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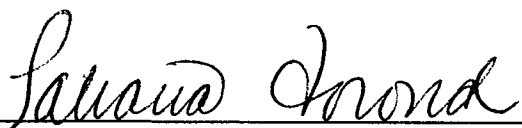
STUDY TO IDENTIFY SUSCEPTIBILITY GENES FOR PARKINSON DISEASE

Nathan Daniel Pankratz


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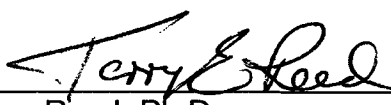


Tatiana Foroud, Ph.D. – Chair
Department of Medical and Molecular Genetics



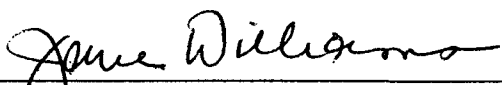
P. Michael Conneally, Ph.D.
Department of Medical and Molecular Genetics

Doctoral Committee



Terry Reed, Ph.D.
Department of Medical and Molecular Genetics

Oral Examination:
October 2, 2003



Jane Williams, Ph.D.
Department of Psychology

STUDY TO IDENTIFY SUSCEPTIBILITY GENES FOR PARKINSON DISEASE

Parkinson disease (PD) is the second most common neurodegenerative disorder and has wide variability in the age of disease onset. A sample of 362 multiplex PD families, each ascertained through an affected sibling pair was rigorously evaluated and study subjects were classified as having verified PD (n=542) or nonverified PD (n=238). Two models of affection status were considered Model I included only those individuals with a more stringent diagnosis of verified PD, while Model II included all individuals as affected. Those families with either an early age of onset (≤ 50 years) or a positive LOD score on chromosome 6q with a marker in the known PD susceptibility gene, *parkin*, were screened for point mutations and exon deletions/ duplications. A genome screen was completed to identify additional PD susceptibility genes. Evidence of linkage was found to chromosomes 2 (LOD=3.4, Model II), 10 (LOD=2.1, Model II), 14 (LOD=2.1, Model II) and X (LOD=2.8, Model II). To further delineate the chromosome 2q linkage, we have performed analyses using only those pedigrees with the strongest family history of PD. Linkage analyses in this subset of 65 pedigrees generated a LOD score of 5.1, obtained using an autosomal dominant model of disease transmission. This result strongly suggests that variation in a gene on chromosome 2q36-37 contributes to PD susceptibility. Analyses also detected gene-by-gene interactions between the *parkin* locus and a region on chromosome 14 and between the regions on chromosomes 2q and 10. Since different genes may contribute to disease susceptibility and to age of onset of disease, we performed a genome screen to identify genes influencing age of

onset. Significant evidence of linkage was observed to chromosome 2p near the PARK3 locus (LOD = 4.8), similar to a previous report. Importantly, this region is distinct from the chromosomal region identified when analyses were performed to identify PD susceptibility genes. These data suggest that variation in PARK3 and the locus on chromosome 2q36-37 may be major factors in the development of PD.

Research Committee Chair:

Tatiana Foroud, Ph.D.
Department of Medical and Molecular Genetics
Indiana University, Indianapolis

Table of Contents

Chapter I	General Introduction	1
	Clinical Features and Findings in PD	2
	Etiology of PD	4
	Genetic Contribution to PD	7
	Genes Known to Cause PD	9
	Pathogenesis of PD	15
	Approaches to Identifying Disease Genes	19
	Determining Significance in Linkage Studies	21
	Association Studies with PD	23
	Age at Onset	25
	Statement of Purpose	26
Chapter II	Genome Screen	29
	<i>Genome Screen to Identify Susceptibility Genes for Parkinson Disease in a Sample without parkin Mutations</i>	
	Subjects and Methods	29
	Subjects	29
	<i>parkin</i> Screening	31
	Genotyping	32
	Statistical Analyses	33
	Results	35
	Discussion	38
Chapter III	Chromosome 2q	48
	<i>Significant Linkage of Parkinson Disease to Chromosome 2q36-37</i>	
	Subjects and Methods	48
	Subjects	48
	<i>parkin</i> Screening	49
	Statistical Analyses	50
	Results and Conclusions	51

Chapter IV Replication and Epistasis	54
<i>Genome-Wide Linkage Analysis and Evidence of Gene-by-Gene Interactions in a Sample of 362 Multiplex Parkinson Disease Families</i>	
Subjects and Methods	55
Subjects	55
<i>parkin</i> Screening	55
Statistical Analyses	56
Tau Screening	57
Results	58
Genome Screen	59
Analyses of <i>parkin</i> Positive Families	60
Analyses after Stratification by the Presence or Absence of a Strong Family History of PD	61
Discussion	62
Chapter V Candidate Gene	68
<i>Evaluation of the Role of <i>Nurr1</i> in a Large Sample of Familial Parkinson Disease</i>	
Subjects and Methods	69
Subjects	69
Molecular Analysis	70
Statistical Analyses	71
Results	73
Discussion	76
Chapter VI Age at Onset Genome Screen	80
<i>Genes Influencing Age of Onset of Parkinson Disease: Replication of the <i>PARK3</i> Locus and Identification of Additional Novel Loci</i>	
Subjects and Methods	80
Subjects	80
<i>parkin</i> Screening	81
Statistical Analysis of the Age of Onset Phenotype	81
Results	82
Sample	82
Analysis of Age at Onset Data	82
Genome Screen	83
Discussion	84
Chapter VII - Summary	89
References	95
Curriculum Vitae	