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A linkage study of candidate loci in familial Parkinson's Disease

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Abstract

Background: Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Most cases are sporadic, however familial cases do exist. We examined 12 families with familial Parkinson's disease ascertained at the Movement Disorder clinic at the Oregon Health Sciences University for genetic linkage to a number of candidate loci. These loci have been implicated in familial Parkinson's disease or in syndromes with a clinical presentation that overlaps with parkinsonism, as well as potentially in the pathogenesis of the disease.

Methods: The examined loci were *PARK3*, *Parkin*, *DRD* (dopa-responsive dystonia), *FET1* (familial essential tremor), *BDNF* (brain-derived neurotrophic factor), *GDNF* (glial cell line-derived neurotrophic factor), *Ret*, *DAT1* (the dopamine transporter), *Nurr1* and *Synphilin-1*. Linkage to the α -synuclein gene and the *Frontotemporal dementia with parkinsonism* locus on chromosome 17 had previously been excluded in the families included in this study. Using Fastlink, Genehunter and Simwalk both parametric and model-free non-parametric linkage analyses were performed.

Results: In the multipoint parametric linkage analysis lod scores were below -2 for all loci except *FET1* and *Synphilin-1* under an autosomal dominant model with incomplete penetrance. Using non-parametric linkage analysis there was no evidence for linkage, although linkage could not be excluded. A few families showed positive parametric and non-parametric lod scores indicating possible genetic heterogeneity between families, although these scores did not reach any degree of statistical significance.

Conclusions: We conclude that in these families there was no evidence for linkage to any of the loci tested, although we were unable to exclude linkage with both parametric and non-parametric methods.

Background

Parkinson's disease (PD) is considered to be a multifactorial disease. Seventy to ninety percent of cases are estimated to be sporadic, while ten to thirty percent are

familial [1]. Several rare PD families have been reported displaying different modes of inheritance. In the majority of families there is no clear inheritance pattern; however, in some cases is the disease clearly inherited in an autosomal dominant or an autosomal recessive mode. Clini-

Table 1: Description, chromosomal location and microsatellite markers for the candidate loci that were investigated.

Locus	Description	Chromosome	Map	Reference
PARK3	Parkinson's disease susceptibility	2p13	D2S441-1.6cM-D2S2113-1.4cM-D2S291-0.5cM-D2S2111-0.1cM-D2S2109-1.9cM-D2S1394	Gasser et al, 1998 [9]
Nurr1	Steroid receptor	2q22-23	D2S142-0.7cM-D2S284	Mages et al, 1994 [39]
FET1	Familial essential tremor	3q13	D3S1278-9.3cM-D3S1267	Gulcher et al, 1997 [30]
DAT1	Dopamine transporter	5p15	DAT1VNTR-5.5cM-D5S1455-8cM-D5S817	Vandenberg et al, 1992 [40]
GDNF	Glial cell line-derived neurotrophic factor	5p12-13	D5S674-4.8cM-D5S426-0.6cM-D5S395	Schindelhauer et al, 1995 [41]
Synphilin-1	Interacts with α -synuclein	5q23	D5S492-13.8cM-D5S657	Engelender et al, 1999 [25]
Parkin	Juvenile recessive Parkinson's disease	6q25-27	D6S305-0.3cM-D6S411	Kitada et al, 1998 [5]
Ret	Receptor of GDNF	10q11.2	D10S141	Ishizaka et al, 1989 [42]
BDNF	Brain-derived neurotrophic factor	11p13	D11S1324-3.4cM-D11S914-0.3cM-D11S1322	Maisonpierre et al, 1991 [43]
DRD	Dopa-responsive dystonia	14q22	D14S583-0.3cM-D14S587-0.3cM-D14S301	Ichinose et al, 1994 [3]

cally and neuropathologically, familial and sporadic PD seem to be similar [1], although in some familial cases atypical features accompany parkinsonism. In frontotemporal dementia linked to chromosome 17 (FTDP-17), patients display frontal lobe dementia and mutations have been identified in the *Tau* gene on chromosome 17 [2]. Dystonia is a prominent feature in dopa-responsive dystonia, a disease in which mutations have been found in the *GTP cyclohydrolase 1* gene on chromosome 4 [3].

To date, ten genes have been implicated in PD. The first PD mutation was found in the α -synuclein gene on chromosome 4 in a large Greek-American kindred with autosomal dominant inheritance [4]. Clinical and neuropathological features were similar to sporadic PD, although with relatively early disease onset and rapid course. In 1998, mutations in the *Parkin* gene were reported to be segregating with juvenile autosomal recessive parkinsonism [5]. Subsequently, a large number of *Parkin* mutations were reported both in familial early-onset PD and sporadic early-onset cases [6]. A mutation was also found in the *Ubiquitin carboxy-terminal hydrolase L1* (*UCH-L1*) gene in one German sib pair with PD [7]. Recently, mutations in the *DJ-1* gene were associated with autosomal recessive parkinsonism in two European families [8]. In addition to the genes described above, studies have linked six previously uncharacterized loci to PD. The *PARK3* locus on chromosome 2 was linked to the disease in several autosomal dominant PD families and the penetrance of the putative gene was estimated at about forty percent [9]. In 1999, a chromosome 4p haplotype was reported to be segregating with the disease in a large pedigree with autosomal dominant PD [10]. In this pedigree individuals who did not have PD but postural tremor also shared the haplotype, suggesting a common mutation for the two phenotypes. In a large Sicilian family with auto-

somal recessive early-onset parkinsonism a locus on chromosome 1p (*PARK6*) was reported to be linked to the disease [11]. Hicks and coworkers reported linkage of another locus on chromosome 1p (*PARK10*) to late-onset PD in 51 Icelandic families [12]. Further, the *PARK8* locus on chromosome 12 was linked to PD in a Japanese family with autosomal dominant parkinsonism [13]; and recently, a PD susceptibility locus on chromosome 2 was reported in 150 PD families [14].

In analyzing 12 Caucasian PD families ascertained in the northwestern US, we previously excluded linkage to chromosome 4q (α -synuclein) and the G209A mutation found in the Greek-American kindred [15]. Dominant mutations within the *FTDP-17* locus were also excluded. Using parametric linkage analysis we found suggestive linkage to the *PARK3* locus in a subset of families, although the locus was excluded in at least one family [16]. In this study we examined this locus further using non-parametric linkage analysis. We also analyzed genes or loci that are related to syndromes with parkinsonism such as juvenile parkinsonism (*Parkin*), dopa-responsive dystonia (*DRD*) and familial essential tremor (*FET1*), as well as genes or loci that are biologically implicated in survival or function of dopaminergic neurons, indicating potential involvement in PD pathogenesis. These included the following: *BDNF* (brain-derived neurotrophic factor), *GDNF* (glial cell line-derived neurotrophic factor), *Ret*, *DAT1* (the dopamine transporter), *Nurr1* and *Synphilin-1*. The candidate loci that were tested are described in Table 1. *BDNF* and *GDNF* are both neurotrophic factors for dopaminergic neurons [17,18] and they also protect nigral dopamine neurons in animal models of PD [19,20]. *Ret* is the receptor of *GDNF* [21]. The dopamine transporter is involved in the reuptake of dopamine into dopaminergic neurons [22]. *Nurr1* is a steroid receptor, and a knockout of its mouse

Table 2: Description of the PD family material. Number of affected and unaffected individuals in each family, mean age at onset and range for affected, and mean age and range for unaffected, as of 1997. In narrow definition PD only individuals with probable PD were assigned as affected. In broad definition PD both individuals with probable and possible PD were assigned as affected.

Family	Narrow definition PD			Broad definition PD			Unaffected		
	N of individuals (total / sampled)	Mean age at onset	Range of age at onset	N of individuals (total / sampled)	Mean age at onset (sampled only)	Range of age at onset (sampled only)	N of unaffected individuals sampled	Mean age	Age range
1	4 / 2	65.8	58–73	9 / 4	69.5	63–73	4	76.8	72–83
2	4 / 3	67.3	49–79	6 / 5	52.4	32–77	9	49.9	24–72
3	4 / 2	55.3	44–77	8 / 3	65.3	44–77	13	56.7	29–85
4	4 / 2	54.3	48–59	6 / 4	55.8	26–85	12	53.7	27–75
5	5 / 3	63.0	48–78	16 / 9	55.8	9–78	16	56.4	41–86
6	4 / 3	24.0	8–35	16 / 3	20.3	8–28	2	29.5	16–43
7	4 / 3	65.8	40–78	14 / 6	42.5	10–78	7	67.7	48–91
8	2 / 2	49.0	15–83	6 / 5	30.0	14–83	10	43.4	23–84
9	3 / 2	59.0	46–76	9 / 3	55.3	46–65	3	55.7	47–73
10	3 / 3	62.3	54–76	9 / 6	59.5	40–79	13	51.7	30–79
11	3 / 3	58.7	39–78	6 / 3	58.7	39–78	8	56.0	46–73
12	2 / 2	66.5	66–67	2 / 2	66.5	66–67	8	68.3	63–74

homologue causes agenesis of dopaminergic neurons [23]. Recently, two mutations in *Nurr1* were found to be segregating with PD in ten families of European descent [24]. *Synphilin-1* interacts with α -synuclein and is also present in Lewy bodies, the neuropathological hallmark of PD [25,26]. With both parametric and non-parametric linkage analysis we found no evidence for linkage to any of these loci. We included a non-parametric approach in which no assumptions about mode of inheritance are made, since the inheritance mode in the present material is not completely ascertained.

Methods

Families

In total 12 families with familial PD, diagnosed at the Movement Disorder clinic at Oregon Health Sciences University, were included in the study. The number of affected and unaffected individuals in each family, age of onset characteristics for affected and age characteristics for unaffected are shown in Table 2. Diagnostic criteria according to the UK Parkinson's Disease Society Brain Bank [27] were used with the exception that family history of PD was not used as an exclusion criterion. Individuals who fulfilled these criteria were classified as probable PD. In addition, individuals who did not fulfill the UK Parkinson's Disease Society Brain Bank criteria but showed at least one cardinal sign (mostly tremor) were classified as possible PD. The majority of families had a segregation pattern that was consistent with an autosomal dominant mode of inheritance. Examples of relationships between affected individuals were son/daughter, sibling, aunt/

uncle, granddaughter/grandson, first cousin and second cousin. In ten families, there were at least three individuals with probable PD. Referring to individuals with both probable and possible PD, there were in total 107 affected individuals. Of these, blood was collected from 53 individuals with the average of 4.4 individuals per family. The largest number of sampled affected individuals in one family was nine (family 5 in Table 2). Previously, the G209A mutation in *α -synuclein* found in the large Greek-American kindred was found to be absent in these families and linkage to chromosome 4q21-23 where this gene is situated was excluded [15]. A subset of the families was also tested for the *PARK3* locus on chromosome 2 [16]. All individuals included in the study signed an informed consent form approved by the Institutional Review Board at the Oregon Health Sciences University in compliance with the Helsinki Declaration.

Statistical power calculation

The statistical power of the family material was assessed by simulations using Simlink version 4.1 [28] under the assumptions of autosomal dominant inheritance with incomplete penetrance (55%) and no phenocopies, no heterogeneity, a disease allele frequency of 0.001 and one marker with four alleles. The simulations were performed assigning individuals who were diagnosed with probable PD as affected in addition to also allowing for those with possible PD to be assigned as affected. We refer to probable PD as narrow definition PD. Probable PD and possible PD taken together is referred to as broad definition PD. For narrow definition PD, the estimated mean maxi-

imum lod score at $\theta = 0$ summarized across all families was 3.75 (standard error 0.046). The lowest mean maximum lod score in an individual family was 0.21 and the highest 0.55. For broad definition PD, the estimated mean maximum lod score at $\theta = 0$ summarized across all families was 7.48 (standard error 0.055), with the lowest value in an individual family being 0.22 and the highest 1.17. Thus, the expected summarized maximum lod scores would reach above 3.0, the commonly used level of statistical significance, for both definitions of the phenotype. Considering both narrow and broad definition PD, families 2, 5 and 11 gave the highest estimated mean maximum lod scores (0.55, 0.46 and 0.55 for narrow definition PD; 0.99, 1.17 and 0.93 for broad definition PD, respectively) and families 1, 6 and 9 gave the lowest (0.21, 0.27 and 0.22 for narrow definition PD; 0.40, 0.22 and 0.35 for broad definition PD, respectively).

Genotyping

Highly polymorphic microsatellite markers were selected for each locus using National Center for Biotechnology Information databases [29]. Markers located in close proximity to the locus or gene of interest were preferentially selected. For those loci where gene information was limited (*PARK3*, *FET1*), the markers that yielded the highest lod scores in previous publications were selected [9,30]. The genetic localization and allele frequencies were determined using publicly available databases [29]. The markers and the genetic maps used are listed in Table 1. The marker D10S141 for the *Ret* locus was an intragenic marker [31] and the only marker selected for this locus. The markers were PCR amplified using standard protocols provided by Research Genetics. The PCR products were separated on an ABI 377 Automatic Sequencer and the genotypes were determined using Genescan™ and GenTyper™ software (Perkin Elmer Applied Biosystems).

Linkage analysis

Two-point parametric linkage analysis was performed with Fastlink version 4.1P [32]. Multipoint linkage analysis was carried out with Genehunter version 2.0 beta [33], which computes both parametric and non-parametric multipoint lod scores. Due to the fact that Genehunter cannot handle large pedigrees without subdividing them, the non-parametric approach was complemented with Simwalk version 2.60, which performs simulated annealing and random walk to compute a location score which is comparable to multipoint lod score [34]. The assumptions for the parametric approach were an autosomal dominant inheritance model with 55% penetrance, no phenocopies, no heterogeneity and a disease allele frequency of 0.001. Allele frequencies were estimated from founders in the families and equal allele frequencies were used for comparison. An affecteds-only and an autosomal recessive model were also applied for the *PARK3* and the

Parkin loci, respectively. All analyses were performed both for narrow definition PD and broad definition PD.

Results

Analysis of narrow definition PD

Parametric linkage analysis

In additional file 1 (Table 3.xls), summarized parametric two-point and multipoint lod scores and non-parametric multipoint lod scores are presented for each marker examined for narrow and broad definition PD. For narrow definition PD two-point lod scores were negative at $\theta = 0$ for all markers examined. At $\theta = 0.1$, two-point lod scores were higher although still negative for all markers except two, the highest value being 0.26 (for marker D2S2113). Parametric multipoint lod scores were negative for all markers and below -2 (the commonly used level for exclusion of linkage) for all markers and loci except *FET1*, for which one of the two markers showed a parametric lod score of -1.50. Equal allele frequencies and allele frequencies estimated from the families yielded similar results. For most of the markers information content as given by Genehunter was above 60%. Information content was above 50% for all markers except DAT1VNTR, D5S492 and D5S657.

In addition to the autosomal dominant model with incomplete penetrance, an affecteds-only model and an autosomal recessive model were applied for the *PARK3* and *Parkin* loci respectively, since these loci were initially identified using these models [5,9]. For five of the six markers covering the *PARK3* locus summarized parametric multipoint lod scores assuming an affecteds-only model were between -2.98 and -2.87. One marker showed a parametric multipoint lod score of -0.73. However, information content decreased significantly from above 70% for the autosomal dominant model to between 20 and 40% for the affecteds-only model. For the *Parkin* locus the autosomal recessive model showed higher parametric lod scores than the autosomal dominant model, although still negative. For the two markers covering the *Parkin* locus summarized parametric multipoint lod scores were -1.40 and -1.46 under the recessive model, compared to -6.00 and -6.33 under the dominant model.

Non-parametric linkage analysis

For three loci (*GDNF*, *BDNF* and *DRD*) summarized non-parametric multipoint lod scores were negative for all covering markers (additional file 1: Table 3.xls). For the other loci non-parametric lod scores were slightly positive although none reached above 1.0. The non-parametric analysis was complemented by Simwalk, which computes a statistic comparable to the non-parametric lod score. The results generated by this approach were consistent with the non-parametric results from Genehunter for all loci except *Parkin*, *BDNF* and *DRD*. For these loci Simwalk

computed higher values for the statistic corresponding to the non-parametric lod score generated by Genehunter, although all values were below 0.8 (data not shown).

Analysis of broad definition PD

When assigning individuals who were diagnosed with possible PD (having one cardinal sign) as affected in addition to those with probable PD, lower summarized two-point lod scores at $\theta = 0$ were observed for all markers except D2S2109, D2DS142, DAT1VNTR, D5S492 and D6S411. Similarly, lower summarized parametric multipoint lod scores were generated at all loci except *Nurr1*, *Synphilin-1* and *Parkin* (markers D2S142, D2S284, D5S492 and D6S411) (additional file 1: Table 3.xls). Slightly higher non-parametric multipoint lod scores were observed for most of the markers, a result that agreed in almost all cases with the Simwalk results. However, for all loci in which non-parametric multipoint lod scores obtained by Genehunter were above 1.0 (*Nurr1*, *FET1*, *Parkin* and *BDNF*), the corresponding statistic generated by Simwalk did not exceed 0.8 (data not shown). For *Nurr1*, *FET1*, *Synphilin-1*, *Parkin* and *Ret*, summarized non-parametric multipoint lod scores were positive for all markers both when narrow and broad definition PD were applied. However, none achieved a level of significant linkage.

Individual pedigree analysis

In additional file 2 (Table 4.xls), parametric and non-parametric multipoint lod scores for narrow and broad definition PD are presented for each family and locus in which both parametric and non-parametric lod scores were positive and either of them exceeded the value of 0.5 for all markers. Most of the families and loci that fulfilled these requirements for narrow definition PD also did so for broad definition PD. These families were family 1 (for the *Nurr1* locus), family 3 (for the *Nurr1* and *Parkin* loci), family 6 (for the *DRD* locus), family 7 (for the *DAT1* locus), family 9 (for the *PARK3* and *FET1* loci) and family 11 (for the *Ret* and *DRD* loci). In the majority of these cases both parametric and non-parametric lod scores were higher for broad definition PD than for narrow definition PD. The highest parametric lod score was observed when broad definition PD was applied in family 11 at the *Ret* locus (1.15; two-point lod score at $\theta = 0$), corresponding to a non-parametric lod score of 1.09. The highest non-parametric multipoint lod score was obtained in family 8 at the *BDNF* locus (2.57), also using broad definition PD, with a corresponding parametric multipoint lod score of 1.05.

Discussion

In these 12 PD families there was no evidence for linkage to any of the loci tested using parametric linkage analysis under a model of autosomal dominant inheritance with

reduced penetrance, as well as non-parametric linkage analysis. When performing parametric linkage analysis it is important to specify both the disease-locus and marker-locus parameters correctly. Generally, multipoint analysis is more sensitive to various types of errors than two-point analysis [35,36]. In two-point analysis misspecification of inheritance mode may result in overestimation of recombination fraction and reduced power to detect linkage, while in multipoint analysis false exclusion of linkage may occur [36]. In addition, genotyping errors may cause false exclusion in multipoint analysis [37] and incorrect allele frequencies and recombination fractions may result in reduced power and/or false positive findings [38]. In the present study we performed both two-point and multipoint analysis, the former being the most robust type of analysis and the latter using the most information. Both when narrow and broad PD were analyzed there were only small differences between two-point parametric lod scores at $\theta = 0$ and multipoint parametric lod scores. At $\theta = 0.1$, differences between two-point and multipoint lod scores were larger, although the scores were still negative for all markers except three. Nevertheless, this fact may indicate possible presence of bias in the parametric multipoint analysis due to errors in specification of the model parameters.

One problem related to the specification of inheritance model is low penetrance. Given the complex phenotype, including only affected individuals in the analysis may be preferable. To compare this approach with the results from the autosomal dominant model with reduced penetrance including all individuals, we performed affecteds-only analysis for the *PARK3* locus, which also initially was identified using this approach [9]. Compared to the autosomal dominant model with incomplete penetrance, multipoint parametric lod scores generated by the affecteds-only model were higher (less negative), indicating a loss of information. Accordingly, information content as given by Genehunter was markedly reduced. Thus, despite the fact that affecteds-only analysis had been preferable, the loss of information content precluded further affecteds-only analyses for the other loci. Since inheritance mode in the families appeared autosomal dominant, it seemed appropriate to perform the analyses under such a model. Using data from a select number of markers we evaluated age-dependent penetrance versus low penetrance for all age groups. The latter model generated somewhat higher (less negative) lod scores, indicating more conservative values, however there were no large differences. Since low penetrance for all age groups imposes fewer restrictions to the model, we subsequently chose to model penetrance in this way.

The parametric linkage analysis was complemented with a non-parametric linkage approach, which has the advan-

tage of not making assumptions about inheritance mode although it is less powerful than parametric linkage analysis. This fact is reflected by the data in the sense that the non-parametric multipoint lod scores often approached zero. Generally, the non-parametric analysis generated higher lod scores than the parametric, a fact that was most apparent when comparing multipoint non-parametric lod scores to two-point lod scores at $\theta = 0$ and multipoint parametric lod scores, respectively. When comparing multipoint non-parametric lod scores to two-point lod scores at $\theta = 0.1$, differences were smaller. The reason for the discrepancy is most likely that in parametric analysis assumptions are made about mode of inheritance, imposing restrictions to the data structure. Again, multipoint parametric analysis is more sensitive to modeling errors than two-point analysis, with the possible effect of inducing false exclusions [35,36]. In summary, although the multipoint parametric results indicated exclusion of linkage, our sample contained too few affected individuals in order to draw definite conclusions from the non-parametric analysis. Thus, we are less inclined to say that linkage is excluded based on the non-parametric results.

One fact that might reduce our possibility to demonstrate linkage is heterogeneity. At present there is substantial evidence that several genes contribute to PD. Unfortunately, we were unable to investigate heterogeneity in this study due to the small sample size. However, some families demonstrated positive lod scores for a few loci, indicating that heterogeneity might exist despite our selection of Caucasian families of European descent from a limited geographical area.

Conclusions

The etiology of PD is considered to be complex, involving several genetic factors as well as potential interactions between genetic and environmental factors [1]. We conclude that using both parametric and non-parametric linkage analyses there was no evidence for linkage to PD in the families included in this study. Although linkage was excluded for the majority of loci under an autosomal dominant model with incomplete penetrance, we could not exclude linkage using non-parametric methods. The fact that none of the loci tested showed negative lod scores in all families demonstrates the possibility that some of them are of relevance to individual families. Alternatively, other loci, known or yet unknown, may be associated with PD in these families.

Competing interests

None declared.

Authors' contributions

KW participated in the design of the study and the genotyping, performed the linkage analyses and drafted the manuscript. CEB participated in the design of the study and the linkage analyses. LW participated in the genotyping. HP was responsible for the collection of blood samples. MS conceived of the study and participated in its design and coordination. All authors read and approved the manuscript.

Additional material

Additional File 1

Table 3. Two-point and multipoint parametric lod scores (lod) and non-parametric multipoint lod scores (NPL) for each marker. Summarized lod and NPL are shown for narrow and broad definition PD. Two-point lod scores were generated by Fastlink [32] and multipoint lod scores by Genehunter [33]. In narrow definition PD only individuals with probable PD were assigned as affected, while in broad definition PD, individuals with possible PD were assigned as affected in addition to individuals with probable PD. Since only one marker was used for the Ret locus, multipoint parametric lod score is not shown.

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Additional File 2

Table 4. Parametric (lod) and non-parametric (NPL) multipoint lod scores in individual families. Lod and NPL for narrow and broad definition PD for each family and locus in which both lod and NPL were positive and either of them exceeded the value of 0.5 for all markers. For the Ret locus, two-point parametric lod score is shown instead of lod since only one marker was used. The GDNF locus is omitted from the table since lod and NPL for this locus did not reach the required values in any families.

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