STUDY TO IDENTIFY SUSCEPTIBILITY GENES FOR PARKINSON DISEASE

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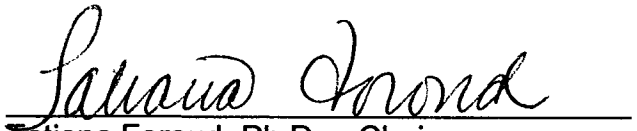
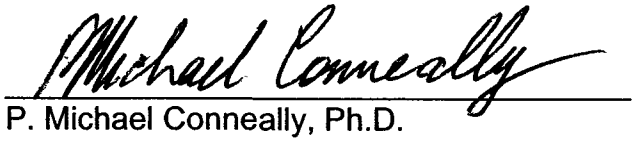


Tatiana Foroud, Ph.D. – Chair
Department of Medical and Molecular Genetics



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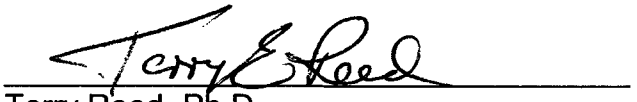

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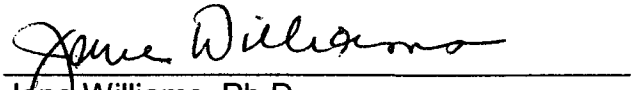
Oral Examination:
October 2, 2003



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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 ($\leq$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.

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