

Dr. Connie Marras
Morton and Gloria Shulman
Movement Disorders Centre
Toronto Western Hospital
399 Bathurst Street
Toronto, Ontario
M5T 2S8

April 14, 2005

Grant Adjudication Committee
Parkinson Study Group research/mentorship grants for new investigators

Dear Committee members,

I am pleased to submit my application for the Research/Mentorship Grant program sponsored by the Parkinson Study Group. The proposed study, "A family study fo LRRK2 mutations: Establishing evaluation and screening methods" will constitute important pilot and preparatory work leading to a longitudinal study of two large families with mutations in the LRRK2 gene causing autosomal dominantly inherited Parkinson's disease. Under the mentorship of Dr. Anthony Lang this project and mentorship year will prepare me to lead the longitudinal family study. We believe that this longitudinal study will not only provide valuable insights into this important form of familial Parkinson's disease but also provide an unprecedented opportunity to study 'biomarkers' of premotor state of Parkinson's disease.

The text of the supporting letters from my proposed mentor and the insitutional representative are provided without signatures in this electronic version; the original signed copies will be provided in hard copy if requested.

Thank you in advance for your consideration of this application.

Yours sincerely,

Connie Marras MD, FRCP(C)

Department of Health and Human Services Public Health Services <h2 style="text-align: center;">Grant Application</h2> <p style="text-align: center;"><i>Do not exceed character length restrictions indicated.</i></p>		LEAVE BLANK—FOR PHS USE ONLY.				
		Type	Activity	Number		
		Review Group		Formerly		
		Council/Board (Month, Year)		Date Received		
1. TITLE OF PROJECT (<i>Do not exceed 81 characters, including spaces and punctuation.</i>) A family study of LRRK2 mutations: Establishing evaluation and screening methods						
2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <i>(If "Yes," state number and title)</i> Number: Title: PSG Mentorship Grant in Patient-Oriented Research						
3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR			New Investigator <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes			
3a. NAME (Last, first, middle) Marras, Connie		3b. DEGREE(S) MD		3h. eRA Commons User Name		
3c. POSITION TITLE Clinical Fellow		3d. MAILING ADDRESS (<i>Street, city, state, zip code</i>) Toronto Western Hospital 7 McL 399 Bathurst Street Toronto, ON Canada M5T 2S8				
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Neurology						
3f. MAJOR SUBDIVISION Movement Disorders						
3g. TELEPHONE AND FAX (<i>Area code, number and extension</i>) TEL: 416-603-6422 FAX: 416-603-5004		E-MAIL ADDRESS: connie.marras@utoronto.ca				
4. HUMAN SUBJECTS RESEARCH <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes		4b. Human Subjects Assurance No.		5. VERTEBRATE ANIMALS <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes		
4a. Research Exempt <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes		4c. Clinical Trial <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes		4d. NIH-defined Phase III Clinical Trial <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes		
If "Yes," Exemption No.		5a. If "Yes," IACUC approval Date		5b. Animal welfare assurance no.		
6. DATES OF PROPOSED PERIOD OF SUPPORT (<i>month, day, year—MM/DD/YY</i>) From July 1, 2005 Through June 30, 2006		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT		
		7a. Direct Costs (\$) \$50,000		7b. Total Costs (\$) \$50,000		
				8a. Direct Costs (\$) \$50,000		
				8b. Total Costs (\$) \$50,000		
9. APPLICANT ORGANIZATION Name Toronto Western Hospital Address 399 Bathurst Street Toronto, ON M5T 2S8 CANADA			10. TYPE OF ORGANIZATION Public: → <input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Local Private: → <input type="checkbox"/> Private Nonprofit For-profit: → <input type="checkbox"/> General <input type="checkbox"/> Small Business <input type="checkbox"/> Woman-owned <input type="checkbox"/> Socially and Economically Disadvantaged			
			11. ENTITY IDENTIFICATION NUMBER DUNS NO. Cong. District			
12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE Name Christopher Adams Title Manager, Research Financial Services Address Hydro Building 8th floor Room 42 800 University Avenue Toronto, ON Canada M5G 1X8 Tel: 416-946-4501 ext 2372 FAX: 416-946-2098 E-Mail:			13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION Name Justine Jackson Title Executive Director, Operations, UHN Address Toronto Western Hospital, 1-McL 399 Bathurst St Toronto, ON Canada M5T 2S8 Tel: 416-603-5065 FAX: 416-603-5122 E-Mail: Justine.jackson@uhn.on.ca			
14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.			SIGNATURE OF PI/PP NAMED IN 3a. <i>(In ink. "Per" signature not acceptable.)</i>		DATE	

15. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.	SIGNATURE OF OFFICIAL NAMED IN 13. <i>(In ink. "Per" signature not acceptable.)</i>	DATE
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Principal Investigator/Program Director (Last, First, Middle): **Marras, Connie**

DESCRIPTION: See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to **public** health. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The long-term objective of the mentored year is to provide Dr. Marras with the skills to independently plan and conduct family studies to advance our knowledge of genetic causes of parkinsonism. The scientific objective is to perform important pilot work for a longitudinal evaluation of two large families with multiple affected members carrying mutations in the LRRK2 gene. The specific aims of this pilot study are to 1. Contact all living family members for willingness to participate in in-person evaluations, 2. Determine the content of in-person evaluations and train study personnel and 3. To determine the sensitivity and specificity of two telephone screening interviews for early symptoms of parkinsonism. This will provide the groundwork for a longitudinal study of mutation carriers, including asymptomatic individuals at high risk for developing Parkinson's disease. Using the methods established in this pilot project we will follow unaffected carriers longitudinally for the development of symptoms using a combination of telephone contact and in-person evaluations.

Dr. Marras is a neurologist completing fellowship training in movement disorders and epidemiology in June, 2005. Dr. Marras' long-term career goal is to establish a program of observational studies in Parkinson's disease and other movement disorders at the Toronto Western Hospital Movement Disorders Centre. Previous training has not included family study methods. Given the rapid evolution of knowledge of genetic forms of parkinsonism, well-conducted family studies are expected to be an essential part of epidemiological study in centres with large clinic populations such as the Toronto Western Hospital.

Relevance: The mutations present in these two families have been estimated to account for at least 5% of cases familial Parkinson's disease in various ethnic groups, which makes this much more common than any other genetic mutations known to cause Parkinson's disease. A well-characterized at-risk population will provide an invaluable opportunity to define the clinical evolution of this form of parkinsonism, investigate whether specific environmental or other genetic factors determine whether or not an individual will become affected, and assess laboratory and radiological tests for their ability to predict who will become affected.

PERFORMANCE SITE(S) (organization, city, state)

Movement Disorders Centre, Toronto Western Hospital, Toronto, Ontario, Canada.

Principal Investigator/Program Director (Last, First, Middle): **Marras, Connie**

KEY PERSONNEL. See instructions. Use continuation pages as needed to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Marras, Connie		Toronto Western Hosp	Principal Investigator
Lang, Anthony E		Toronto Western Hosp	co-Principal Investigator

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
Rogaeva, Ekaterina	Centre for Research in	Consultant

Human Embryonic Stem Cells No Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: <http://stemcells.nih.gov/registry/index.asp>. Use continuation pages as needed.

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Disclosure Permission Statement. Applicable to SBIR/STTR Only. See SBIR/STTR instructions. Yes No

Use this substitute page for the Table of Contents of Research Career Development Awards. Type the name of the candidate at the top of each printed page and each continuation page.

**RESEARCH CAREER DEVELOPMENT AWARD
TABLE OF CONTENTS
(Substitute Page)**

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Letters of Reference* (attach unopened references to the Face Page)

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Checklist

Appendix (Five collated sets. No page numbering necessary.)

Check if Appendix is included

Number of publications and manuscripts accepted for publication (not to exceed 5) _____

List of Key Items: _____

Note: Font and margin requirements must conform to limits provided in the Specific Instructions.

*Include these items only when applicable.

CITIZENSHIP

- U.S. citizen or noncitizen national Permanent resident of U.S. (If a permanent resident of the U.S., a notarized statement must be provided by the time of award.)

Principal Investigator/Program Director (Last, First, Middle): Marras, Connie

**BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY**

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD <i>(from Form Page 4)</i>	ADDITIONAL YEARS OF SUPPORT REQUESTED			
			2nd	3rd	4th	5th
PERSONNEL: <i>Salary and fringe benefits. Applicant organization only.</i>		50,000				
CONSULTANT COSTS						
EQUIPMENT						
SUPPLIES						
TRAVEL						
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
OTHER EXPENSES						
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT					
SUBTOTAL DIRECT COSTS <i>(Sum = Item 8a, Face Page)</i>						
CONSORTIUM/ CONTRACTUAL COSTS	F&A					
TOTAL DIRECT COSTS		50,000				

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD

\$ 50,000

**SBIR/STTR Only
Fee Requested**

SBIR/STTR Only: Total Fee Requested for Entire Proposed Project Period

(Add Total Fee amount to "Total direct costs for entire proposed project period" above and Total F&A/indirect costs from Checklist Form Page, and enter these as "Costs Requested for Proposed Period of Support on Face Page, Item 8b.)

\$

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Dr. Connie Marras: Principal Investigator and Mentee. Percent Effort: 80%

The funds requested constitute only salary support for Dr. Marras. Other costs of the project (as detailed in attached budget, Appendix 4) will be covered by other sources of funding to the Movement Disorders Centre. An application to cover the operating costs of the project has been submitted to the Parkinson Society of Canada (maximum funds requested \$45,000, no salary support costs allowed). The project is considered of sufficiently high importance that other sources of funds (e.g. private donations, clinical trial income) will be used should that application not be successful.

Dr. Marras will be hired as a clinician scientist in the Department of Medicine, University Health Network and University of Toronto. As such, she will be expected to devote approximately 80% of her time to research related activities and will have time protected from clinical duties accordingly. Within the proposed project, (Continued next page)

Budget justification continued:

Dr. Marras will be responsible for training the field team and will provide direct supervision of the research associate and field neurologist. Dr. Marras will also perform the data analysis, review videotapes and neurological information obtained in the field to provide the second diagnosis, and participate in discussions to resolve discrepancies between the field and in-house diagnoses. Under the mentorship of Dr. Lang, Dr. Marras will also fully develop the research plan for the longitudinal study of the two families with LRRK2 mutations. This will include determining the content of the in-person evaluations, developing the logistical plan for prioritizing initial contact across family members and developing the plan for longitudinal evaluation of unaffected carriers. As the longitudinal evaluation of unaffected carriers will include testing of potential biomarkers of susceptibility or the pre-symptomatic state, Dr. Marras will be responsible for establishing the specific tests of interests, and determining the logistics of carrying them out on a geographically widespread study population.

BIOGRAPHICAL SKETCH

NAME		POSITION TITLE	
Marras, Connie		Post-doctoral fellow	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Queen's University, Kingston Ontario Canada	BSc	1990-1992	Life Sciences
Queen's University, Kinston Ontario Canada	MD	1990-1995	Medicine
University of Toronto, Toronto Ontario Canada	FRCP	1995-2001	Neurology
University of Toronto, Toronto Ontario Canada	PhD (candidate)	2001- present	Clinical epidemiology
Parkinson's Institute, Sunnyvale, CA USA	N/A	2001-2003	Epidemiology

Present Positions

2003-present: Neurologist, Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital

2003-present: Clinical Associate, Toronto Western Hospital, University Health Network

2001-present: PhD candidate, Health Policy, Management and Evaluation - Clinical Epidemiology stream University of Toronto

2001-present: Clinician Investigator Program trainee, University of Toronto

Peer-Reviewed Publications:

1. **Connie Marras**, Michael P. McDermott, Paula A. Rochon, Caroline M. Tanner, Gary Naglie, Alice Rudolph, Anthony E. Lang and the Parkinson Study Group. Survival in Parkinson's disease: Thirteen year follow-up of the DATATOP cohort. *Neurology* 2005;64: 87-93.
2. **Connie Marras**, Anthony E. Lang. Outcome measures for clinical trials in Parkinson's disease: Achievements and shortcomings. *Expert Reviews in Neurotherapeutics* 2005 In Press.
3. **Connie Marras**, Samuel Goldman, Peter Barney, Diana A Aston, Monica Korell, Kathleen Comyns, Caroline M Tanner. Smell identification ability in twins discordant for Parkinson's disease. *Movement Disorders* 2005 In Press.
4. **Connie Marras**, Anthony E. Lang, Murray Krahn, George Tomlinson, Gary Naglie and the Parkinson Study Group. Quality of life in Parkinson's disease: Impact of dyskinesias and motor fluctuations. *Movement Disorders* 19(1): 22-28, 2004.
5. **Connie Marras**, Anthony E. Lang. Measuring motor complications in clinical trials for early Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 74(2): 143-6, 2003
6. **Connie Marras**, Anthony E. Lang and Paula Rochon. Predictors of prognosis in Parkinson's disease: A systematic review of the literature. *Archives of Neurology* 59(11):1724-8, 2002
7. **Connie Marras**, David F. Andrews, Elspeth Sime, Anthony E Lang. Botulinum toxin for simple motor tics, a randomized, controlled trial. *Neurology* 2001;56(5):605-610.

8. **Connie Marras**, William R. Geerts, James R Perry. The Incidence of venous thromboembolism is increased throughout the course of malignant glioma: An evidence-based review. *Cancer* 2000;89:640-6.
9. **Connie Marras**, Gyl Midroni. Transient absence of F-waves in acute myelopathy: A potential source of diagnostic error. *International Journal of Electromyography and Clinical Neurophysiology* 2000;40:109-112.
10. **Connie Marras**, Gyl Midroni. Proximal Martin Gruber Anastomosis Mimicking Ulnar Neuropathy at the Elbow. *Muscle and Nerve* 1999;22:1132-1135.
11. Nicolas Phan, **Connie Marras**, Rajiv Midha, Ravid Rowed. Cervical Myelopathy Caused by Hypoplasia of the Atlas: Two Case Reports and Review of the Literature. *Neurosurgery* 43:629-633, 1998.
12. Melanie R. Ursell, **Connie L. Marras**, Richard Farb, David W. Rowed, Sandra E. Black, James R. Perry. Recurrent Intracranial Hemorrhage Due to Postpartum Cerebral Angiopathy - Implications for Management. *Stroke* 1998;29
13. **L.C. Marras**, T.P. Kalamparambath, S.E. Black and D.W. Rowed. Severe Tension Pneumocephalus Complicating Frontal Sinus Osteoma. *Can. J. Neurol. Sci.* 1998; 25:79-81.

Peer-reviewed Abstracts Published

1. **Connie Marras**, Monica J Korelll, Freya Kamel, Jane A Hoppin, David M. Umbach, Anthony E. Lang, Caroline M Tanner et al. The relationship between two measures of postural stability: pull test and functional reach in subjects with and without Parkinson's disease. *Movement Disorders*. Accepted for presentation at the 8th International Congress of Parkinson's disease and Movement Disorders. June, 2004.
2. **Connie Marras**, Alexander Kopp, Anthony E. Lang, Kathy Sykora, Kenneth I Shulman, Paula A. Rochon. Antipsychotic use in patients on dopaminergic therapy in Ontario, Canada. *Movement Disorders*. Accepted for presentation at the 8th International Congress of Parkinson's disease and Movement Disorders. June, 2004.
3. **Connie Marras**, Caroline M Tanner, Stephen K Van Den Eeden, Kathleen S Benedict, Robin D Fross, Amethyst D Leimpeter, Jeff Klingman, Neil J Risch, Lorene Nelson, Andrew Karter, Allan L Bernstein. Minimum incidence of cervical dystonia in a multiethnic health care population. *Neurology* 2003;60(Suppl1):A417. Presented as a platform presentation at the American Academy of Neurology Annual Meeting April, 2003.
4. Samuel Goldman, **Connie Marras**, Caroline M. Tanner. Head Injury and Parkinson's Disease Risk in Twins. *Neurology* 2003;60(Suppl1):A415.
5. Caroline M. Tanner, Samuel M. Golman, Patricia Quinlan, Roert Field, Diana A. Aston, Kathleen Comyns, Amanda Smith, Cheryl Meng, Zhi Hui Wang, **Connie Marras**, Monica Korell, J. William Langston, G. Webster Ross. Occupation and Risk of Parkinson's Disease: A Preliminary Investigation of Standard Occupational Codes (SOC) in Twins Discordant for Disease. *Neurology* 2003;60(Suppl1):A415.
6. **Connie Marras**, Samuel Goldman, Peter Barney, Diana A Aston, Monica Korell, Kathleen Comyns, Caroline M Tanner. Smell identification ability in twins discordant for Parkinson's disease. *Movement Disorders* 2002;17:S137.
7. **Connie Marras**, Elspeth Sime, David Andrews, Anthony Lang. Botulinum toxin for simple motor tics, a randomized, controlled trial. *Neurology* 2000;54:A49

Letters

1. **Connie Marras**, David Oakes, Michael P. McDermott, Anthony E. Lang, Caroline M. Tanner, Karl Kieburtz, Stanley Fahn, Ira Shoulson and the Parkinson Study Group. Re: High dose Vitamin E supplementation increases mortality. *Annals of Internal Medicine*. 2005 In Press.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Lang, Anthony Edward		POSITION TITLE Neurologist	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Toronto	MD	1975	
University of Toronto	FRCPC	1979	Internal Medicine
University of Toronto	FRCPC	1983	Neurology

A. Positions and Honors..Positions and Employment

1975-1980:	University of Toronto	Postgraduate Training in Internal Medicine and Neurology	
1980-1982:	Institute of Neurology	Research Fellowship in Movement Disorders	(Prof.C.Marsden) London, England Medical Staff
1982-Present:	Toronto Western Hospital		
1988-Present:	University of Toronto Associate Professor	Medicine (Neurology)	
1995-Present:	University of Toronto Professor	Medicine (Neurology)	
1984-Present:	Movement Disorders Clinic Toronto Western Hospital	Medicine (Neurology)	
1995-2003:	Co-Editor-in-Chief, Movement Disorders		
2004-	Director, Division of Neurology University of Toronto		

Other Experience and Professional Memberships

Member, Steering Committee, Parkinson's Study Group (PSG): ELLDOPA-I; PRECEPT (Co-PI)
International Executive Committee, Movement Disorders Society
Executive Committee of Movement Disorders Section of American Academy of Neurology
American Academy of Neurology, Annual Meeting Sub-Committee June 1995 - 2000
Member of the AAN Movement Disorders Research Award Subcommittee (2001-2003)
American Neurological Association Council
Chair, PSG Nominating Committee 2002-2003.
Chair - Scientific Advisory Committee for Multiple Systems Atrophy Program Project. (Dr. C. Shults PI)
Elected Membre d'honneur à titre étranger of the French Neurological Society, November 2002.
Member Organizing Comm Movement Disorder Society sponsored International Workshop on Psychogenic Movement Disord. 2003.
Movement Disorders Society Industrial Relations Committee 2003-
Movement Disorders Society Congress Scientific Program Committee Feb. 2003-
American Academy of Neurology Movement Disorders Research Award 2004
President-Elect Movement Disorders Society-January 2005

Selected Peer Reviewed Papers 2003-2004

- Nutt JG, Burchiel KJ, Comella CL, Jankovic J, **Lang AE**, Laws ER, Lozano AM, Penn RD, Simpson RK, Stacy M, Wooten GF, ICV GDNF Study Group. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. *Neurology* 2003;60:69-73.
- Lincoln S, Lynch T, Langston JW, Chen R, **Lang A**, Rogaeva E, Sa DS, Puppi Munhoz R, Harris J, Marder K, Klein C, Bisceglia G, Hussey J, West A, Hulihan M, Hardy J, Farrer M. Parkin-Proven Disease: Common Founders but Divergent Phenotypes. *Neurology* 2003;60:1605-1610.
- Kleiner-Fisman G, Black SE, **Lang AE**. Neurodegenerative Disease and the Evolution of Art: The Effects of Presumed Corticobasal Degeneration in a Professional Artist. *Mov Disord* 2003; 18:294-302.
- Kleiner-Fisman G, Sime E, Saint-Cyr JA, Lozano AM, **Lang AE**. A trial of motor cortex chronic stimulation with subdural electrodes for multi system atrophy. *Arch Neurol* 2003;60:1554-58.
- Kleiner-Fisman G, Rogaeva E, Halliday W, Houle S, Kawarai T, Sato C, Medeiros H, St. George-Hyslop P, **Lang AE**. Benign hereditary chorea: clinical, genetic and pathological findings. *Ann Neurol* 2003;54:244-247.
- Leehey MA, Munhoz RP, **Lang AE**, Brunberg JA, Grigsby J, Greco C, Jacquemont S, Tassone F, Lozano AM, Hagerman PJ, Hagerman RJ. The fragile x premutation presenting as essential tremor. *Arch Neurol* 2003;60(1):117-121.
- Marras C, **Lang AE**. Measuring motor complications in clinical trials for early Parkinson's disease. *J. Neurol Neurosurg Psychiatry* 2003;74(2):143-146.
- Sailer S, Molnar G, Paradiso G, Gunraj C, **Lang A**, Chen R. Short and long latency afferent inhibition in Parkinson's disease. *Brain* 2003;126:1883-1894.
- Hague S, Rogaeva E, Hernandez D, Gulick C, Singleton A, Hanson M, Johnson J, Weiser R, Gallardo M, Ravina B, Gwinn-Hardy K, Crawley A, St. George-Hyslop P, **Lang AE**, Heutink P, Bonifati V, Hardy J, Singleton A. Identification of a compound heterozygous mutation in *DJ-1* causing early-onset Parkinson's disease. *Ann Neurol* 2003;54(2):271-274.
- Litvan I, Bhatia KP, Burn DJ, Goetz CG, **Lang AE**, McKeith I, Quinn N, Sethi KD, Shults C, Wenning GK. SIC Task Force Appraisal of Clinical Diagnostic Criteria for Parkinsonian Disorders. *Mov. Disord* 2003;18:467-486.
- Han F, **Lang AE**, Racacho L, Bulman DE, Grimes DA. Mutations in the epsilon-sarcoglycan gene found to be uncommon in seven myoclonus dystonia families. *Neurology* 2003;61(2):244-246.
- Abosch A, Kapur S, **Lang AE**, Hussey D, Sime E, Miyasaki J, Houle S, Lozano AM. Stimulation of the Subthalamic Nucleus in Parkinson's disease does not produce Striatal Dopamine Release. *Neurosurgery* 2003;53(5):1095-1105.
- Paradiso G, Saint-Cyr JA, Lozano AM, **Lang AE**, Chen R. Involvement of the human subthalamic nucleus in movement preparation. *Neurology* 2003;61:1538-1545.
- Kumar R, Lozano AM, Sime E, **Lang AE**. Long-term follow-up of thalamic deep brain stimulation for essential and Parkinsonian tremor. *Neurology* 2003;61:1601-1604.
- Anca MH, Zaccai TF, Badarna S, Lozano AM, **Lang AE**, Giladi N. Natural history of Oppenheim's dystonia (DYT1) in Israel. *J Child Neurol* 2003;18(5):325-330.
- Postuma RB, Furukawa Y, Rogaeva E, St. George-Hyslop PH, Farrer MJ, **Lang AE**. Dopa-responsive dystonia presenting with prominent isolated bilateral resting leg tremor: Evidence for a role of *parkin*? *Mov Disord* 2003;18(9):1069-1072.
- **Lang AE**. Subthalamic stimulation for Parkinson's disease - living better electrically? *N Engl J Med* 2003;349(20):1888-1891.
- Klein C, Herich K, Wellenbrock C, Kann M, Harris J, Marker K, **Lang AE**, Schwinger E, Ozelius LJ, Vieregge P, Pramstaller PP, Kramer PL. Frequency of parkin mutations in late-onset Parkinson's disease. *Ann Neurol* 2003;54(3)415-416.
- Hague S, Rogaeva E, Hernandez D, Gulick C, Singleton A, Hanson M, Johnson J, Weiser R, Gallardo M, Ravina B, Gwinn-Hardy K, Crawley A, St. George-Hyslop PH, **Lang AE**, Heutink P, Bonifati V, Hardy J, Singleton A. Early-onset Parkinson's disease caused by a compound heterozygous DJ-1 mutation. *Ann Neurol* 2003;54(2):271-274.
- Hedrich K, Djarmati A, Schafer N, Hering R, Wellenbrock C, Weiss PH, Hilker R, Vieregge P, Ozelius LJ, Heutink P, Bonifati V, Schwinger E, **Lang AE**, Noth J, Bressman SB, Pramstaller PP, Riess O, Klein C. DJ-1 (PARK7) mutations are less frequent than Parkin (PARK2) mutations early-onset Parkinson disease. *Neurology* 2004;62(3):389-394.

OTHER SUPPORT STATEMENT

MARRAS, C.

ACTIVE or PENDING

C Marras	2003- June 30, 2005
Parkinson Society Canada Clinical Research Fellowship	\$90,000
Determinants of prognosis in Parkinson's disease	

No active grants or salary support awards after June, 2005

APPLIED (awaiting decision):

C Marras (PI), A. Lang (co-PI)	July 1, 2005-2006
Parkinson Society Canada Pilot Project Grant	\$39,799.72
Phenotype, determinants of expressivity and predictive testing in two families carrying LRRK2 gene mutations	

Overlap: 100%. Operating costs only. No salary support permitted.

LANG, A.E.

ACTIVE

P. Carlen (PI), A. Lang (Co-Investigator)	2003-2005
Michael J. Fox Foundation	\$278,247 US
The role of abnormal gap junction communication in the generation of levodopa-induced dyskinesia in Parkinson's disease.	

Overlap: none

A. Lang (PI)	2004-2005
Novartis	\$150,000
Homocysteine and levodopa: Study of the effects of levodopa with or without vitamin supplementation and entacapone on plasma homocysteine	

Overlap: none

APPLIED (awaiting decision):

C Marras (PI), A. Lang (co-PI)	July 1, 2005-2006
Parkinson Society Canada Pilot Project Grant	\$39,799.72
Phenotype, determinants of expressivity and predictive testing in two families carrying LRRK2 gene mutations	

Overlap: 100%. Operating costs only. No salary support permitted.

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

N/A

Clinical:

The Movement Disorders Centre is located within the Toronto Western Hospital. It is equipped with 10 self-contained clinic rooms that can be used for subjects examinations and interviews. Sufficient space is available to support the proposed research project.

Animal:

N/A

Computer:

Dr. Marras and the research associate are currently provided with a desktop computer. A laptop computer will be purchased and adapted with equipment to fine motor testing. This same computer will also be used for data entry by the research assistant.

Office:

Dr. Marras and the research associate are currently provided with private offices. Private office space is also available for conducting telephone interviews. The research assistant will be provided with a private office.

Other:

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

N/A

Career Development Plan

Candidate's Background:

I am completing fellowship training this year. The fellowship has consisted of clinical training in movement disorders at the Toronto Western Hospital Movement Disorders Centre under the supervision of Dr. Anthony Lang, and PhD training in epidemiology completed jointly at the University of Toronto and the Parkinson's Institute in Sunnyvale, California under the supervision of Drs. Paula Rochon and Dr. Caroline Tanner. The subject of my PhD studies has been prognosis of Parkinson's disease, using the DATATOP database to study factors associated with time to requiring levodopa, health-related quality of life and survival. Defense of my PhD thesis is planned for the end of this academic year (June, 2005). PhD course work included didactic teaching in clinical trials and observational study design, biostatistics, decision analysis, health services research and measurement theory/test performance evaluation and validation. During a two-year fellowship at the Parkinson's Institute under the direction of Dr. Caroline Tanner, I also participated in the development of the methods for field evaluation and subsequent standardized evaluation of field data for two studies: a study of the etiology of Parkinson's disease using a large cohort of elderly male twins (World War II veteran twin cohort), and a nested case-control study within the Agricultural Health Study. She also performed many field examinations, providing insight into the challenges and pitfalls of epidemiologic field work. I acquired additional experience using administrative databases during the fellowship using the Kaiser Permanente Health Maintenance Organization of Northern California databases to conduct a study of the incidence of cervical dystonia. Importantly, I have not had training or experience in family study methods or genetic epidemiology.

Career Goals and Objectives/Scientific Biography:

My goal is to develop a productive program of clinical research specifically directed toward observational studies in the field of movement disorders. The majority of my time will be devoted to research and the remainder to clinical neurology, contributing to the care of outpatients at the Movement Disorders Centre and attending the teaching in-patient general neurology service. The Toronto Western Hospital Administration is supportive of this vision, and have provided a commitment to hiring Dr. Marras as a clinician scientist (see attached supporting statement).

My main research interest lies in understanding the etiology of Parkinson's disease and the determinants of its variable expression. With the rapid discovery of genetic forms of parkinsonism, expertise in family study methods will constitute an important adjunct to my current knowledge base of epidemiologic methods. In several ways past research experience will assist in successful completion of the proposed project. Analysis of the DATATOP database has demonstrated the heterogeneity of this disorder in terms of outcome, and revealed early clinical features that can be used to predict outcome. Heterogeneity of expression has been demonstrated even within the subgroup of individuals with parkinsonism associated with LRRK2 mutations, which will form the basis of the proposed study. A logical extension of my PhD work will be to describe in detail this clinical heterogeneity in our two large families, and to study determinants of expression of the disorder. Previous research experience has also included analysis of data from the study of the World War II veteran twin cohort, through which we described longitudinal evaluation of olfactory identification ability in twin pairs discordant for Parkinson's disease at baseline. This study required consideration of the requirements of a study of predictive testing, which will be an important part of planning the longitudinal evaluation of asymptomatic LRRK2 mutation carriers. Finally, performing field evaluations with the aim of establishing a research diagnosis of Parkinson's disease in the World War II veteran twin Cohort will provide invaluable experience for planning and training personnel for the study of the two families.

Career Development/Training Activities during the award period:

Despite the relevance of this scientific experience to my ability to conduct parts of the proposed project, my training to date has not included consideration of genetic epidemiology (specifically, investigating issues of penetrance, expressivity, and the logistics of planning a family study) nor do I have experience planning a study to thoroughly characterize a poorly understood clinical entity. For these skills, the mentorship of Dr. Lang and the advice of our collaborator Dr. Ekaterina Rogaeva will be very important. Dr. Lang has extensive experience with the development and implementation of diagnostic criteria, and has achieved international recognition for his descriptions of novel and poorly understood movement disorders. He also has considerable experience in the field of clinical and molecular genetics relevant to Parkinson's disease. In collaboration with Drs. Ekaterina Rogaeva and Peter St. George Hyslop he has published numerous papers on familial forms of Parkinson's disease including parkin, PINK1, DJ1, GBA and most recently LRRK2. His close supervision of this project will provide essential guidance to the content of the in-person evaluations and the diagnostic criteria to be used. He will also provide important guidance on the logistics of carrying out the family study, including dealing with challenging ethical issues created by a longitudinal study of a population at risk for a disabling disorder. Dr. Rogaeva's input on the more technical aspects of genetic studies, including approaches to studying penetrance and determinants of expressivity will be important.

Weekly project planning and progress meetings between Dr. Marras and Dr. Lang (and as needed other study personnel) will provide the opportunity to discuss important methodological questions and solve logistical problems as they arise. In addition, regular meetings to resolve discrepancies between field, clinic and videotape diagnoses (as described in the research plan) will provide a forum for discussing diagnostic criteria to be used and the content of clinical descriptions to be gathered in the field. In addition to these study-specific activities, the Movement Disorders Centre of the Toronto Western Hospital provides a rich educational environment. Monthly clinical research rounds are held, which provide didactic teaching on varied topics relevant to clinical research including genetic studies. For example, Dr. Christine Klein, well known for her contributions to the genetics of parkinsonism will spend four months of the coming academic year at our center and will contribute to this lecture series. Weekly journal club and video review rounds add to the educational opportunities in research methods and clinical movement disorders.

Training in the Responsible Conduct of Research

Previous PhD course work has included classes devoted to research ethics in the context of clinical trials and observational studies as well as principles of data management. During the period of funding relevant to this proposal continuing education in the responsible conduct of research will consist of didactic sessions on Good Clinical Practice as part of the Clinical Research Rounds series at the movement disorders center, and monthly lunch seminars on research ethics provided by the Clinical Studies Resource Centre of the University Health Network.

Dr. Anthony Lang
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March 28, 2005

Grant Adjudication Committee
Parkinson Study Group research/mentorship grants for new investigators competition

Re: Application of Dr. Connie Marras

Dear Committee members,

This letter is in support of the application of Dr. Connie Marras, applicant for a research/mentorship grant for new investigators competition, and an agreement to provide mentorship. Dr. Marras is completing a fellowship in clinical movement disorders and epidemiology this year, and will join the staff of the Toronto Western Hospital Movement Disorders Centre in July, 2005.

One of the major thrusts in patient-oriented research in Parkinson's disease over the coming years is anticipated to be in the field of genetic epidemiology as we discover more genes contributing to the etiology of Parkinson's disease. Dr. Marras is a natural candidate to lead these investigations with her previous epidemiology training and experience in observational studies. However, her previous training and experience has not included family study methods. A mentored year as we put in place the methods to launch a longitudinal study of two large families with LRRK2 mutations would be valuable to establishing her as an independent investigator in this field.

We have only requested funding for salary support to Dr. Marras through this award. The operational costs related to the project (equipment, personnel salaries and other costs) will be covered from other sources. The project is considered important enough to our long-term research agenda that these costs will be covered, if necessary from private donations and clinical trials income.

I will be pleased to provide mentorship to Dr. Marras during the award period. The mentorship I will provide will include weekly project planning meetings, as well as the meetings to resolve discrepancies between the field and clinic diagnoses for the pilot evaluations described in the research plan. Dr. Marras and I both have our offices in the Movement Disorders Centre, which will facilitate ad hoc meetings as well. In addition to project-specific mentorship, I am in a position to provide clinical and research mentorship through leading our twice-weekly rounds of video review and journal club dealing with unusual movement disorders and new research in the field. We have also established a monthly series of Clinical Research Rounds which covers topics across the field of clinical research including genetic studies by incorporating guest lecturers.

My research qualifications include extensive work in a variety of fields related to Parkinson's disease and other movement disorders. These include descriptive clinical studies, numerous clinical trials, and research studies involving neurophysiology, imaging, neuropathology, genetics and functional surgical techniques (among others). Recently we have developed a very active collaboration with Drs. Ekaterina Rogaeva and Peter St. George Hyslop in the field of clinical and molecular genetics publishing papers on various genes known to be associated with familial forms of Parkinson's disease including parkin, PINK1, DJ1, GBA and most recently LRRK2. Indeed, it was in collaboration with our group that Dr. A. Singleton from NIA recognized that the G2019S mutation in the LRRK2 gene may be the commonest known genetic cause of the disorder discovered to date (Paisán-Ruíz et al, Neurology in press). As part of this collaborative research program we discovered the 2 large families that Dr. Marras is proposing to study.

I believe that Dr. Marras is an outstanding candidate for PSG support through the New Investigator program. She has already developed a strong academic relationship with the PSG through her PhD research on the DATATOP database. The present funding will help establish her in her chosen career as a Clinician-Scientist in the field of Clinical Epidemiology and will help expand her expertise to family study methodologies.

Yours sincerely,

Anthony E. Lang, MD, FRCPC.



University Health Network

Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

Re: Connie Marras MD, FRCPC
Application for Parkinson Study Group research/mentorship grants for new investigators

To Whom It May Concern:

I am writing in support of the application of Dr. Connie Marras for a Parkinson Study Group Research/Mentorship Grant for New Investigators. In my role of VP UHN and COO Toronto Western Hospital, I would like to confirm that Dr. Marras has the support of this organization and that resources are in place to enable her work.

The Movement Disorders Centre of the Toronto Western Hospital is a National Parkinson Foundation Centre of Excellence and widely recognized for excellence in clinical research. Research performed at the Centre includes clinical trials, clinical genetic research, clinical descriptive research and electrophysiology of movement disorders. A group of 7 clinicians and researchers devoted to the study and treatment of movement disorders currently works together at the Movement Disorders Centre. In addition, an active program of training in Movement Disorders is provided, with several fellowship positions offered and filled each year. Dr. Anthony Lang is the director of the Centre and internationally recognized for his contributions in clinical research of movement disorders. He will provide mentorship to Dr. Marras during the period of the award. The Movement Disorders Centre is well-equipped in office and clinic space to support the proposed project.

The Movement Disorders Centre is affiliated with the University of Toronto and the researchers and clinicians work within the larger academic environment of the University. Research collaborations and educational activities organized jointly with other University departments are facilitated by this relationship. For example, the Centre for Research in Neurodegenerative Diseases (CRND) is well known for its work in the genetics of neurodegenerative disease. Dr. Ekaterina Rogava's (Molecular Geneticist, CRND) collaboration on this project will provide important expertise in the principles of genetics research.

Throughout the year, regular educational rounds are held which would be relevant to the development of an independent investigator in clinical research in movement disorders. These include weekly movement disorders journal club, weekly movement disorders videotape review rounds, monthly clinical research rounds including clinical genetics research topics, and weekly rounds held at the Centre for Research in Neurodegenerative Diseases.

Dr. Marras will be appointed to the University Health Network Department of Medicine, Division of Neurology as a clinician scientist, commencing July 1, 2005. Therefore we are committed to the retention, development and enhancement of Dr. Marras' skills during the period of the award. The University Health Network agrees to provide Dr. Marras with the time and facilities necessary to carry out this project, which we view as entirely in keeping with our long-term vision for Dr. Marras' role in this institution. A clinician scientist position typically consists of approximately 80% of the researcher's time protected for research work as well as appropriate "start up" funding.

Catherine Zahn, MD, MHSc, FRCPC
Chief Operating Officer, Toronto Western Hospital
Vice President, University Health Network

Research plan

Overall goal: The long-term goals of this project are to define the clinical phenotype, penetrance and investigate determinants of expressivity of G2019S mutations in the LRRK2 gene, and to determine the value of potential biomarkers for predicting the development of parkinsonism in unaffected carriers. The following three aims will provide essential groundwork for in-person evaluations of all family members, and provide the basis for determining the sensitivity and specificity of telephone screening for use in longitudinal follow-up of unaffected carriers. Using the methods established in this pilot project we will follow unaffected carriers longitudinally for the development of symptoms using a combination of telephone contact and in-person evaluations.

A. Specific Aims of this pilot project

1. **To contact all living family members at risk for carrying the causative mutation and to determine their willingness to participate in a) A telephone screening interview for symptoms and b) An in-person neurological evaluation.**
2. **To determine the content of the in-person evaluations and train study personnel in the home evaluation methods and to determine the accuracy of field neurologist and video review diagnosis of Parkinson's disease.**

In a sample of individuals with and without Parkinson's disease recruited from the movement disorders clinic, in-person evaluations will be performed. Scripted videotapes and historical information taken during the evaluation will be reviewed by a movement disorders specialist. Both diagnoses will be compared to the gold standard clinic diagnosis. This preliminary work will determine the best algorithm to achieve an accurate diagnosis in the field.

To determine the sensitivity and specificity of two telephone screening interviews for early symptoms of parkinsonism. A sensitive and specific screen for symptoms of parkinsonism will maximize the efficiency of in-person follow-up, by guiding the timing of in-home evaluations in the mutation carriers. The individuals from *Aim 2* will undergo screening for symptoms of Parkinson's disease with two previously published questionnaires prior to in-person evaluations. The best instrument and scoring algorithm will be determined by comparing the screen responses to the gold standard clinic diagnosis.

B. Background and Significance

The etiology of Parkinson's disease: The etiology of most cases of Parkinson's disease is unknown. There is evidence for both genetic and environmental contributions.¹ Recently, mutations in the leucine-rich repeat kinase 2 (LRRK2) gene have been demonstrated to cause autosomal dominantly inherited Parkinson's disease.^{2,3} One particular mutation (G2019S) has been estimated to account for at least 5% of cases familial parkinsonism in various ethnic groups, which makes this much more common than any other genetic mutations known to cause parkinsonism.^{2,4-6} **Parkinsonism due to LRRK2 gene mutations:** Eight multiplex families in which affected cases segregate with mutations in the LRRK2 gene have been described.^{2,3,7,8} The penetrance of these mutations appears to be incomplete as unaffected carriers as old as 82 years of age have been documented,⁸ and parents of affected carriers are often unaffected despite apparent autosomal dominant transmission.⁴ Clinical features appear to be indistinguishable from idiopathic Parkinson's disease, with a widely variable age at onset. The pathology associated with this form of Parkinson's disease has been shown to be variable, with and without classical Lewy body pathology, even within the same family.^{3,5,7,8} The incomplete penetrance, variable age at onset and variable pathology suggests the influence of other genetic and/or environmental factors on the expression of this disorder.

Gaps in current knowledge:

1. Because few families with LRRK2 mutations have been fully characterized clinically, it is not known if there are subtle but important differences between LRRK2-associated and idiopathic Parkinson's disease. Details of the phenotype associated with particular mutations is even more uncertain. Careful clinical characterization of more families is important to investigate the consistency of previous observations.
2. It is currently unknown what determines whether and how the disease will be expressed in a carrier of an LRRK2 mutation. Understanding determinants of expressivity not only has important implications for carriers of LRRK2 mutations, but may also provide clues to the etiology of sporadic Parkinson's disease.
3. No biomarker for Parkinson's disease exists to enable us to identify individuals at a presymptomatic or early symptomatic stage. A biomarker is essential to the optimal testing and application of disease-modifying strategies. Autosomal dominant forms of Parkinson's disease allow individuals at high risk for developing the disease to be followed longitudinally from a presymptomatic stage, thus providing the opportunity to test potential biomarkers.
4. Various telephone screening methods for identifying parkinsonism have been used in epidemiologic studies,⁹⁻¹¹ but the reported sensitivity and specificity have varied widely and none have been directly compared. The feasibility and optimal method of screening for early parkinsonism using telephone interviews is unknown.

Significance: This pilot study will provide essential data regarding the willingness of the family members to participate and the best telephone screening method to guide in-home evaluation frequency. In addition, the personnel will be prepared to begin in-person evaluations. These pilot data and personnel training will be important for successful conduct of a longitudinal study of these two families. The longitudinal study has the potential to be highly significant:

1. Prospective investigations of the clinical evolution and risk factors for Parkinson's disease to date have been hampered by the inability to identify a population at sufficiently high risk. Because this is an autosomal dominant disorder, individuals at high risk for becoming affected can be identified. A well-characterized at-risk population will provide an invaluable opportunity to prospectively define the clinical evolution and identify risk factors and determinants of expression.
2. In a group of individuals at high risk (unaffected carriers of LRRK2 mutations) potential biomarkers can be tested for their ability to predict development of Parkinson's disease due to LRRK2 mutations. Unaffected carriers will be invited to travel for additional testing that may include heart rate variability testing^{12, 13}, dopamine transporter SPECT scanning,¹⁴ and transcranial ultrasound,^{15, 16} and will allow study of the predictive value of each test and of combinations of tests for the development of Parkinson's disease. Newer biomarkers can also be evaluated as they become available. The contribution of olfactory impairment, a motor control task and depression measured in the home evaluation to a battery will also be assessed.
3. Determinants of expression may include polymorphisms in other genes. The genetic material and clinical information collected at the initial visit will allow us to test associations between genetic variations and disease expression. Although assumptions about generalizability to idiopathic Parkinson's disease must be made with caution, the clinical similarity and the pathological overlap (both can be indistinguishable) suggest a very close relationship.

C. Preliminary Studies

We have identified two large families with identical G2019S substitutions in the LRRK2 gene (Partial pedigrees are shown in Appendix 1). The mutation segregates with the disease in five affected members of Family 1. Dr. Lang and colleagues have shown the G2019S mutation to be absent in over 700 North American control subjects.¹⁷ In Family 1, there are known to be seven affected individuals and one individual with a tremor who has not been evaluated neurologically. There are 23 living members over age 40 at risk of carrying the mutation. In family 2, there are 8 individuals who were or are affected with the disease and at least 70 living individuals at risk of carrying the mutation over the age of 40. The clinical features observed in the affected individuals are indistinguishable from idiopathic Parkinson's disease, and the age of

onset is highly variable (41 to 80 years of age in Family 1). Analysis of common coding variations in the LRRK2 gene and APOE genotype did not suggest that either accounted for the variability in age of onset in Family 1. The members of Family 1 are located largely in southern Ontario. The members of family 2 are spread across the United States. Family representatives have recently sent letters of introduction regarding the study to their relatives, with a stamped, addressed reply card enclosed asking if they would be willing to be contacted by our research team. Replies are still being received. Of 55 letters sent to members of Family 1, 13 replies have been received and all have agreed to be contacted. Of 31 letters sent to members of Family 2, 19 replies have been received and 18 have indicated willingness to be contacted.

D. Research Design and Methods

Overview: A flow diagram of the pilot project is shown in the Figure (following Research Design and Methods). In summary, the pilot study will involve contact with two different groups of subjects. Family members will be contacted by telephone to establish willingness to participate in telephone interviews and home evaluations. Volunteers from the movement disorders clinic (unrelated to the families) will participate in pilot telephone interview and in-person evaluations.

Specific Aim 1 (Contact all living family members): A representative from each family has gathered contact information for other family members and an indication of willingness to be contacted by us. When approval by the research ethics board has been obtained, the contact information will be passed on to us by the representative. Family members will be contacted by telephone to determine willingness to participate in a telephone screening interview for parkinsonism followed by a home evaluation. If an in-person evaluation is refused, permission to obtain a blood sample for genotyping and permission to obtain medical records will be requested. This aim will provide essential information for planning the longitudinal study, including willingness to participate and location of subjects.

Specific Aim 2 (Training for in-person evaluations): In this pilot project, a research technician and a field neurologist (clinical research fellow in movement disorders) will be trained in evaluation methods. Pilot in-person evaluations will be performed on 28 clinic patients with early Parkinson's disease and 25 spouses of clinic patients. The sample size is based on *Aim 3* below. The volunteers will be recruited from the large clinic population at the movement disorders centre of the Toronto Western Hospital. A scripted videotape of the evaluation will be reviewed by a second movement disorder specialist (CM). In addition to training study personnel, the pilot evaluations will allow us to determine the most accurate algorithm for assigning the diagnosis using the field neurologist ratings and subsequent video review. The 'gold standard' will be the diagnosis assigned in the clinic prior to the training evaluation.

The in-person evaluation in the longitudinal study is designed to 1. Ascertain the presence or absence of Parkinson's disease, 2. Document the full spectrum of neurological impairment in each individual, 3. Collect blood for genotyping, 4. Collect information on environmental exposures hypothesized to be determinants of disease expression. The evaluation will therefore consist of 1. A structured medical history (including standardized exposure questionnaires regarding exposure to agents known or suspected to be associated with risk for Parkinson's disease), 2. A complete neurological examination, 3. A mental status examination, 4. Olfactory testing 5. A depression inventory and 6. A motor control task. Determining the exact content of the evaluation constitutes an objective of this mentored year.

Diagnostic Criteria: A diagnosis of Parkinson's disease will be assigned by both the field neurologist and the second neurologist reviewing the videotape according to the criteria of the UK Parkinson's Disease Society Brain Bank,¹⁸ modified to permit a family history of Parkinson's disease. The presence of atypical features will result in a classification of 'atypical parkinsonism.' This category acknowledges the incomplete clinical characterization of parkinsonism due to LRRK2 mutations. The presence or absence of signs insufficient to meet diagnostic criteria will also be recorded. The second neurologist will review the videotape, medical history and signs recorded in the in-home evaluation. Neither the field nor the second neurologist will be aware of the clinic diagnosis of the subject. The field and second

neurologists' diagnoses will be compared to the gold standard clinic diagnosis. Discordant diagnoses will be discussed by the investigators and the field neurologist on a case-by-case basis shortly after each evaluation to improve inter-rater reliability as the pilot evaluations proceed and to determine the best diagnostic algorithm.

Specific Aim 3 (Evaluation of two telephone screening interview for parkinsonism): Two goals of the longitudinal study are to determine the penetrance of parkinsonism due to LRRK2 mutations and to determine the predictive value of a number of potential biomarkers for future development of parkinsonism. This will require repeated follow-up of unaffected carriers at intervals. Given the wide geographic distribution of family members, frequent home evaluations are not feasible. A telephone screen with high positive and/or negative predictive value can be used to adjust the timing of home evaluations to avoid unnecessary evaluations or to prompt unscheduled evaluations.

In the pilot study, two brief screens for self-report of symptoms of parkinsonism will be compared for sensitivity and specificity.^{9, 10} The screens (Appendix 2) differ substantially in content and have never been directly compared. The reported sensitivity and specificity of each screen have varied widely depending on the population and scoring algorithm used. The screen published by Duarte et al. has achieved 100% sensitivity and specificity using different algorithms.^{9, 11, 19} Chan et al. have developed a screening instrument that has achieved sensitivity up to 91% and specificity up to 98%.¹⁰ The pilot study will directly compare the screens using different algorithms to identify the best strategy for use in the longitudinal study.

The pilot test population will be the same subjects as for *Aim 2*: 28 patients with mildly symptomatic Parkinson's disease (Schwab and England rating >90%) and 25 spouses of clinic patients not selected for prior complaints of movement disorders. Subjects will be between 40 and 80 years of age and non-demented. For justification of sample size see "Sample size calculation" below. The pilot subjects will be interviewed by telephone prior to their in-person evaluation. The results of the telephone screen will be compared to the gold standard diagnosis to determine the sensitivity and specificity of the screen for a diagnosis of Parkinson's disease. Various scoring algorithms will be tested to optimize the performance characteristics of the test. We suspect that previously diagnosed Parkinson's disease, even if mildly symptomatic, is likely easier to detect than undiagnosed disease. Therefore, the chosen algorithm(s) will be tested in the first round of home evaluations on the family members where several individuals with undiagnosed Parkinson's disease may be found. (Not part of this pilot study).

If the performance characteristics of the telephone screen for parkinsonism are adequate, the results of the questionnaire will be used in the longitudinal study to influence the timing of home evaluations of the family members. If the screen can achieve a negative predictive value of at least 99% it will be used to rule out the need for a regularly scheduled home evaluation. If it achieves a positive predictive value of at least 60% it will be used to prompt an unscheduled home evaluation. If neither telephone screen meets either of these criteria, we will rely only on the regularly scheduled home evaluations for identifying newly affected individuals. The frequency of home evaluations will depend on the age of the mutation carriers and availability of other medical assessments and medical records.

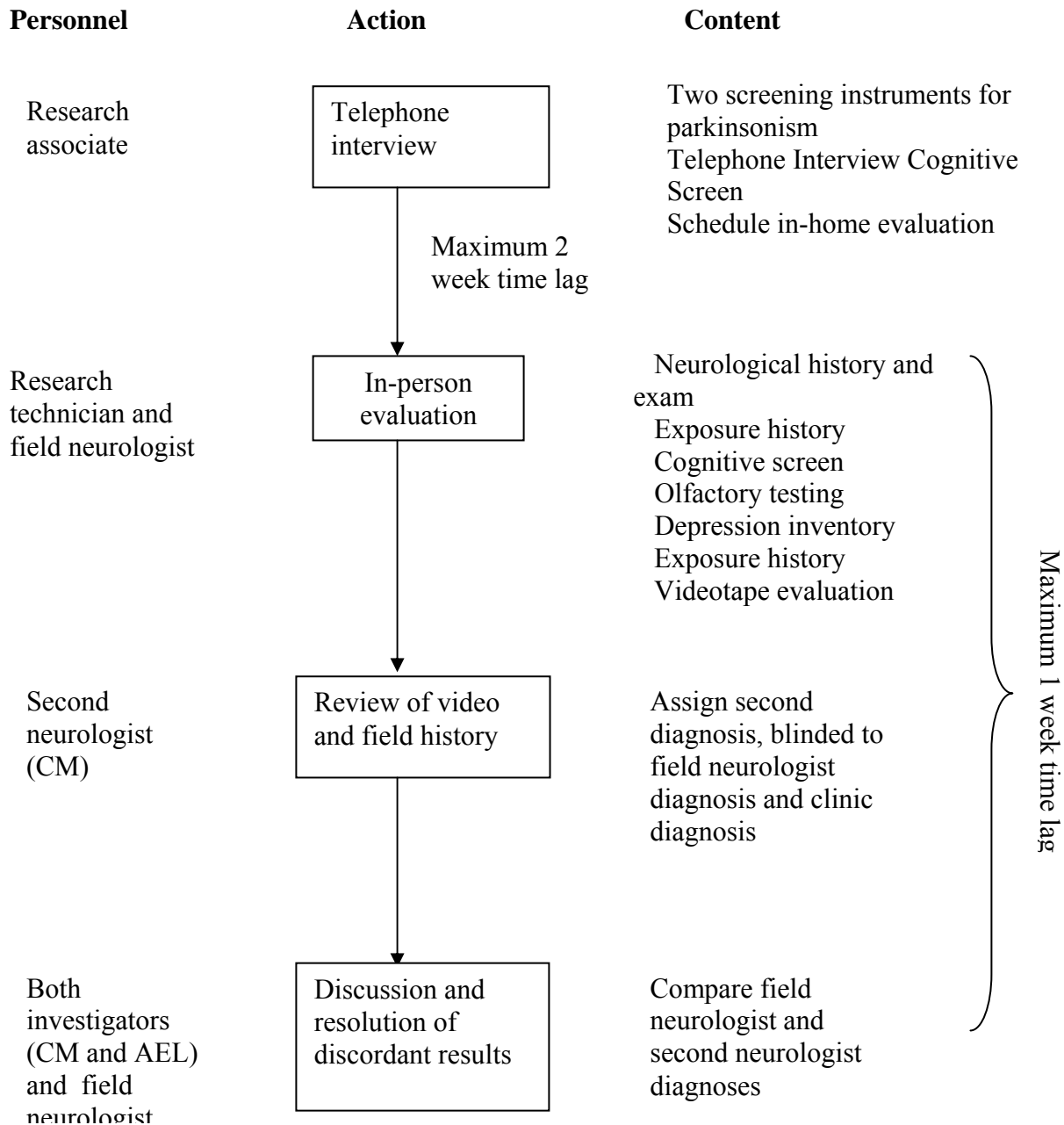
The Telephone Interview for Cognitive Status (TICS) will be applied during the telephone interview to train study personnel for its use in the longitudinal study. It is a highly sensitive and moderately specific instrument for detecting dementia in an unselected population.²⁰ In the event of a score less than 28 on the TICS, the validity of the symptom screen will be questioned and the results for that individual will be excluded from the calculation of performance characteristics of the screen for parkinsonism. A replacement pilot subject will be sought.

Sample size calculation: Assuming a 10% prevalence of parkinsonism across interviews in the mutation carriers and the desired test characteristics of 60% positive predictive value and 99% negative predictive value, a sample size of 53 individuals (28 with Parkinson's disease and 25 without Parkinson's disease) will be required. This will achieve a confidence interval width of

20% (+/- 10%) for both sensitivity and specificity. See Appendix 3 for details of sample size calculation.

Data management: Relational databases will be set up using Microsoft Access software to contain clinical, demographic, exposure and laboratory (genotype) data. Data dictionaries will be established. Each subject will be assigned a unique identification number, and other identifying and contact information will be kept in a separate tracking database. Double data entry will ensure accuracy of the entered information.

Figure: Pilot study flow



Human Subjects Research

This Human Subjects Research meets the definition of 'Clinical Research.'

Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics: The study involves two groups of subjects: 1) Family members at risk for carrying the mutation (these subjects will be called to determine their willingness to participate in in-person evaluations) 2) Subjects from the movement disorders centre who will serve as pilot subjects for telephone screening and in-person evaluation

For the first group, all living adult (over 20 years of age) family members at risk of carrying the mutation will be eligible for contact. For the second group, individuals both with and without Parkinson's disease will be selected. Clinic patients with mildly symptomatic Parkinson's disease (Schwab and England rating >90%) will be asked to participate, as well as spouses of clinic patients not selected for prior complaints of movement disorders. All subjects in the second group will be required to be cognitively intact and English speaking, and will be 40 to 80 years of age. This is the recorded range of age of onset of parkinsonism due to LRRK2 mutations, therefore will represent the population of greatest interest for applying the screening questionnaire.

b. Sources of Materials: Data collected will consist of demographic information, neurological symptoms and signs and history of specific environmental exposures. The data will be collected both over the telephone during the screening interview for parkinsonism and during the in-person neurological evaluation. Unique study-specific identifiers will be used to protect subject identification on all forms. One linking database will contain names and contact information that will be used to link specific subjects to their data. This linking database will be stored on computer only accessible by the investigator's user ID and password. Only Dr. Marras, Dr. Lang and the Ms. Asante (research assistant) will have direct access to the data.

c. Potential risks to Subjects:

There is a risk of loss of confidentiality which will be protected as described below. No other significant risks are anticipated. Although we may make a research determination of parkinsonism during the evaluation of a subjects previously assumed to be unaffected, we will stress before the evaluation that this examination is for research purposes and that we are not in a position to provide examination results to the subject. This is appropriate because there are no known advantages to treatment of Parkinson's disease before it becomes symptomatic.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Family members: The family representatives have sent personal introductory letters to subjects which have enclosed reply cards asking the relatives if they would be willing to be contacted by researchers at the Toronto Western Hospital. The reply cards with contact information and an indication of willingness to be contacted was returned to the family representative. This was done to determine initial feasibility of the study. Once REB approval for the study is obtained, the research assistant at the Movement Disorders Centre will receive contact information for those family members who have indicated willingness to be contacted, and will initiate telephone contact. No consent will be obtained at this time as the purpose of the contact is only to inform the members of the study and to ask about willingness to participate. At the time of the longitudinal study formal consent to participate will be obtained from the family members. Clinic subjects: Once identified by the clinic physician as a possible candidate, the subject will be contacted by telephone to inquire about interest in participating. Consent for the telephone

screening interview will be obtained over the telephone (see attached script). At the time of their in-person evaluation written consent will be obtained (see attached consent form).

b. Protection against risk

Risks to confidentiality will be minimized by assigning study-specific subject identifiers. Only these identifiers will be used on study documents to ensure they cannot be linked to the individuals. At the end of the study the database linking the study identifiers to the subject's identifying information will be destroyed to completely anonymize the data. During the study the linking database will be stored on computer only accessible by the investigator's user ID and password.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There are no direct benefits anticipated to the participants. We believe that the minimal risk is in keeping with this.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The knowledge to be gained in this study will maximize the scientific value of the proposed longitudinal study of the families carrying LRRK2 mutations. The methods established will also have the potential to be transferred to the study of other genetically determined neurological disorders. Careful study of families with LRRK2 mutations in particular has the potential to advance our understanding of the cause of Parkinson's disease. Understanding the cause is an important step toward better treatments, cure and prevention.

We believe that these potential benefits outweigh the minimal risks to the subjects.

Inclusion of Women and Minorities

There will be no exclusion of subjects on the basis of gender or ethnic groups. Consecutive eligible subjects identified through the clinic will be enrolled. Clinic subjects will be required to be English speaking as this will best demonstrate the performance of the telephone screening questionnaires for parkinsonism. The families to be studied are English-speaking.

Justification for Exclusion of Children

The documented age range of individuals affected by parkinsonism associated with LRRK2 mutations is between ages 40 and 82. It is therefore not anticipated that the study is relevant to children.

Literature Cited

1. Tanner CM, Ottman R, Goldman SM, et al. Parkinson disease in twins. An etiologic study. *JAMA* 1999; 281:341-346.
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Appendix 1: Family Pedigrees

Figure 1: Family 1

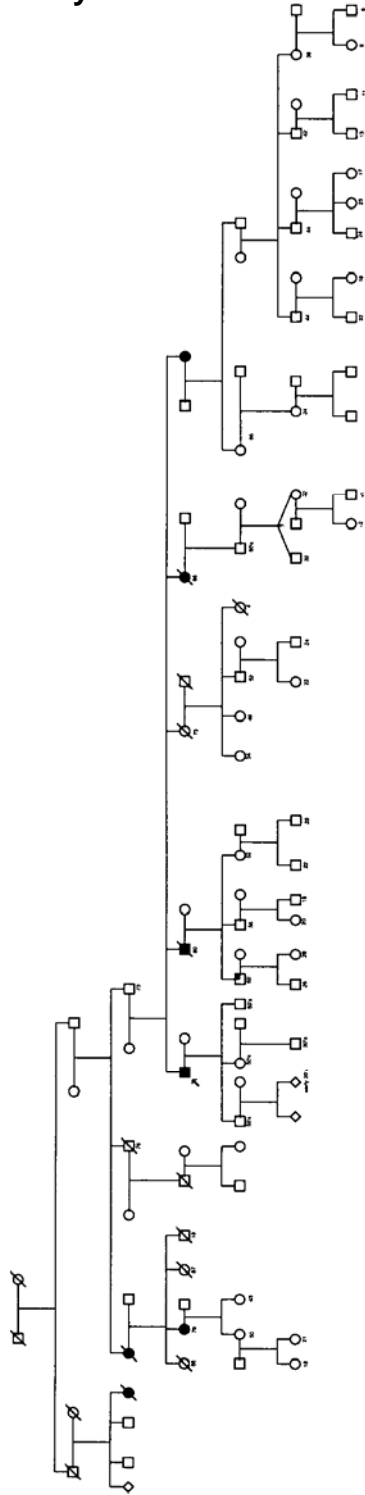
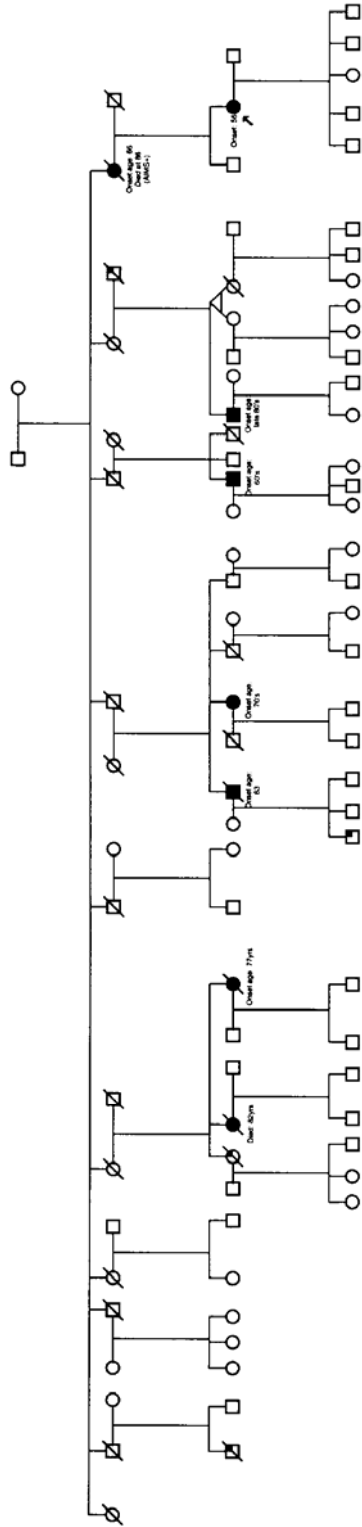


Figure 2: Family 2, partial pedigree



Appendix 2: Screening questionnaires for parkinsonism

A. Duarte et al. *Movement Disorders* 1995;10:643-649.

1. Do you have trouble arising from a chair?
2. Is your handwriting smaller than it once was?
3. Do people tell you that your voice is softer than it once was?
4. Is your balance, when walking, poor?
5. Do your feet suddenly seem to freeze in door-ways?
6. Does your face seem less expressive than it used to?
7. Do your arms and legs shake?
8. Do you have trouble buttoning buttons?
9. Do you shuffle your feet and take tiny steps when you walk?

All questions permit Yes, No or Uncertain as possible responses.

B. Chan et al. *Journal of Neurology, Neurosurgery and Psychiatry* 2000;69:117-120.

1. Have you noticed that you have become more clumsy or have more difficulty with tasks that involve fine hand control?
For example:
Doing up your buttons
Using a screwdriver
BUT not caused by rheumatism, arthritis or strokes
2. Has your handwriting changed and become smaller compared to when you were young?
3. Do you feel you walk more slowly or stiffly?
4. Do you walk with a stooped posture?
5. Have you noticed that you don't swing your arms when you walk as much as you used to?
6. Do you find it difficult to start walking from a standstill or have difficulty in stopping suddenly when you want to?
7. Have you noticed a tremor of your hands, arms, legs or head?
8. Do you have a lack of facial expressions or tend to drool with your mouth half open?
9. Have you noticed that your voice has become softer or more monotonous?
10. When you turn, do you lose your balance or do you need to take quite a few steps to turn around?
11. After you sit down, do you find it difficult to get up again?

All questions permit Yes or No responses only.

Appendix 3: Sample size justification

A. In serial telephone screens of family members, estimated prevalence of true parkinsonism = 0.10

The desired positive predictive value is at least 60%, and the desired negative predictive value 99%. These operating characteristics would translate into a sensitivity of 0.92 and a specificity of 0.93 in a population with a prevalence of parkinsonism of 10%:

	'Truth'		
Telephone screen result	Positive (N=100)	Negative (N=900)	
Positive	92	61	Positive predictive value 92/153 = 0.60
Negative	8	839	Negative predictive value 839/847 = 0.99
	Sensitivity 92/100 = 0.92	Specificity 839/900 = 0.93	

B. Therefore, the sample size calculation was based on a sensitivity of 0.92 and a specificity of 0.93 in the pilot test population and a requirement for a precision of +/- 10% for the confidence interval around the sensitivity and specificity:

95% CI = Point estimate +/- 1.96(SE), therefore desired SE \leq 0.051.

The standard error for a proportion = $\text{SQRT}(p(1-p)/n)$

	Standard error (SE)	p	n
Sensitivity	0.051	0.92	28
Specificity	0.051	0.93	25

Pilot test population: Sensitivity is calculated from the true positives and specificity from the true negatives, therefore given required sample size calculated from B, a total of 53 subjects will be required in the test population, 28 with parkinsonism and 25 without parkinsonism.

Appendix 4: Budget of other costs (not requested in this application)

Operating costs submitted with application to Parkinson Society of Canada

(Does not include salary support for Dr. Marras)

Personnel

Research technician 0.2 FTE @ \$44,044 per year	\$8,808.80
Research associate 0.25 FTE @ \$58,295 per year	\$14,573.75
Movement disorders neurologist 0.2 FTE @ \$50,000 per year	\$10,000.00

Equipment

Olfaction testing material	\$383.20
Laptop computer for field administration of motor control task	\$1600.00
Video camera and accessories	\$793.47

Other expenses

Postage	\$108.00
Telephone charges:	\$382.50
Photocopy costs and other office supplies	\$300.00
Travel expenses for pilot home evaluations	\$1350.00
Travel expenses for presentation of research findings	\$1500.00
Total	\$39,799.72

Detailed Budget Justification

Personnel

1. Research Technician: The research technician will be responsible for the following tasks, expected to require 0.2 full time equivalents:

- Training in instrument use (olfaction, CASI and Beck Depression Inventory)
- Scheduling pilot evaluations
- Preparation and execution of pilot home evaluations x 53 subjects
- Data entry

2. Research associate: The research associate will be responsible for the following tasks, expected to require 0.25 full time equivalents:

- Database development
- Development of case report forms
- Supervision of research technician
- Telephone interview training
- Initial contact interviews of all at-risk familymembers

- Telephone screening pilot interviews x 53 subjects
- Administrative work (subject tracking, arranging telephone contact)
- 3. Movement disorders neurologist:
A clinical fellow will be responsible for conducting all pilot neurological evaluations in the field under the training and supervision of Dr. Marras. They will also participate in all discussions of discordant diagnoses. This is expected to require 1 day per week for the duration of the study.

Equipment and Other expenses

1. Postage: Letters of appreciation will be sent to all family members and pilot subjects after the initial contact and pilot evaluations

Canadian postage:	\$0.50 x 88 = \$44
US postage:	\$0.80 x 80 = <u>\$64</u>
	\$108.00

2. Telephone charges:

Family members	
0.75 hour per subject (scheduling and interview) 35 subjects @ \$6.00/hr =	\$157.50
0.75 hours per subject x 50 American subjects @ \$6.00/hr =	<u>\$225.00</u>
	\$382.50

3. Olfactory testing material

- 40-item smell identification test booklet:
10 booklets for practice examinations \$269.50 US = \$340.00 CAD
 - Smell identification test booklet administration manual \$19.50 US = \$24.50 CAD
 - Picture identification test booklet \$14.95 US = \$18.70 CAD
- \$383.20

4. Video Camera and accessories

- Canon ZR90 Mini DV Camcorder + tax 689.99
- Optex Tripod + tax 68.99
- Camcorder case + tax 34.49

Total	\$793.47
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4. A laptop computer will be necessary for administering the motor control task in the field. Hardware will be adapted for this use. The database development and data entry will also be performed on this computer. Estimated cost: \$1600.00

5. Travel for in-home evaluations (2 subjects per day)

Rental car charges: \$40.00 per day x 27 days	\$1080.00
Fuel: \$10.00 per day x 27 days	<u>\$270.00</u>
	\$1350.00