, and botulinum toxin injections were moderately beneficial in some patients.

X-linked recessive dystonia plus syndrome
Dystonia 3 (X-linked dystonia–parkinsonism; “lubag”); DYT3, TAF1/DYT3; OMIM 314250
Phenotype
Dystonia 3 is an adult-onset (35 ± 8 years) dystonia, frequently accompanied by parkinsonism. Disease can start in either axial musculature, lower or upper extremities, head or neck. In some cases, tremor is the first symptom. The disorder generalizes within 5 years of onset (4.7 ± 2.6 years). Concurrent parkinsonism was described in 35% of a cohort of 42 patients examined (Lee et al., 1991). However, this percentage may be significantly higher (Evidente et al., 2002b). Interestingly, the first two publications on X-chromosomal dystonia parkinsonism syndrome (XDP) described the phenotypic extremes, i.e. only dystonia or mainly parkinsonism. One publication (Lee et al., 1976) reports on ‘dystonia muscularum deformans’ in Filipino men. Parkinsonism was not recognized in this patient sample. The second publication, an abstract only (Johnston and McKusick, 1963), described X-linked parkinsonism in one Filipino kindred, without mentioning dystonia. Figure 2 shows phenotype of four patients with XDP. Although men are primarily affected, XDP has also been detected in a few women (Evidente et al., 2004). In women, involvement is much milder with an average age at onset of 52 years, frequently only minor motor anomalies such as parkinsonism and cervical dystonia, and a slow or no progression of symptoms.

Neuropathology
Astrocytosis and neuronal loss in caudate and lateral putamen was reported in two patient brains (Waters et al., 1993a; Evidente et al., 2002a). A detailed analysis of the striatum of several XDP-brains also demonstrated neuronal loss and astrocytosis in the caudate and putamen (neostriatum). Furthermore, while striatonsomes are dramatically depleted, the striatal matrix is only moderately affected (Goto et al., 2005).

Imaging
CT and MRI appear to be normal in XDP (Evidente, 2009). PET studies using [18F] fluorodeoxyglucose revealed reduction of glucose metabolism in the striatum of three XDP patients. Striatal [18F] fluorodopa uptake was normal, indicating that parkinsonism in XDP has secondary, extranigral causes (Eidelberg et al., 1993). Yet in an additional patient, PET did reveal reduced striatal uptake of fluorodopa (Waters et al., 1993b). Decreased DA D2 receptor expression was shown in the striatum of an XDP patient by 123I-Iodobenzamide (IBZM)-SPECT (Tackenberg et al., 2007).

Prevalence, inheritance and mapping
XDP originated by founder effect in the Philippine island of Panay. Therefore, prevalence is highest on this island, in particular in the
province of Capiz (19/100 000 according to Lee et al., 2002; 25/100 000 according to Kupke et al., 1990b). XDP has only been diagnosed in Filipinos.

XDP is an X-linked recessive disorder (Kupke et al., 1990b). Consecutive linkage and association studies assigned DYT3 to Xq13.1 (e.g. Kupke et al., 1990a, 1992; Graeber et al., 1992, Németh et al., 1999). While some authors group XDP as ‘heredodegenerative disease-associated with dystonia’ (de Carvalho Aguia and Ozelius, 2002) and thus as secondary dystonia (Geyer and Bressman, 2006), I have — in agreement with the original suggestion of Fahn et al. (1987) — grouped it as a dystonia plus syndrome for reasons outlined in the ‘Conclusion’ section.

Molecular genetics

Five disease-specific sequence changes, a 48 bp deletion, and a SVA (composite of SINE, VNTR and Alu) retroposon are found within the complex transcript system TAF1/DYT3 in all XDP patients tested (Nolte et al., 2003; Makino et al., 2007). TAF1/DYT3 is composed of at least 43 exons that are alternatively spliced (Fig. 3). There are alternative transcripts of exons 1–38 that encode isoforms of TATA box binding protein-associated factor I (TAFl) and five exons, referred to as d1–d5, downstream to exon 38. Exons d1–d5 can either form separate transcripts, regulated by separate promoters (Herzfeld et al., 2007) or transcripts spliced to some of exons 1–37 of TAFl (Nolte et al., 2003).

Molecular mechanisms

It is currently not clear how the changes within the TAF1/DYT3 transcript system cause disease. It has been argued that the SVA transposon might specifically reduce expression of one alternative transcript (34’, Fig. 3) and also affect expression of the DA receptor D2 gene (Makino et al., 2007). However, some of these findings are controversial (Müller et al., 2007; Tamiya et al., 2007). Preliminary data from the author’s own lab indicate that a sequence change within one of the d exons causes disturbed regulation of various genes expressed in the striatum. Finally, the differential neuronal death within the striatum described by Goto et al. (2005) might cause an imbalance in activity of striosomal and matrix-based pathways thus giving rise to abnormal movements.

Treatment

Most medications including L-dopa, anti-cholinergic agents such as trihexyphenidyl, benzodiazepines such as lorazepam, diazepam and clonazepam were initially thought to be ineffective in XDP (Lee et al., 1991). However, more recent studies suggest some benefited, in particular if anti-cholinergic drugs and clonazepam are given in combination (Evidente, 2009). One patient appeared to benefit from a combination of L-dopa/benserazide with propranolol (Tackenberg et al., 2007). Zolpidem, an imidazopyridine, was also found to benefit some patients (Evidente et al., 2002). Botulinum toxin A injections can alleviate dystonia, such as torticollis in some patients. Finally, positive results in one patient give hope that deep brain stimulation might become an effective treatment (Evidente et al., 2007).

Diagnostic procedure in primary dystonia

The findings in the various dystonias are summarized in Table 3 and facilitate standardized diagnostic procedure. First, the phenotype needs to be clinically evaluated. Pure dystonias can easily be distinguished from dystonia plus syndromes and paroxysmal dystonias.

If a patient presents with pure dystonia, age of onset, site of first symptoms, dystonic involvement and family history need to be determined. Although the finding of affected relatives is highly indicative of a monogenic form, frequently no affected family members are reported owing to reduced penetrance in many dystonias. However, an early age of onset can indicate a monogenic form. Of the monogenic pure dystonias, dystonia 1 is...
most common. This diagnosis should be considered in early-onset cases with first involvement in limbs and rapid generalization. Testing for the GAG-deletion in TOR1A will provide the definite diagnosis. If preliminary findings turn out to be correct, dystonia 6 is the second most frequent monogenic pure dystonia. Clinical indication for this form comes from cervical involvement, a mixed phenotype, and an older age of onset than in dystonia 1. The definite diagnosis rests on the detection of a mutation in the THAP1 gene. Here the possibility of deletions should be considered if no base changes can be found upon sequencing of the three exons of the gene. The remaining pure dystonias, i.e. dystonias 2, 4, 7, 13 and 17 are much less common with dystonias 4 (whispering dystonia), 7, 13 and 17 each described in one family only. If large families are found with findings consistent with those in these families, linkage analyses can be attempted. Dysphonia may indicate dystonia 4, juvenile-onset with first symptoms in cranial–cervical region and slow progression might indicate dystonia 13. Dystonia 17 can be considered in persons from the Middle East with adolescent-onset segmental or generalized dystonia. Similar to dystonia 2, which is also autosomal recessive, it is a possible diagnosis especially in consanguineous families.

DRD (Segawa syndrome) is probably the most common dystonia plus syndrome. DRD is a potential diagnosis in patients with early-onset dystonia and a rapid therapeutic response to low doses of l-dopa. Mutation analyses of the gene GCH1 should be performed in all patients with dystonia and responsiveness to l-dopa. DRD is phenotypically very heterogeneous and needs to be contemplated even in adult-onset focal dystonia (Steinberger et al., 1999) or in patients presenting with parkinsonism only. An important differential diagnosis is juvenile parkinsonism, an autosomal recessive disorder that can present with symptoms characteristic of DRD such as circadian fluctuation of symptoms and dystonia. This heredodegenerative dystonia is caused by mutations in the gene PARK2 on 6q25.2-q27 (e.g. Matsumine et al., 1997; Lüicking et al., 2000). Furthermore, dystonia 5b with mutations in the gene TH needs to be considered.

If DRD is excluded, the diagnosis autosomal recessive dystonia parkinsonism (dystonia 16) can be entertained, especially in consanguineous settings. Here mutation analyses in the PRKRA gene can result in a definite diagnosis. Abrupt onset of dystonia and parkinsonism within minutes to days of onset are characteristic of equally rare dystonia 12 (rapid-onset dystonia–parkinsonism). This dystonia can be diagnosed by mutation analysis of the gene ATP1A3. Dystonia and Parkinsonism in people of Filipino extraction are frequently caused by mutations in the TAF1/DYT3 multiple transcript system. In patients with M-D responsive to alcohol, dystonia 11 needs to be considered. A definite diagnosis should be attempted by mutation analysis of the gene SGCE. A mutation in another gene, i.e. the gene coding for the D2 DA receptor (DRD2) has been reported in one family with M-D. The nucleotide change results in a Val–Ile substitution in a conserved region at the cytoplasmic end of transmembrane helix 4 of DRD2 (Klein et al., 1999). However, experiments in a cell system did not reveal abnormal function of the receptor carrying the amino acid substitution (Klein et al., 2000). Therefore, rather than being a pathogenic mutation the nucleotide change may be a rare neutral polymorphism. Definite diagnosis of other M-Ds such as dystonia 15 awaits the identification of the disease gene.
It should be kept in mind that the phenotype of both pure primary dystonias and dystonia plus syndromes can vary dramatically. For example, several cases tested for GCH1 mutations based on a clinical diagnosis of DRD turned out to have been afflicted by dystonia 1 based on findings of the GAG deletion in TOR1A (author’s own observations). Testing of alternative genes should be considered in various mutation-negative forms of dystonias as outlined in Fig. 4.

Finally, the paroxysmal dystonias can be distinguished clinically on the basis of being kinesigenic or non-kinesigenic. Kinesigenic forms include dystonias 9, 10, 18 and 19. Note that dystonias 9 and 18 might be identical conditions as might dystonias 19 and 10. Dystonias 8 and 20 are non-kinesigenic forms and probably identical. In kinesigenic paroxysmal dystonias, especially those associated with epileptic seizures, migraine, decreased cognitive function, developmental delay, impulsive/aggressive behaviour, mutation analysis of the gene SLC2A1 should be performed to explore the possibility of the diagnosis dystonia 18/(dystonia 9?). Dystonias 10/(19?) can currently only be diagnosed by linkage analysis which requires large families. In non-kinesigenic hereditary paroxysmal dystonias, detection of mutations in the gene PNKD1/MR1 can identify dystonia 8/(20?). This diagnosis is particularly likely if symptoms can be precipitated by alcohol and caffeine.

### Conclusions

There are now at least 17, possibly 20 primary dystonias, which are distinguished by genetic criteria. Definitive distinction becomes possible once the disease gene has been identified. According to this strict criterion dystonias 1, 3, 5a, 5b, 6, 8, 11, 12, 16, 18 are definitely distinct entities. Furthermore, those forms which have been genetically mapped to regions clearly removed from chromosomal intervals carrying known loci or disease genes can also be considered distinct (dystonias 7, 10, 13, 15, 17). Dystonias only assigned based on phenotype and apparent mode of inheritance but without chromosomal mapping, such as dystonias 2 and 4, are less certainly different entities. In three cases, i.e. dystonias 9, 19 and 20 the disease gene has been assigned to an interval in close proximity to the known loci DYT18/SLC2A1, DYT10 and DYT8/PNKD1. Furthermore, the phenotype of dystonias 18, 10 and 8 is quite similar to that of putative dystonias 9, 19 and 20, respectively. As long as no disease-causing

### Table 3 Characteristic manifestations in the various forms of primary dystonia

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dystonia</th>
<th>Mode of inheritance</th>
<th>Age of onset</th>
<th>Clinical findings</th>
<th>Additional characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure dystonia</td>
<td>1</td>
<td>AD</td>
<td>Childhood</td>
<td>Generalized, onset in limbs</td>
<td>Whistling dystonia</td>
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<tr>
<td></td>
<td>2</td>
<td>AR</td>
<td>Adolescence</td>
<td>Generalized or segmental</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>AD</td>
<td>Adolescence or adulthood</td>
<td>Generalized brachial, cranio-cervical onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>AD</td>
<td>Childhood or adolescence</td>
<td>Focal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>AD</td>
<td>Adulthood</td>
<td>Cranio-cervical or brachial onset, mainly segmental</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>AD</td>
<td>Childhood, adolescence or adulthood</td>
<td>Cervical onset; Segmental or generalized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>AR</td>
<td>Adolescence or early adulthood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia plus</td>
<td>3</td>
<td>XR</td>
<td>Adulthood</td>
<td>Generalized dystonia, parkinsonism</td>
<td>Striatal neurodegeneration</td>
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<tr>
<td></td>
<td>5a</td>
<td>AD</td>
<td>Childhood</td>
<td>Generalized dystonia, parkinsonism</td>
<td>Therapeutic response to L-dopa</td>
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<tr>
<td></td>
<td>5b</td>
<td>AR</td>
<td>Childhood</td>
<td>Generalized dystonia, parkinsonism</td>
<td>Therapeutic response to L-dopa</td>
</tr>
<tr>
<td></td>
<td>11</td>
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<td>Focal, segmental dystonia, myoclonus</td>
<td>Responsive to alcohol</td>
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<td></td>
<td>12</td>
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<td>Sudden onset of dystonia and parkinsonism</td>
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<td>15</td>
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<td>Childhood or adolescence</td>
<td>Dystonia and myoclonus</td>
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<tr>
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<td>16</td>
<td>AR</td>
<td>Childhood, generalized dystonia</td>
<td>Dystonia and parkinsonism</td>
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<td>8</td>
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<td>Childhood</td>
<td>Paroxysmal dystonia, chorea, ballism, non-kinesigenic</td>
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<tr>
<td>dystonia</td>
<td>9 (identical to 18?)</td>
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<td>Childhood, adolescence</td>
<td>Paroxysmal dystonia, choreoathetosis, kinesigenic</td>
<td></td>
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<tr>
<td></td>
<td>10</td>
<td>AD</td>
<td>Childhood, adolescence</td>
<td>Paroxysmal dystonia, kinesigenic</td>
<td>Seizures</td>
</tr>
<tr>
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<td>18</td>
<td>AD</td>
<td>Childhood</td>
<td>Paroxysmal dystonia choreatosis, ballism, kinesigenic</td>
<td>Seizures, migrane, decreased cognitive function, developmental delay, impulsive/aggressive behaviour, Seizures</td>
</tr>
<tr>
<td></td>
<td>19 (identical to 10?)</td>
<td>AD</td>
<td>Childhood</td>
<td>Paroxysmal dyskinesia, kinesigenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (identical to 8?)</td>
<td>AD</td>
<td>Childhood, adolescence, or adulthood</td>
<td>Paroxysmal dyskinesia, non-kinesigenic</td>
<td></td>
</tr>
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</table>
gene has been identified, designations ‘dystonia 9’, ‘dystonia 19’ and ‘dystonia 20’ should be accepted under reserve. This caveat is emphasized by the erroneous designation of a ‘novel’ DYT14 locus based on linkage analysis in one family in close proximity to the chromosomal interval containing the disease gene GCH1 of dystonia 5a. In this instance, further studies clearly showed that the disease locus ‘DYT14’ was in fact DYT5a (Grötzsch et al., 2002; Wider et al., 2008).

As outlined in the ‘Introduction’ section, I propose to divide the monogenic primary dystonias into three groups, the pure dystonias, the dystonia plus syndromes and the paroxysmal dystonias. Seven (dystonias 1, 2, 4, 6, 7, 13 and 17) of the monogenic dystonias discussed here are ‘pure’ dystonias. In this group, dystonia is the only symptom apart from tremor that is observed in some cases. Thus perinuclear inclusions were detected in the brainstem of some patients who had dystonia 1 and minor morphological anomalies and/or depigmentation in substantia nigra and striatum were found in several cases of dystonia 5a. Clearly, absence/presence of morphological findings does not allow classification of a monogenic dystonia as ‘dystonia plus’ (i.e. primary) versus ‘secondary dystonia’. A better criterion might be clinical findings, i.e. the extent of dystonic versus non-dystonic involvement. Given the clinical phenotype of the XDP (dystonia 3), with dystonia as the most striking feature (Fig. 2), I have grouped this heredodegenerative disorder among the primary rather than secondary dystonias despite the detection of clear neurodegenerative changes.

Findings in dystonias 5a and 5b demonstrate that abnormal function of the DA system can cause dystonia. Mutations in GCH1 or SPR (dystonia 5a) disturb normal synthesis of tetrahydrobiopterin, which eventually results in decreased synthesis of L-dopa/DA and reduced levels of this neurotransmitter in the striatum. Similarly, loss of TH activity in dystonia 5b causes decreased levels of L-dopa/DA. Both neuroanatomical and imaging findings in other forms also point to disturbed striatal function as one underlying cause of dystonia. Pronounced degeneration of neurons within the caudate and putamen (neostriatum) is found in dystonia 3 (XDP). Abnormal striatal MRI or SPECT findings were reported at least in a few cases of dystonia 11 (reduced regional blood flow in the caudate of one patient), dystonia 8 (low-intensity signals in globus pallidus and substantia nigra in one patient), dystonia 5 (reduced metabolic activity in basal ganglia) and dystonia 1 (decreased D2 receptor binding in caudate and putamen). It needs to be emphasized that neuropathology and imaging also indicate that, apart from the basal ganglia, additional cerebral regions are affected in various types of monogenic dystonias.

The detection of mutations in genes other than those involved in the bioterin/DA pathway does not permit the delineation of an obvious common pathway with the end-point dystonia. Thus, mutations can affect proteins involved in (i) the function of other proteins such as the putative chaperone protein torsinA (dystonia 1), THAP1 which is involved in apoptosis (dystonia 6), ATP1A3, a Na+/K+-ATPase (dystonia 12) or PRKRA acting as a protein kinase (dystonia 16); (ii) maintenance of cellular structure such as PNKD1/MR1 (dystonia 8) and e-sarcoglycan (dystonia 11) and (iii) regulation of cellular function and metabolism such as TAF1/DYT3 transcript system (dystonia 3), glucose transporter 1 (dystonia 18), and probably torsinA as well. All these mutations appear to disturb the normal function of striatal (and other?) neurons. Yet, the gene products involved do not appear to be part of one interdependent pathway. Obviously, disturbances affecting very different proteins in neuronal cells can have the same effect by incapacitating a specific cell type. They need not necessarily be part of a common pathway as is the case in dystonias 5a, b. Although this makes development of causative therapies for most primary dystonias more difficult, it can be hoped that the ongoing and ever accelerating elucidation of the genetic basis of these disorders will open up new avenues towards their effective treatment.
Acknowledgement

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