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Fibroblast Growth Factor 20 Polymorphisms and Haplotypes Strongly Influence Risk of Parkinson Disease

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The pathogenic process responsible for the loss of dopaminergic neurons within the substantia nigra of patients with Parkinson disease (PD) is poorly understood. Current research supports the involvement of fibroblast growth factor (FGF20) in the survival of dopaminergic cells. FGF20 is a neurotrophic factor that is preferentially expressed within the substantia nigra of rat brain. The human homologue has been mapped to 8p21.3-8p22, which is within an area of PD linkage revealed through our published genomic screen. To test whether FGF20 influences risk of PD, we genotyped five single-nucleotide polymorphisms (SNPs) lying within the FGF20 gene, in a large family study. We analyzed our sample (644 families) through use of the pedigree disequilibrium test (PDT), the genotype PDT, the multilocus-genotype PDT, and the family-based association test to assess association between risk of PD and alleles, genotypes, multilocus genotypes, and haplotypes. We discovered a highly significant association of PD with one intronic SNP, rs1989754 ($P = .0006$), and two SNPs, rs1721100 ($P = .02$) and ss20399075 ($P = .0008$), located in the 3′ regulatory region in our overall sample. Furthermore, we detected a haplotype (A-G-C-C-T) that is positively associated with risk of PD ($P = .0003$), whereas a second haplotype (A-G-G-G-C) was found to be negatively associated with risk of PD ($P = .0009$). Our results strongly support FGF20 as a risk factor for PD.

Introduction

Parkinson disease (PD [MIM 168600]) is a late-onset neurodegenerative disorder that typically develops in the 5th or 6th decade of life and affects more than one million Americans. The inability to control movement in patients with PD results from severe loss of dopaminergic neurons within the substantia nigra (SN). The mechanism causing dopaminergic cell death in PD has not been defined, although it is generally accepted that environmental and genetic sources act together in the disease cascade.

In familial PD, 11 loci, including 5 known genes (parkin, α-synuclein, UCH-L1, DJ-1, and NR4A2) have been identified as causative for the Mendelian patterns of PD (see Dekker 2003). Several genomic screens have demonstrated areas of linkage that may harbor important genetic risk factors for the common, late-onset form of PD (Scott et al. 2001; Pankratz et al. 2003). The strongest linkage result overall in our study was obtained on chromosome 8p (LOD score 2.2 at D8S520) (Scott et al. 2001). In an attempt to identify physical and biological candidate genes in this region that influence risk of PD, we chose to examine fibroblast growth factor 20 (FGF20), since it is located ~6.2 Mb from peak marker D8S520 on 8p21.3-p22 (Kirikoshi et al. 2000), and its encoded protein exerts strong neurotrophic properties within brain tissue (Jeffers et al. 2001).

FGF20 is a member of the highly conserved growth factor polypeptides that regulate central nervous development and function (Jeffers et al. 2001; Dono 2003). Specifically, FGF20 is a neurotrophic factor that is preferentially expressed within dopaminergic neurons of the midbrain SN within rat brain (Ohmachi et al. 2000) and is also expressed in human cerebellum and SN tissue (Jeffers et al. 2001; Hauser et al. 2003). Evidence suggests that expression of FGF20 significantly enhances the survival of rat midbrain dopaminergic neurons and that this activity operates by way of binding to the FGF receptor FGFR-1c (Ohmachi et al. 2003). Furthermore, a recent study demonstrated that FGF2, closely related to FGF20, added to cultured rat ventral midbrain dopaminergic neurons induces upregulation of α-synuclein (Rideout et al. 2003). Therefore, FGF20 presents as a strong biological and positional candidate for investigation of PD susceptibility.

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Material and Methods

Samples

Affected individuals and family members were collected by the Duke Center for Human Genetics (DCHG) Morris K. Udall Parkinson Disease Research Center of Excellence family ascertainment core and the 13 centers of the Parkinson Disease Genetics Collaboration. A standard clinical evaluation involves a neurological examination, including assessment by use of the Unified Parkinson's Disease Rating Scale (Fahn et al. 1987). Affected individuals possessed at least two cardinal signs of PD (resting tremor, bradykinesia, and rigidity). Rigorous clinical assessment was performed by all participating clinicians to provide a clear diagnosis of PD and to exclude any individuals that displayed atypical features of parkinsonism (Scott et al. 2001). Unaffected participants demonstrated no signs of the disease, and "unclear" participants showed only one cardinal sign and/or atypical features. To maintain diagnostic consistency across participating clinics, a clinical adjudication board consisting of a board-certified neurologist with fellowship training in movement disorders (B.L.S.), a dually board-certified neurologist and Ph.D. medical geneticist (J.M.V.), and a certified physician assistant (J.M.S.) reviewed the clinical data for all participants. Parkin mutation carriers were excluded from this study. All participants signed informed consents prior to blood and data collection. Study protocols and consent forms were approved by institutional review boards at each participating center.

The families ($N = 644$) used in this association study were drawn from two data sets ascertained for genetic studies of PD. The first data set consists of singleton families ($N = 355$), characterized by having only one sampled affected individual, with any number of unaffected family members. The second data set consists of multiplex families ($N = 289$), comprising nuclear families (families with at least two sampled affected siblings and any number of unaffected individuals) or extended pedigrees (families with at least two sampled affected individuals who are not siblings or a parent-child pair, with any number of unaffected individuals). For this study, all subjects analyzed were white.

DNA Extraction and Genotyping

DNA samples were prepared and stored by the DCHG DNA bank Core. Genomic DNA was extracted from whole blood through use of the PureGene system (Gentra Systems) with the Autopure LS. Primers and probes were designed using the Primer Express 2.0 program (Applied Biosystems). PCR amplification was performed in 5-μl reactions (3 ng dried DNA, 1 × TaqMan universal PCR master mix from Applied Biosystems, 900 nM of each primer, and 200 nM of each probe) using GeneAmp PCR system 9700 thermocyclers (Applied Biosystems) for a 40-cycle program (50°C for 2 min; 95°C for 10 min; 40 × [95°C for 15 s, 60°C for 1 min]). The fluorescence generated during the PCR amplification was detected using the ABI Prism 7900HT sequence detection system and was analyzed with SDS software (Applied Biosystems). Stringent quality control measures were taken to ensure data consistency. Internal controls consisted of 24 duplicated individuals per 384-well plate. In addition, two samples from CEPH were plated eight times per plate to identify any Mendelian inconsistencies. All technicians were blinded to these internal controls. Quality control samples were compared in the Duke Center for Human Genetics Data Coordinating Center. Data were stored and managed by the PEDIGENE system (Haynes et al. 1995). To pass quality control, data plates had to meet with 100% matching for quality control samples and at least 95% plate efficiency.

Statistical Analysis

A single affected and unaffected individual were selected at random from each family, for tests of Hardy-Weinberg disequilibrium. These tests were conducted using Genetic Data Analysis software, applying a permutation test with 3,200 permutations to estimate each P value (Lewis Lab Software Web site). Two measures of linkage disequilibrium (LD), squared correlation coefficient (r^2) and Lewontin's standardized disequilibrium coefficient (D'), were computed between pairs of SNPs through use of the Graphical Overview of Linkage Disequilibrium (GOLD) software package (Abecasis and Cookson 2000). Single-locus association analysis was performed in the families through use of the pedigree disequilibrium test (PDT) (Martin et al. 2000). We used the PDTsum version of the statistic to compare allele frequencies between affected individuals and their unaffected parents (when available) or siblings within families (Martin et al. 2001). Similarly, single-locus genotype frequencies were compared between affected individuals and their parents or unaffected siblings within pedigrees through use of the genotype PDT (geno-PDT) (Martin et al. 2003). The multilocus geno-PDT was used to test for association with disease, using genotypes jointly at more than one locus (E.R.M., unpublished data). This test can be used to dissect possible interactive effects observed between alleles at multiple loci. Haplotype analysis was conducted using the family-based association test (FBAT) (Horvath et al. 2004). Haplotypes with frequencies <1% were not included in the analysis. The empirical variance option of the FBAT program was used to ensure validity as a test of association in this linked region.

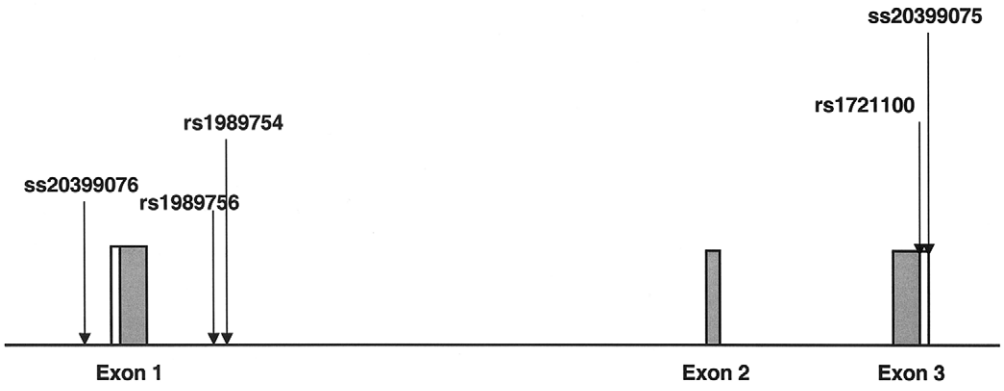

Figure 1 Gene structure of FGF20. Exons are denoted by blocks; coding regions are shown in gray, and UTRs are shown in white. Locations of SNPs are indicated by arrows.

Bioinformatics

Sequence alignment of human and mouse FGF20 3′ UTR (GenBank accession numbers NM_019851 and NM_030610, respectively) was performed using ClustalW multiple sequence alignment software (Pearson and Lipman 1988; Clustal W Web site). The alignment was imported into GeneDoc version 2.6 for editing and shading (Nicholas et al. 1997; GeneDoc Home Page).

Results

To test the possible influence of FGF20 on risk of PD, we first sequenced four pools, each containing five unaffected individuals, to screen exons and UTRs for polymorphisms (denoted throughout the article by their dbSNP rs and ss numbers). No sequence variations were discovered within exons. However, we discovered novel polymorphisms within sequence upstream from exon 1 (ss20399076) and a 3′ UTR (ss20399075) SNP. We also verified one 3′ UTR SNP (rs1721100) and two intronic SNPs (rs1989754 and rs1989756) (fig. 1). A total of 644 pedigrees including 3,655 individuals were genotyped in this study. No mismatches of internal controls were reported, and average plate efficiency was 98%.

All five SNPs tested showed no evidence for deviation from Hardy-Weinberg equilibrium (data not shown). The LD analyses based on r^2 revealed strong LD between SNPs rs1989754 and ss20399076 and moderate levels of LD between SNPs rs1721100 and rs1989754 and between rs1721100 and ss20399075 in the affected individuals (table 1). Values of D' were large for most SNP pairs, suggesting that there has been little historic recombination in the region over time. Levels of LD were similar in the unaffected set (data not shown).

Table 2 shows single-locus results from the PDT. Single-locus tests demonstrated strong evidence of association of an intronic SNP, rs1989754 ($P = .0006$; C allele positively associated), and a novel 3′ UTR SNP, ss20399075 ($P = .0008$, T allele positively associated), with risk of PD in the overall sample. Weaker evidence of association was found between a second SNP located within the 3′ UTR, rs1721100 ($P = .02$; C allele positively associated), and risk of PD (table 2). Tests based on individual genotypes demonstrated that genotypes rs1989754CC ($P = .006$) and ss20399075CT ($P = .0004$) increase risk. Global tests for genotype association also showed significant results for rs1989754 and ss20399075 (table 3).

The strongest associations were found with markers rs1989754 and ss20399075; however, these markers are in strong LD ($D' = 0.96$), suggesting that little recombination has occurred between these SNPs over

Table 1

Measures of Linkage Disequilibrium between FGF20 SNPs

	ss20399076	rs1989756	rs1989754	rs1721100	ss20399075
ss20399076	…	.086	.652	.045	.097
rs1989756	1	…	.058	.018	.009
rs1989754	.986	1	…	.268	.073
rs1721100	.315	.724	.943	…	.259
ss20399075	.968	1	.961	1	…

NOTE.—r^2 values are given above the diagonal, and D' values are given below the diagonal.

Table 2

Allele Frequencies and *P* Values of Single-Locus Association Analysis

SNP Allele	Frequency among Families[a] (N = 188)		Frequency in Discordant Siblings[b]		PDT *P* Value
	Parental Transmissions[c]	Parental Nontransmissions[d]	Affected (N = 553)	Unaffected (N = 716)	
ss20399076A	.476	.488	.514	.524	.1616
rs1989756A	.077	.099	.080	.073	.3942
rs1989754C	.617	.553	.597	.561	.0006
rs1721100C	.323	.204	.307	.289	.0196
ss20399075T	.114	.057	.107	.089	.0008

[a] Computed frequencies in families including parental and affected offspring genotypes.
[b] Computed frequencies from all affected and unaffected siblings.
[c] Frequencies among alleles transmitted from parents to affected offspring.
[d] Frequencies among alleles not transmitted from parents to affected offspring.

time. This high degree of LD complicates the interpretation of the data as to whether independent or interactive effects of these markers are being observed. To test for independent effects of SNPs rs1989754 and ss20399075, we removed all families carrying the positively associated ss20399075T allele from the data set. The PDT was used to analyze SNP rs1989754 in the remaining 316 families, consisting of 63 triads and 693 discordant sib pairs. This stratified analysis revealed no significant evidence of association for increased risk of PD at rs1989754 when tested without the ss20399075T-carrying families (P = .09). This suggests that, if rs1989754C has an effect on PD risk, it is an interactive effect that occurs only the presence of the T allele at ss20399075. The opposite stratified analysis, removing all families carrying the high-frequency rs1989754C allele, was not performed, since a large proportion of families would have to have been removed, thus reducing power in the analysis. The results of the stratified analysis are further supported by the joint (multilocus and haplotype) analysis of the SNPs.

FBAT was used to search for association of PD with haplotypes that include the five genotyped SNPs. This method estimated 18 possible haplotypes, but only 5 haplotypes were found at frequencies >1% in our sample. We observed that haplotype A-G-C-C-T is positively associated with risk of PD (P = .0003), whereas haplotype A-G-G-G-C is negatively associated with risk (P = .0009) (table 4). The global test that simultaneously tests whether any haplotype is associated with disease also demonstrated that the haplotype effect is highly significant (P = .002). The combination of alleles within haplotypes is congruent with the single-locus results, since the A-G-C-C-T haplotype carries risk alleles ss20399075T and rs1989754C. Importantly, the C allele at rs1989754 occurs on haplotypes with both the C and T alleles at the ss20399075 locus, but only the haplotype carrying ss20399075T shows significant positive association with PD risk.

Similarly, analysis of multilocus genotypes showed significant positive association only with carriers of ss20399075T (table 5). In this genotypic analysis, however, we found that ss20399075CT was positively associated only in individuals homozygous for CC at rs1989754. Despite the fact that a comparable number of informative families were heterozygous for GC-CT, this multilocus genotype showed no evidence for association. This suggests a possible interactive effect between the rs1989754CC and ss20399075CT genotypes. However, formal tests for interaction were not performed, because of the diverse family structures and high degree of LD between the SNPs.

Discussion

FGF20 and its family members are expressed in both embryonic and adult tissues, suggesting that they are critical factors in brain development and cell homeostasis (Dono 2003). Studies have shown that FGF20 acts as a neurotrophic factor in dopaminergic cells, substantially enhancing their survival in culture (Ohmachi et al. 2000). This effect is mediated by the binding of FGF20 to its receptor, FGFR-1c, which activates the mitogen-activated protein kinase pathway, resulting in the phosphorylation of extracellular regulated kinase (Ohmachi et al. 2003). Given the role that FGF20 plays in the

Table 3

Genotype PDT Results (Based on Global Test) for FGF20 SNPs

SNP	GenoPDT *P* Value
ss20399076	.4077
rs1989756	.4355
rs1989754	.0056
rs1721100	.0713
ss20399075	.0004

Table 4

Haplotype Analysis of FGF20

Base at SNP					No. of Families	Frequency	Z[a]	P Value[b]
ss20399076	rs1989756	rs1989754	rs1721100	ss20399075				
A	G	G	G	C	228	.42	−3.318	.0009
G	G	C	G	C	205	.21	.294	NS
G	G	C	C	C	179	.19	.691	NS
A	G	C	C	T	80	.08	3.587	.0003
G	A	C	G	C	89	.06	.465	NS

[a] Z = normal statistic.
[b] NS = not significant; global test P = .002.

survival of dopaminergic neurons, FGF20 presents an excellent candidate susceptibility gene for PD risk.

We demonstrated that one intronic SNP and two SNPs located within the 3′ UTR of FGF20 are significantly associated with PD risk. Furthermore, haplotype A-G-C-C-T, which carries the positively associated alleles of each of these SNPs, significantly increases risk of PD. Stratified analysis and haplotype analysis suggest that rs1989754C does not have an independent effect on risk; however, its effect is observed in the presence of ss20399075T. Tests for interaction between alleles at both loci cannot be performed, since the ss20399075T allele occurs exclusively with rs1989754C in our data set; ss20399075T was not observed with the rs1989754G allele.

Taken together, the analyses suggest three possible interpretations for the observed association of FGF20 polymorphisms with PD risk. First, the association may be caused by the ss20399075T allele alone. Given the location of ss20399075, we suggest that this polymorphism may disrupt a regulatory binding sequence within in the 3′ UTR and alter message expression. Therefore, if an RNA-binding protein is unable to bind to the regulatory site of the 3′ UTR sequence, the FGF20 transcript stability, translation, or transport to subcellular locations may be compromised (Conne et al. 2000).

The FGF20 3′ UTR sequence is largely conserved between human and mouse (fig. 2). SNP rs1721100 lies within a highly conserved segment of sequence but is not homologous to mouse, whereas the C allele of SNP ss20399075 is conserved between mouse and human. It is possible that the conservation of this region may be important in message regulation and that the ss20399075C/T change disrupts a binding site or creates a conformational change in the sequence.

A second possible interpretation of our results is that the association between ss20399075T and risk is enhanced by rs1989754C. The haplotype analysis indicates that A-G-C-C-T, which carries both risk alleles, is strongly associated with PD risk. This analysis, as well as the multilocus genotype test, suggests that these two polymorphisms may be acting together to influence risk. It is possible that both SNPs act in concert to regulate transcription and expression of FGF20, although they are located in two different gene regions. Alternatively, these associated SNPs may be in LD with an untested polymorphism, occurring on haplotype A-G-C-C-T, that is associated with PD risk. To test these possibilities, molecular studies are needed to verify the effects of these polymorphisms on the expression level of FGF20.

We have conducted several statistical tests and have

Table 5

Multilocus Genotype PDT Analysis

Genotype		Frequency among Families (N = 176)		Frequency in Discordant Siblings			
rs1989754	ss20399075	Parental Transmissions	Parental Nontransmissions	Affected (N = 535)	Unaffected (N = 694)	Z[a]	P Value[b]
GG	CC	.051	.073	.166	.194	−2.480	.013
GG	CT	.000	.000	.001	.001	NA	NA
GC	CC	.232	.267	.394	.412	−.912	.362
GC	CT	.039	.022	.074	.072	.000	.946
CC	CC	.113	.102	.237	.224	.697	.486
CC	CT	.051	.034	.117	.089	2.785	.005
CC	TT	.011	.000	.007	.005	.810	.423

Note.—NA = not analyzed.
[a] Z = normal statistic.
[b] Global test P = .03.

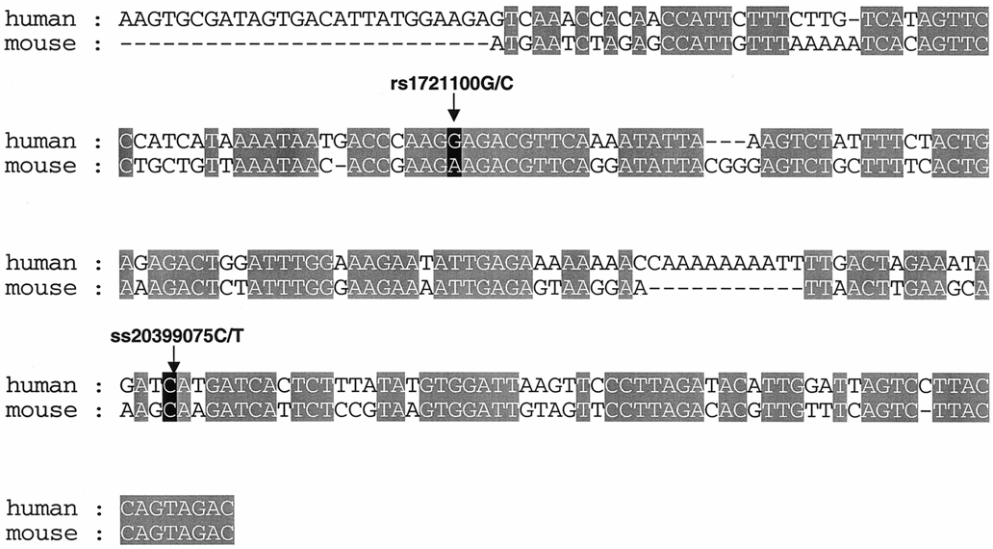

Figure 2 Sequence alignment of human and mouse 3′ UTR sequences. Sequence homology is indicated by gray shading, dashes represent insertions, and black boxes illustrate SNP locations.

not attempted to correct for multiple testing in this presentation. It is noteworthy that, even with a standard Bonferroni correction for multiple tests at the five SNPs, the single-locus *P* values for rs1989754 and ss20399075 are still significant, with an experimentwise significance of .05. A less conservative approach is to use the false discovery rate (Benjamini and Hochberg 1995). With this adjustment, under the assumption that no SNP is associated with disease ($\alpha = 0.05$), polymorphisms rs1989754, rs171100, and ss20399075 are all still considered significant. This further supports the significance of our findings.

Studies have shown clearly that FGF20 is critical in the survival of dopaminergic neurons within the substantia nigra; however, the mechanistic process of this protective action and its regulation has not yet been elucidated. A recent study has shown that the protective effect of the related FGF2 polypeptide acts with glial-cell-line–derived neurotrophic factor (GDNF) to promote repair of lesioned hippocampal cells (Lenhard et al. 2002). GDNF is also a key neurotrophic factor that is important in the maintenance and development of dopaminergic neurons (Lin et al. 1993). Expression levels of FGF20 may be vital to a signaling cascade involved in the repair of damaged dopaminergic neurons. We have demonstrated that polymorphisms in FGF20 are strongly associated with increased risk of PD, as observed in parental transmission of alleles to affected offspring and transmissions of alleles in phenotypically discordant sib pairs. We have also demonstrated that an allelic combination in a haplotype significantly influences PD susceptibility. We suggest that the associated polymorphisms may affect regulation of FGF20 expression and thereby influence PD pathogenesis. Molecular studies are under way to verify the causative role of ss20399075 and rs1989754 SNPs and whether these polymorphisms impact PD risk independently or collectively.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Clustal W, http://clustalw.genome.ad.jp/

dbSNP Home Page, http://www.ncbi.nlm.nih.gov/SNP/ (for SNPs ss20399076, ss20399075, rs1721100, rs1989754, and rs1989756)

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for human FGF20 [accession number NM_019851] and *Mus musculus* FGF20 [accession number NM_030610])

GeneDoc Home Page, http://www.psc.edu/biomed/genedoc/

Lewis Lab Software, http://lewis.eeb.uconn.edu/lewishome/software.html (for Genetic Data Analysis: computer program for analysis of genetic data)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PD)

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