The molecular genetics of the dystonias

Since the introduction of the term dystonia by Oppenheim in 1911 to describe altering muscle tone and postural deformities seen in patients,1 there has been considerable controversy surrounding its aetiology, classification, and genetics. Dystonia can describe a symptom, a syndrome, or a clinical sign that is part of a more severe neurological disorder. Dystonia is now defined as a syndrome of sustained involuntary muscle contractions, often causing twisting and repetitive movements or abnormal posture.2

The dystonias are a relatively common group of neurological disorders with conservative estimates of 30 000 affected people in the United Kingdom.3 Dystonia has been divided into primary, in which there is no identifiable underlying cause, or secondary to other neurological conditions, which include structural lesions of the basal ganglia, exposure to drugs and toxins, and cerebral palsy. It was from the study of secondary dystonia that it became clear that disruption of basal ganglia motor circuits produces dystonia.2,4 Primary dystonia is distinguished by the lack of other neurological involvement and absence of distinct neuropathology. Central dopaminergic pathways have been implicated in the production of dystonic movements from the study of tardive dystonia4 (secondary to D2 receptor blockade) and dopa responsive dystonia (see later).

In recent years, advances in molecular genetic techniques have led to exciting discoveries which have expanded our knowledge of the pathogenesis of dystonia and led to a revision of its classification (table).4 This classification incorporates the advances in our understanding of the genetics and aetiology of dystonia, and also the increasing number of distinguishable clinical phenotypes. To date, eight genes causing dystonia have been mapped and three of these have been cloned. The following sections review these recent discoveries.

**Primary torsion dystonia**

Primary torsion dystonia (also known as idiopathic torsion dystonia) is the commonest form of dystonia with an estimated prevalence of 329 per million of which focal dystonia accounted for 294 per million. It consists of dystonic movements and postures (with or without tremor) with no other neurological features or identifiable cause.5 The range of severity is wide, including severe generalised dystonia (formerly known as dystonia musculorum deformans), segmental and multifocal dystonia, and focal dystonia (including torticollis, blepharospasm, and writer’s cramp). Dystonia can develop at almost any age and this often determines its severity. Onset in childhood, particularly in a limb, is strongly predictive of subsequent generalisation,6 and this form of dystonia is reported to be more prevalent in the Ashkenazi Jewish population.7 By contrast, dystonia arising in cranial or axial muscles tends to develop in adult life and remain focal or segmental in distribution.8

Genetic studies in both Jewish and non-Jewish populations have shown that early onset severe primary dystonia is caused by an autosomal dominant gene(s) with reduced penetrance (30%-40%) and variable expression.9-11 In 1989, Ozelius et al reported linkage between a dystonia locus (DYT1) and a polymorphism on chromosome 9q34 in a large non-Jewish French Canadian family with generalised dystonia.12 Linkage to this region was also found in Ashkenazi Jewish and other European non-Jewish kindreds.13 In non-Jewish kindreds, genetic heterogeneity was detected, indicating that defects in more than one gene can cause familial generalised dystonia.14 An interesting feature was that dystonia in chromosome 9q34 linked families invariably began in a limb before subsequent generalisation, whereas, in most non-linked kindreds, the dystonia often had onset in the craniocervical region.

The finding of strong allelic association in Ashkenazi Jewish patients suggested a founder mutation causing the dystonia in this particular population and localised DYT1 to a 1cM region.15 The haplotype identified was specifically associated with limb onset generalised dystonia.16 It was estimated that this founder mutation arose about 350 years ago in the historic Jewish Pale of settlement in Lithuania and Byelorussia.17

Recently the DYT1 gene has been cloned and analysed for mutations.18 The fascinating finding was of a 3 bp deletion in the coding sequence found in all affected and obligate carriers with chromosome 9 linked primary dystonia, regardless of ethnic background and surrounding haplotype. The mutation specifically causes early limb onset generalised dystonia. Assuming this mutation arose independently in different ethnic groups, the finding suggests that only one variation in the encoded protein can give rise to early onset dystonia. The deletion results in the loss of one of a pair of glutamic acid residues near the carboxy terminus of a novel protein named torsinA. TorsinA contains an ATP binding domain and a putative N-terminal leader sequence. It has homology to three mammalian genes and a nematode gene on database searches, and distant similarity to the family of heat shock proteins and Clp proteases. However, its function and putative role in the nervous system remains uncertain.

The genetic studies of primary dystonia have enabled more accurate genetic counselling for families. For a familial case of generalised, segmental, or multifocal primary dystonia in the United Kingdom, the risk to first degree relatives is estimated at 21%. If the index case is isolated, the risks are 14% to children and 8% to siblings.19 The identification of a single mutation will facilitate both predictive and prenatal genetic testing with appropriate counselling. However, the low penetrance and variable expression of the DYT1 gene means that such tests should be performed with caution, as the phenotype cannot be accurately predicted.

For focal and segmental primary dystonia, the role of DYT1 and other genes is less clear. Focal primary is the most common form of dystonia, has onset in adult life, and often appears to be sporadic.20 There is, however, evidence that genetic components play a part in focal dystonia with families showing autosomal dominant inheritance.21-23 In addition, a genetic study of index cases with focal dystonia found affected relatives in 25% of patients.24 Linkage studies have excluded the DYT1 gene as a cause for focal dystonia in two families with cervical dystonia25 and, in another study, no persons with craniocervical dystonia or writer’s cramp were found to have the DYT1 GAG deletion.26
Linkage to chromosome 18p has been found in a large German kindred with adult onset cervical dystonia and spasmodic dysphonia. A follow up study of apparently sporadic cases of focal dystonia in northern Germany showed linkage disequilibrium for a common haplotype of the PDYN locus, suggesting that a common founder mutation of low penetrance may be an important cause of focal dystonia in this population. Whether this finding is applicable to other European populations is uncertain, but, if replicated, it would suggest that genetic factors play a larger part in the causation of primary focal dystonia than previously thought.

A further dystonia locus has been identified on chromosome 8 in two German American Mennonite families. Affected people had a mixed phenotype with craniofacial and limb dystonia and a varied age of onset. It is possible that this locus may be unique to this genetically distinct population.

**Dystonia plus syndromes**

**DOPA RESPONSIVE DYSTONIA**

Dopa responsive dystonia (DRD) accounts for around 5% of all childhood onset dystonia. It typically presents with dystonia of the lower limbs affecting gait, or occasionally as a focal dystonia. Patients may also develop concurrent parkinsonism. Symptoms and signs may worsen late in the day or after exertion. The clinical importance of recognising this condition lies in the fact that there is a dramatic and sustained response to low doses of levodopa, indicating a deficit in the dopamine pathway.

DRD shows autosomal dominant inheritance with reduced penetrance and sex related expression with female predominance. The gene was mapped to chromosome 14, and more recently, Ichinose et al identified point mutations in the gene for GTP cyclohydrolase 1. This is the rate limiting enzyme involved in the formation of tetrahydrobiopterin, a cofactor of dopamine biosynthesis. Subsequently, mutations have been found in the gene in European patients with DRD and molecular diagnosis is possible by sequence analysis. However, as each family seems to have distinct mutation, this is not routinely available. The importance of the dopamine pathway in DRD was confirmed by Knappskog et al who identified a recessively inherited mutation in the gene for tyrosine hydroxase in two brothers.

**RAPID ONSET DYSTONIA-PARKINSONISM**

Two unrelated families have been described with this unusual condition, both of which show autosomal dominant inheritance. The clinical picture is of sudden onset dysarthria, dysphagia, severe dystonic spasms, bradykinesia, and postural instability developing over hours, with little response to levodopa. Some patients had stable limb dystonia for several years preceding the onset of dystonia-parkinsonism. Cranial imaging is normal. Involvement of the dopaminergic system has been implicated by low CSF homovanillic acid concentrations. To date, no linkage for the gene(s) involved has been found.

**MYOCLOMY DYSTONIA**

Myoclonic dystonia is a rare variant characterised by dystonia and myoclonus with onset in adolescence or early adult life, affecting predominantly the arms and axial muscles. It is extremely sensitive to alcohol. The families described exhibit autosomal dominant inheritance with reduced penetrance and variable expression. Linkage analysis with chromosome 9q markers has excluded the DYT1 region in a Swedish family.

**Secondary dystonia**

The term secondary dystonia implies an identifiable cause such as neuroleptic exposure, physical insult to the brain (stroke, tumour), and cerebral palsy. Bressman et al examined the possible role of genetic susceptibility in the development of secondary dystonia. They analysed chromosome 9q34 haplotypes in 40 Ashkenazi Jewish patients with secondary dystonia; the majority due to neuroleptic exposure or perinatal asphyxia. Nine patients were considered phenocopies of dystonia caused by DYT1. No evidence that the DYT1 foundermutation contributed to secondary dystonia was found. It was emphasised that accurate diagnostic criteria which included questioning about dopamine antagonists and perinatal asphyxia should discriminate primary dystonia due to the DYT1 founder mutation. This is an important factor when considering genetic counselling.

**Heredodegenerative diseases**

These represent a group of heredodegenerative diseases that can present as a dystonias plus syndrome. By definition, there is an underlying genetic defect, many of which have been identified. The group includes X linked dystonia-parkinsonism (or “lubag”) described in natives of the island of Panay in the Philippines. Onset is in early adult life with focal dystonia, followed by development of parkinsonism unresponsive to levodopa. The gene, which has high penetrance, has been mapped to Xq12–13.1 and the presence of a common haplotype in over 85% of affected people indicates the presence of a founder mutation.

Dystonia can also develop in other hereditary neurodegenerative conditions, including Wilson’s, Huntington’s, and Halleworden-Spatz diseases with mutations in a copper transporting ATPase, Huntington’s and proteolipid protein genes respectively. In addition, dystonia can occur in mitochondrial diseases, as part of Leigh’s syndrome or in association with Leber’s hereditary optic atrophy. The progressive nature of the condition and presence of additional neurological features help to distinguish these disorders from primary dystonia.

**Paroxysmal dystonias**

The paroxysmal dystonias are an unusual group of hyperkinetic movement disorders in which dystonia can occur with chorea and ballism in episodic attacks. Between attacks, the person is normal. Paroxysmal kinsigenic choreathetosis is characterised by frequent brief attacks, precipitated by movement or startle, and responds to anti-convulsants. It is often sporadic, but families with autosomal dominant inheritance have been described. Paroxysmal dystonic choreathetosis (PDC) is distinguished by longer (minutes to hours), less frequent attacks which may be precipitated by caffeine or alcohol.

Both these conditions may be caused by mutations in channel genes, as some other paroxysmal neurological disorders have such defects. Mutations in sodium and calcium...
channel genes have been identified in these “channelopathies”, including the periodic paralyses (hypokalaemic and hyperkalaemic), episodic ataxia, and familial hemiplegic migraine.

Families with PDC show autosomal dominant inheritance, and in three large kindred, linkage to chromosome 2q35–37 has been shown. A possible candidate gene in this region is a chloride bicarbonate anion exchanger. A second locus for a more complicated form of PDC, in which there is associated spastic paraplegia, has been mapped to chromosome 1p in a single kindred. Some potassium channel genes also map to this region and may represent channel candidates for this unusual episodic movement disorder.

Conclusions

The recent improvement in positional cloning techniques has led to the identification of loci for various forms of dystonia and the cloning of three. These advances have helped to clarify the nosology of the dystonias and also to improve genetic counselling and testing. More importantly, the study of these genes and their products will help to unravel the pathogenesis of these complex movement disorders. In particular, understanding the function of the novel class of ATP binding protein encoded by DYT1 will provide a fascinating insight into the role of neuronal mechanisms involving basal ganglia cortical circuits which produce normal and dystonic movements.

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