Genes and parkinsonism

Parkinsonism is a common disabling condition, characterised clinically by akinesia, rigidity, and tremor. There is a long list of potential causes, of which the commonest is idiopathic Parkinson's disease. Its frequency increases with age and prevalence figures vary across the world.\(^1\) A recent population based study estimated the age dependent prevalence at 1-4%, 2%, and 3-4% in those aged 55, 65, and 75 years or over respectively.\(^2\) The clinical diagnosis of idiopathic Parkinson’s disease includes the presence of parkinsonism plus other supportive features including classic rest tremor, a unilateral onset, and most important of all, a significant response to levodopa. There are several exclusion factors including supranuclear gaze palsy; pyramidal or cerebellar signs or dyspraxia; severe, early loss of postural reflexes; prominent autonomic abnormalities; early cognitive impairment; neuroleptic drug ingestion, encephalitis; or possible toxic exposure in the six months before onset. Exclusion criteria may also be supplemented by investigative data, including cerebellar atrophy on imaging, denervation on external sphincter EMG; Wilson’s disease and other metabolic causes of parkinsonism should be excluded if the onset is before 40 years of age.

Although the neurological deficit of idiopathic Parkinson’s disease is ameliorated by levodopa therapy, the effect of the drug wears off after a few years, leading to severe disability for which there is no effective treatment and despite its frequency and intensive research efforts over several decades, the cause of Parkinson’s disease remains unknown.\(^3\) The role of genetic factors in the aetiology of idiopathic Parkinson’s disease was controversial for many years—ever since Gowers noted in 1893 a family recurrence risk of 15%.\(^4\) However, family studies have been hampered by variable diagnostic criteria and the difficulties of assessing the significance of a common disorder occurring in more than one member of a family.\(^5\) Recent progress in the capabilities of genetic analyses now permits a search for responsible genes, the identification of which it is hoped will further elucidate the pathogenesis and lead to more rational therapy.

**Genetic epidemiology of Parkinson’s disease**

There is accumulating evidence that genetic factors play a significant part in the susceptibility to idiopathic Parkinson’s disease.

**TWIN STUDIES**

Twin studies are the classic methods of providing an estimate of heritability, while controlling for the environment. Unfortunately this ideal is more difficult to achieve in practice and most twin studies in idiopathic Parkinson’s disease have been prone to bias. Ward et al\(^6\) found similar concordance rates for monozygotic (8%) and dizygotic (5%) twin pairs leading the authors to conclude that genetic factors were unimportant. However, this study can be criticised on methodological grounds; in an analysis of 65 twin pairs, only 19 were dizygotic, which is lower than that expected in a truly population based study. Moreover, in the original analysis insufficient allowance was made for the possible inclusion of other non-genetic akinetic rigid syndromes, the presence of which would be expected to lower the apparent concordance of idiopathic Parkinson’s disease. Conversely, strict clinical criteria excluded “atypical” cases, whereas it is recognised that atypical phenotypes can still result from “typical” Lewy body pathology.\(^7\) Marsden reported a similar result but from a much smaller sample size and many of the cases were not personally examined.\(^8\) Johnson et al reanalysed the reported twin studies taking the above factors into account and reviewing the statistical methodology and came to the conclusion that the genetic hypothesis was neither proved or disproved.\(^9\)

The age dependent prevalence of Parkinson’s disease\(^10\) and the related concept of preclinical Parkinson’s disease adds further limitations to twin studies. The advent of PET studies using ligands such as \(^12\)C dopa\(^11\)\(^12\) has made possible an in vivo estimate of nigrostriatal function. Burn et al\(^13\) analysed 17 twins and estimated concordance at 45% in monozygotes and 29% in dizygotes,\(^13\) thus supporting the genetic hypothesis. However, limitations of the technique and in, particular, the binding of the ligands should promote caution in overinterpreting these results.

Many authors have concentrated on the deficiencies of twin studies but Sommer and Rocca have proposed an interesting hypothesis to explain the discrepancies.\(^14\) They suggest that if the genes causing Parkinson’s disease were analogous to prion proteins then the observed data could be explained. This is purely hypothetical at present but does raise the important issue of not forcing the data to fit existing dogma.

**FAMILY STUDIES**

There is an increasing recognition of large families with an autosomal dominant mode of inheritance of apparent idiopathic Parkinson’s disease, pathologically established in some cases.\(^15\)\(^16\)\(^17\) It is also clear that the clinical features of familial Parkinson’s disease broadly conform to modern diagnostic criteria for idiopathic Parkinson’s disease and...
that there is statistically no difference between familial and sporadic cases. Golbe et al reported a large kindred originating from a small town in southern Italy. The age of onset of these families was earlier (mean 45-6 years) than is normal for sporadic Parkinson’s disease and the duration of the illness was shorter (9-7 years); however, in all other respects, including pathology (two cases), the disease resembled idiopathic Parkinson’s disease. A segregation ratio of 40-1% strongly supports autosomal dominant inheritance and this family has recently been mapped to chromosome 4q21-23. The maximum lod score of 6.0 (θ = 0.0) provides very strong evidence that the gene responsible for the parkinsonian syndrome in this family is tightly linked to this region. It remains to be seen whether this gene will play a part in both sporadic and other parkinsonian families. Preliminary data from the European collaborative group suggest that the gene on chromosome 4q is not important in 10 other autosomal dominant families (T Gasser, personal communication), nor in a large number of sibling pairs (N Wood, unpublished data).

Other pedigrees have also been described, but closer inspection of these suggest some unusual features, including early age of onset, rapid progression, prominent dementia, or slightly unusual pathology. Nevertheless, these reports show that a single gene can produce a dopa responsive akinetic rigid syndrome with Lewy body pathology.

Case-control studies have indicated a significantly increased risk (odds ratio 3.5) of Parkinson’s disease in first degree relatives of patients with the disease, and the maximum age adjusted prevalence of Parkinson’s disease in such relatives approaches 20%. Bonifati et al studied 100 consecutive patients with Parkinson’s disease and used their spouses as controls. A family history of Parkinson’s disease was positive in 24% of patients compared with only 6% of the controls (O < 0.001). If tremor alone was permitted as an inclusion criterion then the number of positive cases rose to 43% compared with 9% in controls.

Table 1 summarises other studies and a broad consensus emerges—namely, that a positive family history is one of the most consistent associated factors contributing to risk. There is much less agreement regarding the number of genes involved and modes of inheritance. These include autosomal dominant with reduced penetrance and in both of these studies a unilateral distribution of ancestral secondary cases was shown. There is, however, a potential for ascertainment bias in this type of study. Moreover, an excess of paternal transmission and an equal sex ratio, points against a major X linked gene or mitochondrial inheritance. De Michele et al found that a family history of Parkinson’s disease provided the strongest association (odds ratio = 14.6, 95% confidence interval (95% CI) 7.2-29.6).

In summary, it is clear that a few patients with a disease resembling idiopathic Parkinson’s disease have a single, dominant gene causing their illness. It is extremely important to find these genes to determine their role not only in families with idiopathic Parkinson’s disease but also to assess the impact of these genes in all patients with this disease. It is also clear that most patients with idiopathic Parkinson’s disease either have no family history or only one other affected relative and it is therefore reasonable to assume that the aetiology of this disorder is complex and probably involves an interplay of genes and environment in these patients. The most robust way to investigate this phenomena is via the affected sibling pair method, which has proved itself useful in other disorders including diabetes and multiple sclerosis.

### Table 1: Summary of family recurrence risk studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Affected/at risk (%)</th>
<th>Controls</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mjones et al 26</td>
<td>276/674 (41)</td>
<td>None</td>
<td>AFFECTED had various tremors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spouses as controls, therefore produced bias</td>
</tr>
<tr>
<td>Duvoisin et al 24</td>
<td>4/146 (2.7)</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Kondo et al 54</td>
<td>52/263 (19.8)</td>
<td>None</td>
<td>Detailed analysis supported polygenic inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relatives not examined</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spouses as controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potentially biased recruitment</td>
</tr>
<tr>
<td>Maritan et al 55</td>
<td>14/243 (5.8)</td>
<td>18.8%</td>
<td>First degree relatives only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specialist clinic but consecutive patients</td>
</tr>
<tr>
<td>Payami et al 28</td>
<td>18/114 (16)</td>
<td>4%</td>
<td>Specialist clinic but consecutive patients</td>
</tr>
<tr>
<td>Lazzarini et al 56</td>
<td>58/211 (27.5)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Bonifati et al 57</td>
<td>24/100 (24)</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

CANDIDATE STUDIES

In an attempt to circumvent the costly and rather laborious technique of random genome screening many authors have utilised knowledge of the pathogenesis of the disease to generate putative candidate genes. Generally the loci involved in dopamine synthesis and metabolism have been investigated using various linkage and association methods. An excess of mutant cytochrome P-450 (CYP2D6) alleles, associated with impaired debrisoquine metabolism, has been reported in patients with Parkinson’s disease compared with controls. An association between one allele of the tyrosine hydroxylase (TH) gene and sporadic Parkinson’s disease has not been confirmed, and there is no evidence for linkage to this locus in familial Parkinson’s disease. Allelic association has also been suggested for Parkinson’s disease and a monoamine oxidase B (MAO-B) polymorphism but a recent report by Ho et al refuted this association; no association was detected for MAO-A. Others have suggested an association between sporadic Parkinson’s disease and an MAO-A allele. The CYP2D6 locus, although showing association with Parkinson’s disease, is not the major determinant of genetic susceptibility in familial Parkinson’s disease.

Linkage to other candidate loci (glutathione peroxidase, catalase, amyloid precursor protein, superoxide dismutase 1, and brain derived neurotrophic factor) has been excluded in three large families. Higuchi et al compared allele frequencies for dopamine receptors D2, D3, and D4 and dopamine transporter (DAT), between patients and controls and found no evidence to support a role for these in the aetiology of Parkinson’s disease. Other researchers have taken the direct route of sequencing candidate genes and using such an approach Parboosingh et al have excluded abnormalities in catalase and superoxide dismutase.

The role of mitochondrial function had been suggested by two studies, which reported a decreased complex I activity in platelets and substantia nigra of patients with Parkinson’s disease. This tentative link was further enhanced by the finding that MPP+, an end product of MPTP metabolism, is toxic to complex I. As only a few of the subunits that constitute complex I are encoded by the mitochondrial genome, an absence of maternal transmission does not exclude a role for mitochondrial function in the aetiology of this and perhaps other neurodegenerative conditions. It is unclear whether the observed reduction in complex I is a primary or secondary effect (for a review see Schapira). A recent study by Swerdlow et al gave further support to an impairment of complex I and moreover
indicated that the defect lay in the mitochondrial DNA (mtDNA). Neuroblastoma cell lines in which mitochondrial DNA had been removed (by treatment with ethidium bromide) were fused with platelets from patients with Parkinson’s disease (containing only patient mtDNA). The resulting cybrids showed significant complex I impairment from which the authors concluded that the abnormalities of complex I are derived from the mtDNA and are not “correctable” by the insertion of a “normal” nuclear DNA component. It is extremely difficult to reliably exclude all mtDNA from these cell lines and it will be important to reproduce these findings using other cybrid systems.

Mitochondrial polymorphisms (mutations) have been reported including a tRNA\(^{\text{th}}\) (bp4336), a missense at bp3397, and a 9bp insertion in the 12S rRNA\(^{\text{t}}\) and a point mutation at bp 5460.\(^{\text{40}}\) All of these have been found in slightly greater numbers in a few patients compared with controls. Bandmann et al\(^{\text{41}}\) have studied 100 necropsied brain samples from patients with Parkinson’s disease and showed no significant differences between patients and controls, and the rates of polymorphism in their patients were almost identical to those found in the control patients of the other studies. Therefore there is no convincing evidence for a pathological role for these polymorphisms in the aetiology of Parkinson’s disease. These findings are difficult to synthesise into a single coherent story. Family studies and mtDNA candidate polymorphisms have so far failed to support a mtDNA derived susceptibility factor. On the contrary, the biological data support a complex I deficiency that seems to be mtDNA dependent. It may therefore be necessary to investigate the role of mtDNA and complex I in the subgroup of familial cases with inheritance compatible with matrilineal inheritance.\(^{\text{42}}\)

Patil et al\(^{\text{43}}\) recently described point mutations in the H5 pore region of a potassium channel (mGirk2) in weaver mice, the brain pathology of which has some similarities to those in Parkinson’s disease. In 50 patients with Parkinson’s disease (23 with a positive family history), Bandmann et al\(^{\text{44}}\) sequenced the pore region of the human homologue (hiGIRK2) but found no abnormalities.

Anticipation, the concept of increasing severity and earlier age of onset in successive generations, is now recognised in some inherited neurological conditions and to date all are caused by the expansion of unstable trinucleotide repeats. Genetic anticipation has been suggested in Parkinson’s disease.\(^{\text{45-48}}\) The data should be viewed with great caution as there are inherent problems in this sort of analysis including ascertainment and observer biases. These are extremely difficult to remove, particularly in the absence of known loci, as identification of gene carriers is impossible.

Using a method which screens for an excess of repeats Carrero-Venezuela et al assessed 46 unrelated patients with Parkinson’s disease and 11 families in whom “anticipation” was suspected and found no evidence of an association between prolonged CAG repeats and either sporadic or familial Parkinson’s disease. Huntington’s disease can present as a parkinsonian syndrome, particularly in the juvenile onset form. Rubinsztain et al\(^{\text{49}}\) studied 45 patients for the CAG repeat expansion in the Huntington gene and found no differences between the patients and a control group.

Other parkinsonian syndromes

There are syndromes incorporating both parkinsonism and additional features, including multiple system atrophy, progressive supranuclear palsy, and parkinson-dementia complex. It is still unclear how many of these disorders have a genetic basis but there are reports of multiple affected relatives for some.

MULTIPLE SYSTEM ATROPHY

A possible clinical and pathological overlap between patients with an autosomal dominant ataxia (SCA1) and multiple system atrophy has recently been suggested by Gilman et al.\(^{\text{50}}\) However, there were several features in this family which would be unusual for multiple system atrophy, including early age of onset (19 years), long survival, and absence of pyramidal or extrapyramidal signs in the proband. None of the cases fulfilled the proposed clinical criteria of Quinn\(^{\text{51}}\) for probable multiple system atrophy and some members of the family had very reduced sensory nerve conduction velocities. Bandmann et al have analysed DNA samples from the blood of 65 patients and 15 DNA samples obtained from the brains of pathologically confirmed patients.\(^{\text{52}}\) No expansion of the CAG repeats in either of the SCA1 or SCA3 genes were detected and they also excluded a role for HLA A32, ciliary neurotrophic factor, IGF-1, and the pore region of hiGIRK2 in these cases.

X LINKED DYSTONIA-PARKINSONISM

This disorder seems to have originated from a common ancestor in the Ilongo ethnic group on the island of Panay in the Philippines. Parkinsonism is present in over 50% of cases but it differs from idiopathic Parkinson’s disease; the mean age of onset is 35, there is early development of dystonic features, including blepharospasm and torticollis, and it responds poorly to levodopa. There is a strongly associated haplotype on Xq12-13.1 in over 85% of affected patients which has been localised to a 1.8Mb region.\(^{\text{53}}\) The entire region has now been cloned and sequence data are awaited.

DOPA RESPONSIVE DYSTONIA

Recently the GTP cyclohydrolase I gene (GTPCH) on chromosome 14 was isolated as the first causative gene for dopa responsive dystonia.\(^{\text{54}}\) This is the rate limiting enzyme in the production of tetrahydrobiopterin, which is a vital cofactor for tyrosine hydroxylase. Patients with the disease show autosomal dominant inheritance with reduced penetrance. Bandmann et al\(^{\text{55}}\) have shown that abnormalities in this gene occur outside of Japan, and to date no family or patient has had the same mutation (allelic heterogeneity). Further evidence for the importance of the biopterin pathway was provided by Ludecke et al,\(^{\text{56}}\) who identified a pair of affected siblings with dopa responsive dystonia due to a homozygous mutation in tyrosine hydroxylase.

The identification of mutations within the GTPCH I gene has permitted a broadening of the phenotype from the classic leg-onset childhood dystonia, to include “benign” parkinsonism. Bandmann et al\(^{\text{57}}\) have sequenced the entire coding region of GTPCH I in 29 patients selected on the basis of shared features with dopa responsive dystonia, either a positive family history, benign course with prolonged and excellent response to levodopa, or absence of classic pathology in otherwise typical Parkinson’s disease. No abnormality in this gene was found in any of these cases, and therefore there is no evidence that this enzyme is involved in idiopathic Parkinson’s disease.

DISINHIBITION DEMENTIA-PARKINSONISM-AMYOTROPHY COMPLEX

This complex is defined by familial adult onset behavioural disturbance, followed by dementia of frontal type,
Table 2  Genetically determined atkin rigon syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Locus</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson’s disease</td>
<td>13q14.3</td>
<td>Cu binding ATPase</td>
</tr>
<tr>
<td>Dopa responsive dystonia</td>
<td>14q</td>
<td>GTP cyclohydrolase*</td>
</tr>
<tr>
<td>Juvenile HD</td>
<td>4p</td>
<td>Huntington</td>
</tr>
<tr>
<td>SCA3/MJD</td>
<td>14q32.1</td>
<td>Protein of unknown function</td>
</tr>
<tr>
<td>DRPLA</td>
<td>12q23.24</td>
<td>Atrophin</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher</td>
<td>X</td>
<td>Proteolipid protein</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>11q</td>
<td>ATM</td>
</tr>
<tr>
<td>Lech-Nyhan syndrome</td>
<td>Xq26</td>
<td>Hgp deficiency</td>
</tr>
<tr>
<td>Hallervorden-Spatz</td>
<td>20p12.3</td>
<td>Unknown</td>
</tr>
<tr>
<td>Familial prion diseases</td>
<td>20pter-12</td>
<td>Prion protein</td>
</tr>
<tr>
<td>Autosomal dominant PD</td>
<td>4q21-23</td>
<td>Unknown</td>
</tr>
<tr>
<td>Juvenile parkinsonism</td>
<td>11p</td>
<td>Linked to tyrosine hydroxylase</td>
</tr>
<tr>
<td>Parkinsonism (Lubag)</td>
<td>Xq12-13.3 (DVT3)</td>
<td>Unknown</td>
</tr>
<tr>
<td>DDPAC</td>
<td>17q21-22</td>
<td>(wild) Unknown</td>
</tr>
</tbody>
</table>

*Most cases are autosomal dominant (with reduced penetrance). However, autosomal recessive inheritance has been shown to be due to mutations in the tyrosine hydroxylase gene (chromosome 11p). Probably more than one cause.

SCA/MJD = Spinocerebellar ataxia type 3/Machado-Joseph disease; DRPLA = Dentato-rubral-pallido-luysian atrophy; HD = Huntington’s disease; PD = Parkinson’s disease; DDPAC = Disinhibition dementia-parkinsonism-amytrophic complex.

parkinsonism (without tremor), and amyotrophy. Wilhemsen et al. 1984 showed that linkage to 17q21-22 established a single locus for this phenotype and it is now apparent that the gene for autosomal dominant parkinsonism and dementia with pallidopontineral degeneration maps to the same region. 1984 This disease produces rapidly progressive (average duration 8–9 years) parkinsonism with prominent abnormalities of eye movement. A third familial phenotype with a pathological substrate of progressive subcortical gliosis may also have the same genetic basis, as, in a small family, segregation to 17q21 has been shown. 1984 The gene for this conditions has yet to be identified but there are autosome from the region including microtubule associated tau and low affinity nerve growth factor. Once the gene is isolated it will be important to establish how many other complicated parkinsonian syndromes are associated with abnormalities in its function.

Conclusions

Positional cloning techniques have shown their worth in a growing list of single gene neurological diseases, many of which have parkinsonian features (table 2). Of most recent interest is the finding that a single locus at 4q21-23 is responsible for a disease that closely resembles idiopathic Parkinson’s disease. However, it is certain that more than one gene for autosomal dominant pure parkinsonism exists and it is unclear what the role of the gene will be in most cases of idiopathic Parkinson’s disease. Recent developments in mapping the human genome including fluorescent technology, improved automation, and increasing density of both anonymous markers and expressed sequence tags are placing the identification of genetic factors within reach and it is to be hoped that this will provide clues to the environmental components and increase our understanding of the gene-environment interactions.

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23. Blatt SE, Daniel SE, Marinescu DJ. Familial Parkinson’s disease: clinical-pathological study of a new kindred with autosomal dominant, levodopa responsive parkinsonian and antici-

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Editorial


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