The Genetics of Basal Ganglia Disorders

It is remarkable to think that only fifteen years ago we knew practically nothing about the genes involved in Parkinson’s disease (PD) or dystonia. Over the last decade there has been a flurry of publications describing new genetic loci associated with familial PD and different familial dystonia syndromes. Causative DNA mutations have been identified in some instances (for example, the recently identified DJ-1 gene at the PARK7 locus, Table 1). As in other areas of neurogenetics, these exciting findings have raised many more questions, providing us with tantalising clues about the underlying mechanisms behind rare autosomally inherited forms of a disease that may have broader relevance for more common sporadic cases.

The PARK1 locus

The first gene to be identified was found in the now famous Italian-American Contursi kindred. An early-onset, rapidly progressive, L-Dopa responsive phenotype was linked to chromosome 4q21-q23 (PARK1), and subsequent work identified an alanine to threonine substitution at codon position 53 of the -synuclein gene (A53T). The same mutation has also been found in Greek kindreds with a similar clinical presentation, while a second -synuclein gene mutation has been found in a German family (A30P). This work provided the first direct evidence of a genetic link for PD, and it led to the identification of -synuclein protein in Lewy bodies from patients with sporadic PD, providing further insight into the general disease mechanism in PD. -synuclein gene mutations are, however, an exceptionally rare cause of PD in the general population 1.

The second locus, PARK2, is a more common cause of PD. The locus was identified in 13 Japanese families with autosomal recessive young-onset parkinsonism (6q24.2-25), and subsequent work identified a range of different deletions and point mutations in a novel gene called Parkin 2. Parkin mutations have been found in 77% of patients developing Parkinsonism in their first two decades, but only 3% of patients developing symptoms between the ages of 30 and 45 years 3. An even smaller proportion of later-onset cases have mutations in the Parkin gene. Parkin functions as an E3 ubiquitin ligase that may be involved in the ubiquitin-proteasome system 4, an essential cellular pathway for the degradation and recycling of unwanted proteins. An intriguing finding is that Parkin interacts with -synuclein 5, suggesting there may be common mechanisms for various forms of genetically determined PD, and that these may be relevant to the late-onset sporadic PD. This is supported by recent work identifying a missense mutation in the ubiquitin hydrolase L1 (UCH-L1) gene in a German family with autosomal dominant PD 6. UCH-L1 is also involved in same ubiquitin-proteasome pathway 7.

Familial parkinsonism syndromes have also been linked to a number of other genetic loci, and at the last count we reached PARK 10 (Table 1). Most loci have only been implicated in one or a few families, and their real impact will only be realised after the identification of the underlying gene allows large-scale mutational screening in carefully defined clinical cohorts. There are subtle differences in the clinical phenotype and neuropathology of these different genetic disorders (Table 1).

PD genetics has also been tackled from other directions. There have been two genome-wide genetic linkage studies designed to identify new PD loci in co-affected sib-pairs, or in families with multiply affected members 8,9. These studies have implicated additional genetic loci in familial PD, and further work is underway to try and characterise the responsible genes. It may transpire that certain loci are only implicated in specific clinical subgroups of the disorder 10.

An alternative strategy has been to look for an association between known genetic polymorphisms in candidate genes and PD (i.e. sequence variations in the general population in genes hypothesised to be of relevance to the pathogenesis of PD). Although there have been many reported associations (reviewed in 11), relatively few have been reliably replicated. There are a number of possible reasons for this lack of consistency, but the most likely explanation is that most of the studies were underpowered and that the associations are spurious (false positive, or type I errors) 12-14. Two recent association studies deserve mention. In the first 15, 20 single nucleotide polymorphisms in 18 candidate genes were studied in 232 PD patients and 249 normal controls. Homozygosity for the V66M polymorphism of the brain-derived neurotrophic factor (BDNF) was more frequent in PD than in controls. This is of potential relevance, since previous studies have demonstrated reduced concentrations of BDNF in the nigra of PD patients, and this growth factor has also been shown in open pilot studies to be effective in improving parkinsonian symptoms. In the second study, a collection of polymorphisms of mitochondrial DNA (mtDNA) were associated with a reduced risk of PD in a large cohort of 609 PD cases, particularly in women 16. This is intriguing because there are various strands of evidence linking mitochondria with PD 17,18, and this study provides a potential genetic link. However, it would be unwise to draw firm conclusions before these results have been substantiated by others.

The DYT collection

Dystonia can be divided into primary, dystonia-plus, heredodegenerative and secondary forms. Primary dystonias are phenotypically "pure" and are generally thought to have a genetic origin. Dystonia-plus syndromes include dystonias with other neurological features such as myoclonus and parkinsonism. Heredodegenerative forms occur in degenerative diseases where dystonia may be a prominent feature but is not always present. Secondary dystonias result from acquired disease, for example infections, brain trauma and cerebrovascular disease.

Autosomal dominant early-onset idiopathic torsion dystonia (ITD) was linked to chromosome 9q34 in Ashkenazi Jews (DYTI) 19. The underlying gene defect is a deletion of three base pairs (CAG) in the Torsin A gene 20, and it has arisen many times on different genetic backgrounds (that is to say, all affected individuals are not related to a single common founder individual) 21. DYT1 idiopathic torsion dystonia has a reduced penetrance (30-40%) and usually begins before 26 years of age in one limb, becoming generalised over a few years 22. Other forms of familial dystonia have been mapped to different forms of dystonia with different inheritance patterns (Table 2). At the last count there were fifteen DYT loci. Some of these disorders have only been described in single families (for example, DYT4, or whispering dystonia in an Austrian family 23), or ethnic groups (for example, DYT6, in Mennonite families 24), but others seem much more common (for example, DYT11, or alcohol responsive myoclonic dystonia 25). There is considerable variation in the clinical phenotype of these disorders and there may be additional neurological (e.g. DYT3, DYT12) or psychiatric (e.g. DYT11) features.
Late-onset cystic degeneration of the basal ganglia

We recently described a dominantly inherited movement disorder in a large family from Cumbria in the northwest of England due to an adenine insertion at position 460-461 in the ferritin light polypeptide gene (FTL)\(^a\). Serum ferritin levels were low in the presence of normal serum iron, transferrin and haemoglobin levels, and we suggested the name “neuroferritinopathy” for this disease, providing a direct link between a primary disorder of iron storage metabolism and a late-onset neurodegenerative movement disorder\(^b\).

Looking back through the case notes of affected individuals it is clear that different family members had been labeled with a range of different diagnoses. Some family members developed a late-onset asymmetric akinetic-rigid syndrome resembling PD, and were started on L-dopa with some improvement. Others presented with a focal onset lower-limb dystonia in teenage years which gradually involved other limbs, becoming generalised within a decade (similar to DYT1 dystonia), while one branch of the family developed generalised chorea in mid adult-life and was thought to have had Huntington’s disease (diagnosed clinically in the pre-molecular era)\(^c\). Brain imaging in affected individuals revealed basal ganglia cavitation (Figure 1), confirmed at autopsy. Neuronal loss was accompanied by the formation of neuroaxonal spheroids, with intraneuronal and extraneuronal iron deposition\(^d\). Recent genetic studies have shown that all of the UK patients descend from a common founder\(^e\) - but the whole range of movement disorders has been documented in this one family.

**PARK and DYT – never the twain shall meet?**

We all recognise the rigid or “Westphal” variant of Huntington’s disease presenting in early adult life, and many of us look for biochemical markers of Wilson’s disease in patients with young onset parkinsonism or dystonia. On closer scrutiny it is clear that many of the PARKs have dystonia as a prominent feature (Table 1), and many of the DYT1s have parkinsonism (Table 2). For example, what appears to be the most common monogenic form of parkinsonism – mutations in the Parkin gene at the PARK2 locus - characteristically presents with a lower limb dystonia that melts away with L-dopa\(^f\); and many Parkin patients were understandably mis-diagnosed as having L-dopa-responsive dystonia (DRD or DYT3)\(^g\). This has profound implications for the patient because L-dopa is an effective long-term treatment for patients with DRD, but causes profound early motor fluctuations in patients with Parkin mutations\(^h\). If we look at DRD/DYT5 in more detail, many families have individuals who present with parkinsonian features in late adult life\(^i\). Since this disorder responds to L-dopa par excellence, not surprisingly this leads mis-diagnosis. There are many more examples, such as X-linked dystonia parkinsonism (DYT3)\(^j\), pallidopontocerebellar atrophy (PARK7), and the hereditary spastic paraparesis 2 (SCA2)\(^k\), precluding reliable clinical definition of common molecular pathways in disease. In the short term, it may be better to think about inherited movement disorders, rather than DYT or PARK. Naturally, there will be overlap with other systems (such as the pyramidal tracts, or cerebellum and connections), but the predominant system that is involved, whether it be clinically or pathologically, should form the basis of the classification.

Finally, we must make sure that scientists and clinicians work together – both in research and in clinical practice. This will help to advance our understanding of the genetics of movement disorders, elucidate the most important disease mechanisms and facilitate the development of fundamental new treatments.

**Is this just semantics?**

At this point we run the risk of irritating some readers. Who cares what the name is, and why not just leave that to the laboratory scientists? Unfortunately it is not that simple. Clinical classification is fundamentally important to patient management, molecular diagnostics and research. Not surprisingly, many review articles by experts in the field restrict their content to homo territory, and a reader new to the genetics of dystonia may be left with an incomplete picture of inherited parkinsonian syndromes with prominent dystonia (there are, however, a few notable recent exceptions, for example\(^m\)\(\^{\text{n}}\)). On the research side, the mis-classification of individuals can lead to spurious or unexplainable results, and samples sent to the molecular diagnostic lab labelled “teenage onset lower limb dystonia” may not be tested for Parkin mutations. The report may come back negative (for DYT1), leading to an incorrect interpretation.

**How can we solve this problem?**

In time, all of the underlying mutations at the PARK and DYT loci will be identified, and it is likely that there will be a re-classification of these disorders based upon gene function rather than clinical phenotype (for example, we have seen in mitochondrial DNA disorders). This has its own problems, of course, particularly if the phenotype is diverse – but at least it will ensure that we have an accurate list of genes that are implicated in a particular clinical syndrome. This approach will hopefully facilitate the identification of common molecular pathways in disease. In the short term, it may be better to think of the genetics of neurological systems, rather than clinical features or syndromes. In this way, we would think about inherited movement disorders, or basal ganglia disorders, rather than DYT or PARK. Naturally, there will be overlap with other systems (such as the pyramidal tracts, or cerebellum and connections), but the predominant system that is involved, whether it be clinically or pathologically, should form the basis of the classification.

Finally, we must make sure that scientists and clinicians work together – both in research and in clinical practice. This will help to advance our understanding of the genetics of movement disorders, elucidate the most important disease mechanisms and facilitate the development of fundamental new treatments.

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\(^{\text{a}}\) Cushing, unpublished observations.

\(^{\text{b}}\) Curtis, unpublished observations.

\(^{\text{c}}\) See also Richard, unpublished observations.

\(^{\text{d}}\) Curtis, unpublished observations.

\(^{\text{e}}\) Curtis, unpublished observations.

\(^{\text{f}}\) Curtis, unpublished observations.

\(^{\text{g}}\) Curtis, unpublished observations.

\(^{\text{h}}\) Curtis, unpublished observations.

\(^{\text{i}}\) Curtis, unpublished observations.

\(^{\text{j}}\) Curtis, unpublished observations.

\(^{\text{k}}\) Curtis, unpublished observations.

\(^{\text{l}}\) Curtis, unpublished observations.

\(^{\text{m}}\) Curtis, unpublished observations.

\(^{\text{n}}\) Curtis, unpublished observations.
### Table 1. Genetic loci linked to parkinsonism.

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chromosomal region</th>
<th>Mutations</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1</td>
<td>4q21-q23</td>
<td>α-synuclein</td>
<td>Autosomal dominant early onset rapidly L-dopa responsive progressive parkinsonism.</td>
</tr>
<tr>
<td>PARK2</td>
<td>6q25.2-27</td>
<td>Parkin</td>
<td>Autosomal recessive early-onset parkinsonism beginning with focal lower limb dystonia. Responds to L-dopa but treatment leads to early disabling dyskinesias.</td>
</tr>
<tr>
<td>PARK4</td>
<td>4p</td>
<td>?</td>
<td>Autosomal dominant early onset rapidly progressive parkinsonism with good L-dopa response. May only cause a postural tremor.</td>
</tr>
<tr>
<td>PARK5</td>
<td>4p</td>
<td>UCH L1</td>
<td>Begins with a tremor. Good treatment response to L-dopa.</td>
</tr>
<tr>
<td>PARK6</td>
<td>1p36-35</td>
<td>?</td>
<td>Autosomal recessive. Early onset, benign course with prominent tremor. Good response to L-dopa but early dyskinesias.</td>
</tr>
<tr>
<td>PARK7</td>
<td>1p36</td>
<td>DJ-1</td>
<td>Autosomal recessive early onset, benign course, may be dystonia. Good response to L-dopa.</td>
</tr>
<tr>
<td>PARK9</td>
<td>1p36</td>
<td>?</td>
<td>Parkinsonism with pyramidal features, supranuclear gaze paresis and dementia in a consanguineous Jordanian family (Kufor-Rakeb syndrome).</td>
</tr>
<tr>
<td>PARK10</td>
<td>1p32</td>
<td>?</td>
<td>Susceptibility locus for late onset parkinsonism found by genome-wide linkage.</td>
</tr>
</tbody>
</table>

### Table 2. Genetic loci linked to dystonia.

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chromosomal region</th>
<th>Mutations</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>9q34</td>
<td>CAG deletion in TorsinA</td>
<td>Autosomal dominant early-onset dystonia beginning in a limb and rapidly spreading. Oppenheim's dystonia (see text for a more detailed description).</td>
</tr>
<tr>
<td>DYT2</td>
<td>(unconfirmed)</td>
<td>?</td>
<td>Autosomal recessive in Gypsies.</td>
</tr>
<tr>
<td>DYT4</td>
<td>?</td>
<td>?</td>
<td>Autosomal dominant whispering dysphonia in a single large Australian family.</td>
</tr>
<tr>
<td>DYT5</td>
<td>14q22.1</td>
<td>GCH1</td>
<td>Segawa's syndrome. Dopa-responsive dystonia with diurnal variation.</td>
</tr>
<tr>
<td>DYT6</td>
<td>8p21-p22</td>
<td>?</td>
<td>Autosomal dominant, only in Mennonites, mixed phenotype (focal or generalised).</td>
</tr>
<tr>
<td>DYT7</td>
<td>18p</td>
<td>?</td>
<td>Autosomal dominant with reduced penetrance. Late onset in German families.</td>
</tr>
<tr>
<td>DYT8</td>
<td>2q</td>
<td>?</td>
<td>Autosomal dominant paroxysmal non-kinesogenic dystonia.</td>
</tr>
<tr>
<td>DYT9</td>
<td>1p</td>
<td>?</td>
<td>Autosomal dominant episodic choreoathetosis with spasticity.</td>
</tr>
<tr>
<td>DYT10</td>
<td>16p11</td>
<td>?</td>
<td>Autosomal dominant paroxysmal kinesogenic dystonia.</td>
</tr>
<tr>
<td>DYT11</td>
<td>7q21</td>
<td>SCGE</td>
<td>Autosomal dominant alcohol responsive myoclonus-dystonia.</td>
</tr>
<tr>
<td>DYT12</td>
<td>19q</td>
<td>?</td>
<td>Autosomal dominant rapid onset parkinsonism-dystonia.</td>
</tr>
<tr>
<td>DYT13</td>
<td>1p36.32-p36.13</td>
<td>?</td>
<td>Autosomal dominant dystonia in a large non-Jewish family not linked to DYT1.</td>
</tr>
<tr>
<td>DYT14</td>
<td>14q13</td>
<td>?</td>
<td>Autosomal dominant dopa-responsive dystonia in a German family not linked to the GCH1 gene.</td>
</tr>
<tr>
<td>DYT15</td>
<td>18p11</td>
<td>?</td>
<td>Autosomal dominant alcohol responsive myoclonus dystonia not linked to other loci in a large Canadian kindred.</td>
</tr>
</tbody>
</table>
References


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