REVIEW

The genetic basis of Parkinson's disease

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Although the mechanisms underlying neurodegeneration in Parkinson's disease are not fully understood, considerable evidence suggests that genetic factors can influence susceptibility to the disease. In this article, we critically review this evidence and examine studies estimating patterns of inheritance. In a few families, Parkinson's disease is clearly inherited in a Mendelian fashion, and in some of these the disease causing genes have already been identified. Possible pathogenic mechanisms by which these genes cause Parkinson's disease are discussed. Further candidate genes and systematic efforts to identify genes influencing susceptibility to the disease in general are also summarised. The identification of such susceptibility genes will eventually enable us to more accurately classify this complex disease.

The possibility of a genetic contribution to the risk of Parkinson's disease (PD) was first described by Gowers,[1] who found 15% of his patients had a family history of the disease. Later Mjones[2] described positive family histories in 41% of his patients and suggested that the disease was inherited as an autosomal dominant with high penetrance. This high recurrence risk may be partially explained by Mjones' inclusion of relatives with atypical forms of the disease and even those with isolated tremor.

This paper aims to review the current evidence for a genetic susceptibility to PD and critique the methods used. The studies included were identified by means of a systematic search of the PubMed database, using the MeSH headings "genetic" and "Parkinson". Further references were identified from the bibliographies of these studies.

Epidemiological studies can explore the frequency with which PD tends to be a familial disease, whereas studies of monozygotic and dizygotic twins can distinguish the exact contribution of genetics and environmental exposures on familial risk. Segregation analyses can be used to identify patterns of inheritance among families with multiple cases of PD.

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EPIDEMIOLOGICAL STUDIES

Case selection

Our systematic search identified nine modern case control studies[3–11] exploring the frequency of a family history of PD among affected people (see table 1). Seven[3–9] of these studies were clinic based and therefore possibly subject to selection bias, as families with more affected members may be more likely to attend a movement disorders centre. Only two of these studies were population based, one identifying patients using door to door screening,[10] the other using multi-source case ascertainment.[11]

Case diagnosis

PD case definition among all these studies is based on varying clinical criteria rather than pathologically confirmed disease, which tend to have specificities around 70%–80%.[12 13] This might dilute any association found between PD case status and family history of disease, or may result in a false positive association if the non-PD patients actually have familial diseases such as essential tremor. Whether or not patients with an isolated resting tremor *should* be included in these studies is controversial as there is now some evidence that isolated resting tremor may be part of the spectrum of Lewy body disease.[14 15] Broadening the inclusion criteria in this way would inevitably lower the specificity of the diagnosis even further.[16]

Control selection

A particularly important issue is the method of selecting control subjects. Volunteer controls may represent a "genetically healthy" cohort, and may not be adequately representative of the population from which the PD cases are derived. Random selection of age matched controls should be from a source comparable to that from which the cases were selected, and exclusion criteria used in the identification of cases should also apply to the control group. Randomly selected control subjects may however be less aware of the symptoms and signs of the disease than cases, and thus be less aware of the diagnosis among relatives. The selection of spouses as controls attempts to diminish this awareness bias[3 8 9] as the spouse of a PD patient is likely to have comparable disease awareness among their relatives. The use of spouses as controls in family studies assumes spouses are genetically unrelated, however the non-random selection of spouses known as assortative mating implies that spouses and their families may also share similar genes to the PD cases, which may lead to lower estimates of familial relative risk. The presence of PD symptoms among control subjects should obviously result in exclusion from these studies, however subclinical cases may be included in a

Abbreviations: PD, Parkinson's disease; MZ, monozygotic; DZ, dizygotic

Table 1 Case-control studies estimating the frequency of PD among relatives of cases in comparison with controls

Author	Source of cases	Source of controls	Percentage of cases with family history of disease	Percentage of controls with family history of disease	Familial relative risk (crude)
Martin 1973	Clinic series	Case spouses	26.8	14.8	1.8
Semchuk 1993	Clinic series	Age, sex matched community	22.7	6.3	3.6
Payami 1994	Clinic series	Case spouses or friends	15.8	4.0	4.0
Vieregge 1995	Clinic series	Non-neuro hospital patients	9.1	1.4	6.5
Bonifati 1995	Clinic series	Case spouses	24.0	6.0	4.0
de Michele 1996	Clinic series	Spouses and neuro hospital patients	33.0	3.4	9.7
Marder 1996	Population based	Community volunteers	6.4	4.9	1.3
Taylor 1999	Clinic series	Case in-laws or friends	18.6	6.8	2.7
Elbaz 1999	Population based	Community	10.3	3.5	2.9

control group although it is unlikely that this figure would be higher than 1% among randomly selected control subjects.

Assessment of family history

The majority of our identified studies use self reporting or self administered questionnaires to assess family history of PD.[3–6 8 10 11] Categorising PD cases who have relatives with isolated tremor as having a positive family history, can significantly increase the number of familial cases,[8] especially among early onset PD cases.[17]

Performing individual examinations may increase the precision with which a diagnosis of PD is made in relatives of cases and controls, rather than reliance on patient reporting of diagnoses or symptoms such as tremor. It has also been shown that significant numbers of previously unrecognised PD patients can be identified by examination despite a negative family history.[18] It can often however be difficult verifying familial diagnoses in diseases affecting the elderly as relatives are often deceased and not subjected to postmortem examination. Subclinical Parkinson's disease, diagnosed on the basis of Lewy body pathology in people without prior symptoms of PD, is observed in up to 10% of individuals subjected to postmortem neuropathological examination.[19] No study includes pathological examination of all relatives of both cases and controls, which currently represents the gold standard in diagnosing PD.

Despite these concerns, when comparisons are restricted to relatives with verifiable diagnoses by examination or medical records, the association between PD status and positive family history of PD seems to persist.[7 9] One case series[20] vigorously investigated patient relatives reported to be affected by PD, using individual examinations, medical records, or postmortem findings to confirm diagnoses and assess the frequency of familial disease. This series did not however examine relatives reported as normal and therefore may include false negative reports, and also did not recruit a control group for comparison.

The length of follow up of relatives of both cases and controls can also have profound effects on the results of these studies, because not all relatives who may eventually become affected have passed through the age of risk. Results may be more usefully presented as the cumulative risk of the disease among relatives of cases or controls by a certain age.[3] Most studies however have not routinely recorded the ages of siblings or parents and therefore are unable to calculate cumulative risks at sequential ages based on their data.

Some of the variation in frequency of family history of PD is attributable to whether first degree (parents and siblings) or second and third degree relatives are included. Within particular studies, the inclusion of second or third degree relatives is consistent between cases and controls so relative risks are appropriate but variation between studies makes comparison difficult. In many cases the proband is unable to give complete information on the health status of all or any of their more distant relatives, and reported information is reliable only for first degree relatives. One method of overcoming the lack of information among more distant relatives has been investigated in a study in Iceland, using genealogical information built up over centuries. PD cases were identified from two population based studies and death certificates. Measures of relationship (kinship coefficients) between cases compared with randomly selected controls were calculated. PD patients were found to be more likely to be related to each other than controls.[21]

All nine of the studies we identified in our search found higher rates of the disease in the relatives of those affected compared with controls. The crude familial relative risks, calculated by dividing the rate among relatives of cases by the rate among relatives of controls, show some variation but is seems reasonable to conclude that familial clustering of the disease is genuine. Familial clustering of PD may be related to either shared genetic risks or shared exposures to environmental factors.

TWIN STUDIES

The precise contribution of genetics in this observed familial clustering of IPD can be elucidated by studying disease concordance rates in monozygotic (MZ) and dizygotic (DZ) twins. A simple Mendelian trait that is autosomal dominant and 100% penetrant will produce concordance rates of 100% in MZ twins and 50% in DZ twins, assuming no influence from mitochondrial DNA or the environment. The rate will fall to 25% among DZ twins if inheritance is autosomal recessive. A rate of less than 100% among MZ twins implies reduced penetrance, mitochondrial, or environmental influences on the disease. Comparing exposure status of discordant MZ twins may also be used to search for significant environmental factors. The early twin studies,[22–25] found low concordance rates (5%–8%) in both MZ and DZ twins with little evidence for an excess concordance in MZ twins.

Follow up time was short in these early studies, which may contribute to the low observed concordance rates because a substantial genetic predisposition might be expressed at two different times by two MZ twins, or there may be a differential interval to disease onset in the second twin between the MZ and DZ groups. Clinical concordance may actually only become apparent after an interval of up to 26 years.[26] A later study performed by Tanner in 1999[27] found similar concordance rates in MZ twins (16%) and DZ twins (11%) when twins with any age at disease onset were included, but a concordance rate for the disease of 100% in MZ twins, and 16% in DZ twins if age at onset was below 50 years (RR of 6.0). This strongly supported a primarily inherited cause of *early onset* PD. Although this study included examination of all cases and co-twins by a qualified neurologist, the presence of subclinical disease among the "unaffected " twins could not be excluded. It is possible that the interval to disease onset in

the second twin may be longer in late onset PD and follow up information is awaited. This study was based on 71 MZ twin pairs and 90 DZ twin pairs and is therefore sufficiently powered to detect increased risks of the order of 20% (based on standard power equations[28]), but not genetic risks of smaller magnitude that may have important roles in non-Mendelian forms of PD.

The development of 18F-dopa PET scans as a research tool, has enabled imaging of the pre-synaptic re-uptake mechanism of surviving nigro-striatal dopaminergic neurons, and thereby enabled the identification of pre-clinical cases of PD. Using decline in 18F-dopa uptake over four years as a marker for pre-clinical disease, concordance was found in 75% of MZ twins compared with 22% of DZ twins.[29 30] This was not confined to young onset pairs of twins or cases with other affected family members and establishes that a genetic component is extremely important in PD patients although does not diminish the possibility of important concomitant environmental factors, either interacting with genetic risks or acting independently.

MODE(S) OF INHERITANCE

Segregation analysis has been used to formally test hypotheses of environmental and genetic models as possible explanations for familial clustering of a trait. Observation of patient sex ratios, rates of disease among the siblings and parents of a proband, and rates of maternal and paternal transmission permit exploration of autosomal dominant, recessive, X-linked, or mitochondrial inheritance models. Studies have proposed both dominant models with reduced penetrance[2 3 31] and the existence of a rare familial factor, with non-Mendelian transmission.[32] The concept of polygenic inheritance, implying the interaction of many genes of minor influence is particularly appealing in diseases such as PD with a definite familial tendency, but with segregation ratios lower than would be expected for a dominant disorder.[33]

The discovery of large extended pedigrees[34–36] with recognisable patterns of inheritance (monogenic forms) has suggested heterogeneity within genetic risks for PD. Within the Contursi kindred in Italy in which 60 people in five generations are known to have had PD, and necropsy cases have confirmed the presence of Lewy bodies, male to male transmission confirms that autosomal dominant inheritance is responsible for the familial clustering rather than either a sex linked, or mitochondrial form of inheritance.

These large PD kindreds are however rare, and autosomal dominant genes do not seem to underlie the majority of cases of PD.

LINKAGE ANALYSES

On the basis of epidemiological studies, twin studies, and segregation studies, all suggesting a genetic contribution to PD susceptibility, attempts to map the position of responsible genes have been made. Linkage analysis is a useful tool to detect the chromosomal location of disease genes. Linkage detects co-segregation of a particular marker (allele) with a defined phenotype (disease state) *among pedigrees with multiple affected family members*. The likelihood of linkage is presented as the logarithm of the odds (LOD) score, and assumes a range of different recombination frequencies. LOD scores greater than 3.0 amount to significant evidence for linkage. Recombination refers to the exchange of DNA sequences between two copies of the same chromosome in meiosis, which may lead to separation of a marker allele and disease causing allele.

The technique is robust and permits genome wide mapping, but becomes weak if small pedigrees are used and is less effective for diseases caused by common genes with modest individual effects (low penetrance).[37] Linkage analysis in PD is further limited as parental DNA is rarely available because of the late age at onset of the disease. Linkage analysis in Mendelian forms of the disease has however been highly successful and has made significant contributions to our understanding of these unusual forms of the disease.

PARK1

The first PD gene locus was discovered within a large Italian family (Contursi kindred) linked to Chromosome 4q.[38] The gene at this site codes for α–synuclein, which is a major component of Lewy bodies.[39] Subsequent explorations have revealed single base-pair changes within the gene (mis-sense mutations) that result in amino acid substitutions in the α–synuclein protein (A53T)[40] and (A30P)[41] in several unrelated kindreds. These observations have lead to much work to identify the role of α–synuclein in PD.

Although the A53T mutation has been shown to increase α–synuclein assembly into filaments,[42] this has not been consistently shown for the A30P mutation.[43] Both α–synuclein mutations however accelerate the production of oligomers (protofibrils) of α–synuclein in nerve cells,[43] which may be neurotoxic by binding to and permeabilising membranes of synthetic vesicles.[44] Catecholamines including dopamine inhibit the conversion of toxic α–synuclein protofibrils to the stable α–synuclein filaments that may explain the selective susceptibility of the dopaminergic system to PD.[45]

PARK2

A second form of parkinsonism inherited in an autosomal recessive fashion has been identified and mapped to chromosome 6q 25,[46] and the gene at that site that is subjected to either partial deletions or point mutations has been named "parkin". Patients with these mutations have juvenile onset disease with degeneration of the SNc but usually without the formation of Lewy bodies. This gene has been found to be responsible for 77% of patients with parkinsonism with an age of onset of 20 years or younger, but only 3% of patients with an onset between 30 and 45 years.[47] The gene product "parkin" is a ubiquitin protein ligase thought to be involved in the degradation of abnormal proteins by the proteasome.[48] Mutations in the parkin gene cause the enzyme to lose its activity, and the subsequent accumulation of non-ubiquitinated proteins cannot form Lewy bodies and lead to earlier selective neural cell death.[49] This observation brings into question the relevance of the Lewy body in the pathological definition of PD. It has also been suggested that the normal form of parkin ubiquitin ligase has a role in degrading the glycosylated form of α–synuclein, as well as other proteins known to be neurotoxic if they accumulate.[50 51] This observation has stimulated hypotheses that defects in protein degradation may be a common aetiopathogenic factor unifying the different causes of PD.[48]

PARK3

Another gene locus has been mapped to chromosome 2p13 after linkage analysis of six European families with autosomal dominant PD, finding a LOD score of 3.96. The gene responsible for disease has not been identified yet.[36] The predicted penetrance of this gene could be as low as 40%, thus certain patients may have PD due to PARK 3 mutations without obvious family histories of the disease and thus may be misclassified as "sporadic PD".

PARK4

A further locus on chromosome 4p has been found to segregate with disease in another family with autosomal dominant Lewy body parkinsonism—the 4p 14-15 haplotype.[52] The gene responsible for the disease in this pedigree has also not yet been identified. Carriers of this haplotype within the same pedigree may also suffer from essential

Table 2 Summary of the phenotypic appearance and neuropathology findings from patients with the known PARK mutations

	Phenotype	Neuropathology
PARK 1	Onset typically in 30 s and 40s Rapid disease progression Tremor uncommon Good response to L-dopa Early cognitive impairment	Nigral degeneration Lewy bodies
PARK 2	Early onset typically, 20s, 30s or 40s Slow disease progression Symmetrical involvement Focal dystonia Sleep benefit	Nigral degeneration No Lewy bodies except in rare case reports
PARK 3	Onset in 50s Good response to L-dopa Cognitive impairment	Nigral degeneration Lewy bodies
PARK 4	Early onset Early weight loss Rapid disease progression Good response to L-dopa Some individuals have postural tremor only	Nigral degeneration Lewy bodies
PARK 5	Onset age 50 Initial tremor prior to bradykinesia Good response to L-dopa	Nigral degeneration Lewy bodies
PARK 6	Early onset typically in 30s Benign course Predominant rest tremor Good, Persistent response to L-dopa Early onset of drug induced dyskinesias	Unknown
PARK 7	Early onset typically in 30s Asymmetrical onset Benign course Good persistent response to L-dopa Focal dystonia	Unknown
PARK 8	Onset in 40s and 50s Asymmetrical onset Good response to L-dopa	Nigral degeneration No Lewy bodies

tremor, rather than typical Lewy body parkinsonism suggesting that in some cases, essential tremor represents a *forme fruste* of this parkinsonian syndrome.

PARK5

Two patients in a German pedigree have been found to have a mis-sense mutation in the ubiquitin carboxy-terminal hydrolase L1 (UCH L1) gene on Chromosome 4p,[53] leading to an amino acid substitution. UCH-L1 is an enzyme involved in the de-conjugation of ubiquitin and has been found in Lewy bodies.[54] Dysfunction of this enzyme may lead to loss of recycling of ubiquitin momomers[55] and subsequent dysfunction of the proteasomal-proteolytic pathway.[53] It is still the subject of debate whether this mutation is necessarily a cause of PD or is merely a chance finding within this family.[56]

PARK6

Further families with multiple cases of young onset PD all occurring within the same generation have been investigated for autosomal recessive forms of parkinsonism. These families had no abnormality in the parkin gene, but 8 of 28 of the families showed strong linkage (LOD score of >4.0) to a gene on the short arm of chromosome 1 (1p35-p36).[57] No neuropathological data are available for these families as yet.

PARK7

Very close to the PARK6 locus, but separated by a distance of 25 centimorgans is another recently discovered PD locus (1p36), which is significantly linked to another family with early onset autosomal recessive PD.[58]

PARK8

There has been a further description of another locus on chromosome 12 linked to the development of PD[59] in a Japanese family with autosomal dominant disease, but again with low disease penetrance. This suggests that environmental or other genetic factors may also modify expression of PD because of a gene at this locus. The gene causing PD in this family has not been identified.

The phenotypes of patients with these known mutations differ slightly from one another and these differences are presented in table 2. Other families affected by autosomal dominant PD have been examined, and known mutations in the above genes have been excluded suggesting that novel genetic variability underlying the condition remains to be found.[60–62]

To date only two genome wide searches for linkage in non-Mendelian PD have been published.[63 64] The first consisted of 113 co-affected sibling pairs and sought to identify alleles shared by sibling pairs at a frequency higher than that expected by chance.[63] No evidence of linkage was found for the regions PARK1, PARK2, PARK3, or PARK4 in these patients. The maximum LOD score across the whole genome was 1.30 on chromosome 9. The second of these linkage studies examined 174 families with multiple affected family members, finding evidence for linkage at five distinct chromosomal regions—PARK2, 17q, 8p, 5q, and 9q.[64]

Table 3 Meta analysis of association studies investigating genes for PD[67]

Gene	Gene Product	Significant association in meta analysis
DRD2	Dopamine receptor 2	No
DRD4	Dopamine receptor 4	No
DAT	Dopamine transporter	No
MAOA	Monoamine oxidase A	No
MAOB	Monoamine oxidase B	Yes (OR 2.58)
COMT	Catechol-o-methyl-transferase	No
NAT2	N-acetyl transferase 2 detoxification enzyme	Yes (OR 1.36)
APOE	Apo-lipoprotein E	No
GSTT1	Glutathione transferase detoxification enzyme T1	Yes (OR 1.34)
GSTM1	Glutathione transferase detoxification enzyme M1	No
GSTP1	Glutathione transferase detoxification enzyme P1	No
GSTZ1	Glutathione transferase detoxification enzyme Z1	No
tRNA Glu	tRNA Glu mitochondrial gene	Yes (OR 3.0)
ND2	Complex 1 mitochondrial gene	No

OR, odds ratio of developing PD.

ASSOCIATION STUDIES

An alternative method of seeking genetic causes of disease is to look for the relation of alleles and disease status at a frequency greater than predicted by chance *within a population*. These types of study are analogous to traditional case-control studies, and have greater power at detecting genes with small effects. These studies tend to use either single nucleotide polymorphisms or repeat polymorphisms known as microsatellites, as genetic markers to infer the phenotypes of cases and controls.

The discovery of an association between an allele and a disease state may be attributable to; the allele causing the disease, the allele lying close to the disease causing allele (linkage dysequilibrium), or the allele being more common within a population subgroup who also have a high frequency of the disease (population stratification)—that is, a false association rather than part of the disease process.

The simplicity of association studies has resulted in their frequent use to investigate various candidate genes, such as those coding for enzymes involved in the bio-transformation of various chemicals including MPTP[65]—the most notable of which is cytochrome P450 2D6 (CYP2D6). The activity of CYP2D6 is genetically determined, with some people having undetectable activity because of two defective alleles, these people referred to as "poor metabolisers". Three polymorphisms are responsible for 95% of poor metaboliser phenotypes in white people. A meta-analysis of available studies shows an overall risk of borderline significance (odds ratio 1.47) for the poor metaboliser status of the CYP2D6 enzyme and PD.[66] It has been proposed that poor metabolisers are genetically susceptible to PD because of an impaired ability to detoxify neurotoxins that are metabolised by CYP2D6. Such gene-environment interactions are discussed further in the next section.

In addition to CYP2D6, many other genes have been associated with PD in numerous studies. A review of all PD polymorphism association studies excluding CYP2D6 was published in 2000.[67] One hundred and seventy two studies looked at genetic polymorphisms in 14 genes, all of which had been evaluated in at least four or more separate studies (see table 3).

Four polymorphisms survived the meta-analysis and continued to show significant association with PD. MAO-B is particularly of interest because it is involved in dopamine metabolism, activation of MPTP, and its inhibition by the drug selegiline may retard progression of PD symptoms.[68 69]

Significant association does not however imply a causal relation between a polymorphism and PD, and almost every association study has been contradicted by others. In addition to difficulties with diagnostic criteria and population stratification bias, reviews of association studies need to account for publication bias for positive studies, variability in control subjects, and heterogeneity of genetic causes for the disease. Two studies have found that polymorphisms in dopamine receptor genes vary in frequency between PD patients with and without hallucinations,[70 71] suggesting that certain genes are able to influence the clinical phenotype of patients.

Since the discovery of α-synuclein as the cause for PD in several families with autosomal dominant inheritance, further comparisons of the α-synuclein gene have been made in patients with apparently sporadic PD. Early reports suggested that specific haplotypes of the α-synuclein gene may also be significantly associated with sporadic PD[72 73] although this has not been confirmed in a later study.[74]

MITOCHONDRIAL INHERITANCE

A marked deficiency in the activity of "complex 1" of the mitochondrial respiratory chain in the nigrostriatal system has been described in a proportion of PD patients.[75] Whether this deficiency is attributable to the presence of neurotoxins or is genetically determined has not been established and many people do not have a detectable change in complex 1 activity. Mitochondrial DNA encodes some of the subunits of complex 1, and a high rate of mutations has been observed in the mitochondrial DNA of PD patients compared with that of control patients, although no specific mutation has been found. Mitochondrial dysfunction might lead to increased production of reactive oxygen species, which leads to the oxidative stress observed in PD tissues.[76] Another hypothesis is that deficiency of ATP production attributable to mitochondrial dysfunction may lead to failure of the proteasomal proteolytic system.[77]

The genetic risk for PD however is not restricted to the maternal pattern of mitochondrial DNA inheritance, although one PD family with matrilineal inheritance and complex 1 dysfunction has been described in detail.[78] Other factors such as endogenous or exogenous toxins including the nigral toxins MPTP and rotenone,[79] neuroleptic drugs,[80] or enzyme products of other genes have all been implicated in the production of complex 1 deficiency. It has therefore been proposed that the mechanism of complex 1 deficiency and the initiation of a neurodegenerative process might vary between different PD patients.[81]

GENE-ENVIRONMENT INTERACTION

Genetic susceptibility to PD, mediated by deficient enzyme systems involved in the disposal of neurotoxins, may explain a role for both genes and environment in the development of the disease. An increasing number of studies are assessing the interaction between gene status and history of previous exposures for people with and without PD, or in different subgroups of patients. Within all studies of gene-environment

interaction, measurements of exposure status including precise exposure type, time, and duration of exposure and exposure dose, are particularly difficult to ascertain in retrospective case-control studies, and the possibility of recall bias persists.

One study of 100 patients meeting clinical criteria for PD has shown an increased risk of PD among people with a poor metaboliser CYP2D6 genotype who had also been exposed to solvents.[82] Gene-environment studies have also found that cigarette exposure may have variable effects on risk depending on patient genotype. Cigarette smoking has long been associated with a lower risk of PD,[83] however the protective effect of tobacco smoking may be lost among patients with the GSTM1*0 detoxification enzyme phenotype,[82] and may even increase the risk of PD in patients with the "A" polymorphism at the MAO-B gene with any protection being limited to those patients with the "G" polymorphism for that gene.[84] Limited numbers of cases and controls with "at risk" genotypes means these findings should always be checked in larger groups of patients, to exclude the possibility of chance findings or publication bias. This would also permit stratification for the effect of gender, and permit gene-gene interactions to be evaluated.

The involvement of another of the detoxification enzymes, GSTP1 in the metabolism of pesticides and the development of PD has also been evaluated.[85] Heterozygosity at the GSTP1 locus was found to be significantly associated with PD but only in those patients exposed to pesticides.

The coexistence of PD and dementia may reflect a particular disease phenotype, and there is a consistent association with older age at disease onset. The involvement of three gene loci and a range of environmental exposures have been investigated in subgroups of clinic based PD patients with and without dementia defined on the basis of the Mattis dementia rating scale.[86] This study concluded that PD patients with a poor metaboliser CYP2D6 genotype and also exposed to pesticides, are more likely to develop dementia, although pesticide exposure status was both retrospective and arbitrary, and only occurred in 12% of patients. It may well be that pesticide exposure is a risk factor for PD + dementia in only a subset of patients.

GENETIC ANTICIPATION

A younger age of onset of PD seen in successive generations of familial PD in one pedigree lead to the proposal that the pattern of inheritance was consistent with genetic anticipation due to a trinucleotide repeat containing gene.[87] Observations of anticipation may be biased as young onset probands may be more likely to have living affected relatives than late onset probands, and young onset PD patients may be more likely to be ascertained for inclusion in analysis. Moreover fewer cases of late onset disease will have developed within the younger generations at the time of study.

Several neurodegenerative diseases showing the phenomenon of anticipation have an expansion of an intragenic CAG/CTG repeat sequence. This was not found in 11 families with PD exhibiting anticipation in age at onset.[88]

DISCUSSION

The discovery of the α-synuclein (PARK1) and parkin (PARK2) genes has shown without doubt that genetic mutations can lead to the development of phenotypes of Parkinson's disease. It is not yet clear whether the known gene mutations contribute the majority of the genetic risk of developing PD or whether new genes remain to be found. Searches for mutations in α-synuclein in various populations of patients with early onset or familial PD has confirmed that this gene is a very rare cause of PD[89–91] and thus far cases of parkinsonism associated with a mutation in the PARK5 gene have only been found in one family[53] despite further searches for UCH-L1 mutations in other cases with familial PD.[56 92 93]

The parkin gene (PARK2) is thought to be responsible for up to 49% of early onset parkinsonism with clear autosomal recessive inheritance, but only 18% of isolated parkinsonism occurring below the age of 45 years.[47] Within European families with autosomal recessive early onset parkinsonism not attributable to the parkin mutation, a further 8 of 28 (29%) have PARK6 linked disease.[94] Carriers of only one abnormal parkin allele (heterozygotes) may also be at increased risk of PD based on the results of PET studies[95] and therefore the role of parkin mutations in susceptibility to PD may be even greater than first thought. It is however likely that we have still to identify further genes responsible for phenotypes of PD inherited in a Mendelian fashion.

Mendelian forms of PD are however unusual, and the evidence from epidemiological studies, reports of twin studies with PET scan data, and genealogical studies, all supports a genetic contribution to the risk of PD for more than just the small number of cases with Mendelian forms of the disease. Sporadic cases of PD are clinically indistinguishable from familial cases, with both having variable phenotypes and disease courses.[96] Epidemiological evidence regarding the frequency of familial PD is however limited by imprecise diagnostic criteria, inability to completely assess disease status of relatives, and difficulty finding appropriate control groups for comparison. Follow up data from an ongoing large twin cohort study with accompanying 18F-dopa PET scans should conclusively identify the extent of the genetic contribution to sporadic PD.

In addition to PARK1–8, genome wide linkage screens for further susceptibility loci suggest several further chromosomal regions of interest[64] including the "tau" gene on chromosome 17q, which may be associated with late onset forms of PD,[97 98] as well as regions on chromosomes 8p, 5q, and 9q. Association studies have also highlighted the possible importance of mitochondrial genes and detoxification enzymes in disease susceptibility that may also lead to non-Mendelian patterns of disease.

Accurate evaluation of the role of genetics in populations with PD is difficult because of the observed heterogeneity of genetic risk in different individuals and families. Even if a single gene mutation is responsible for many cases of the disease, other phenotypically indistinguishable cases could be attributable to alternative mutations in the same gene, chromosome aberrations or non-genetic phenocopies. The ability of linkage studies and association studies to detect disease susceptibility genes is limited by the existence of this genetic heterogeneity. Further analysis of patient groups might exclude patients carrying any of the existing PD gene mutations in order to reduce the heterogeneity within the patient group and increase the likelihood of detecting new susceptibility genes.

It has been suggested that if different genes were responsible for disease in different families, the onset age would show a better intra-familial than inter-familial correlation. Significant correlations of the order of 0.5 have been found in some studies[8 31] however families with parkinsonism linked to the PARK6 locus have had wide ranges of onset ages (up to age 68 years),[94] and concordance in MZ twins may be observed only after periods as long as 26 years apart.[26] Studies involving only patients with similar ages of onset may not be sufficient to reduce genetic heterogeneity and patient stratification techniques according to particular clinical phenotypes may be required to facilitate the ability of genome wide screens to identify genes for specific disease phenotypes.

There is mounting speculation that a common pathway may exist underlying varying genetic and environmental risk factors for PD. Inheritance of certain genes may inevitably lead to the clinical and pathological features of PD, whereas other genes, may require the exposure to environmental agents, or multiple other gene mutations before the disease can evolve.[26] Association studies are more useful than linkage analysis for diseases attributable to multiple genes with small effects. An

association study including a screen of the entire genome either directly, or indirectly using a dense map of markers, would allow for a systematic exploration of the influence of all of these candidate genes. Despite the limitations of both linkage and association studies, it is likely that further genome wide approaches will discover new or confirm suspected susceptibility loci, and ultimately permit the discovery of all major genes involved in increased risks for PD.

Our approach to the classification of neurodegenerative diseases as clinicopathological entities may become outdated.[99] Advances in molecular genetics may lead to new methods of classifying neurodegenerative diseases, and together with cell biology may lead to better understanding of the pathophysiology underlying PD, and permit us to target better informed treatments. Phenotypic variation within patients may depend on the precise gene mutation, the level of penetrance of the mutation, and genetic variability at loci other than the pathogenic locus, in addition to unknown environmental factors.

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