An association between Gaucher disease and Parkinson disease has been demonstrated by the concurrence of Gaucher disease and parkinsonism in rare patients and the identification of glucocerebrosidase mutations in probands with sporadic Parkinson disease. Using a different and complementary approach, we describe 10 unrelated families of subjects with Gaucher disease where obligate or confirmed carriers of glucocerebrosidase mutations developed parkinsonism. These observations indicate that mutant glucocerebrosidase, even in heterozygotes, may be a risk factor for the development of parkinsonism. Understanding the relationship between altered glucocerebrosidase and the development of parkinsonian manifestations will provide insights into the genetics, pathogenesis, and treatment of Parkinson disease.

Gaucher disease (MIM 230806), the inherited deficiency of glucocerebrosidase (E.C. 3.2.1.45), presents with wide phenotypic variation. Parkinsonian symptoms are now included in this spectrum based upon the concurrence of Gaucher disease with parkinsonism in about 25 reported cases. After noting that several of these probands with Gaucher disease and parkinsonism had obligate carrier relatives with Parkinson disease, we identified a young proband with type 3 Gaucher disease whose extended family had several members in successive generations with Parkinson disease. This prompted questioning of all of our subsequent patients with Gaucher disease without parkinsonism, seen under NIH Institute Board approved clinical protocols, regarding a family history of Parkinson disease or dementia. In this preliminary study of relatives of Gaucher probands, we demonstrate multiple cases of parkinsonism among Gaucher disease carriers, further strengthening the association between these two disorders and providing evidence that heterozygosity for this Mendelian disorder may be a risk factor for a complex disease.

**METHODS**

The initial proband was a 5 year old child diagnosed with type 3 Gaucher disease, born to non-consanguineous parents of Irish/English origin and with no family history of Gaucher disease. His 42 year old father developed a resting tremor at age 34 and had asymmetrical reduced arm swing on exam. The paternal grandfather, great aunt, and great uncle have Parkinson disease and, by history, family members from previous generations also died with Parkinson disease (fig 1). Six family members, including both affected and unaffected individuals, were examined and DNA samples were obtained. Three subjects with clinical evidence of parkinsonism carried the L444P allele, while two asymptomatic subjects did not. Thus, in the paternal lineage, parkinsonism appeared to be associated with heterozygosity for a mutation in glucocerebrosidase.

Nine of approximately 40 other unrelated patients with the diagnosis of Gaucher disease evaluated at the NIH Clinical Center between August 2002 and December 2003 had a
family history in which obligate or confirmed carriers of glucocerebrosidase gene mutations showed parkinsonian manifestations. Pedigrees were constructed by questioning probands with Gaucher disease and/or their relatives regarding a family history of parkinsonism, tremor, or dementia. All participants provided informed consent under NIH Institute Review Board approved clinical protocols.

Mutations were identified by sequencing all of the exonic sequences and most flanking intronic sequences of the glucocerebrosidase gene, selectively amplified in three segments. All mutations were confirmed by direct sequencing with both forward and reverse primers, using the Dye Terminator Sequencing kit on a 373A or 3100 DNA Sequencer (Applied Biosystems, Porter City, IO, USA). Southern blots were performed to determine the presence of a recombinant allele as previously described.

**RESULTS**

The pedigrees of nine families where Gaucher carriers were found to have parkinsonism, including two (families 2A and B) where the proband had both Gaucher disease and Parkinson disease, are shown in fig 2. In all families, the parkinsonian symptoms generally appeared at an early age, often with an atypical course (table 1). Neurocognitive changes were present in the majority (families 2A, D, E, F, G, H, and I). The mutations identified were mostly missense and included L444P, N370S, and c.84insG. The recombinant allele RecNciI was found in one family (G). The age at the initial presentation of the parkinsonian manifestations varied between families (table 1) but ranged from age 34 to 63 years, with an approximate mean of 52 years.

**DISCUSSION**

A growing body of evidence from clinical, pathologic, and genetic studies suggests that mutant glucocerebrosidase may be related to the development of parkinsonism. Initially, 17 subjects were identified with Gaucher disease and L-DOPA refractory parkinsonian manifestations that included tremor, bradykinesia, rigidity, and often cognitive decline. Several of the subjects had Lewy bodies and gliosis specifically localised

![Pedigrees of Gaucher probands with a family history of parkinsonism. (A–I) The probands (shown with arrows) and family members affected with Gaucher disease are represented by diagonally shaded symbols. Where known, the Gaucher genotype is indicated. Individuals with parkinsonian manifestations are denoted by solid grey symbols. Open symbols indicate unaffected family members and slashes indicate deceased individuals. Numbers beside the symbols correspond to the age of onset of parkinsonian symptoms.](http://jmg.bmj.com/)
carrier frequency for Gaucher disease alleles is estimated at 0.034. In the at risk Ashkenazi Jewish population, the frequency of parkinsonian symptoms should be carefully ascertained in all families with Gaucher disease, and prospective studies are needed to further strengthen this association and to better establish its frequency. An improved understanding of the relationship between altered glucocerebrosidase and parkinsonism may lead to advances in our understanding of the resultant pathology.

In the present study, families of probands with Gaucher disease were surveyed for a history of Parkinson disease and/or dementia. The parkinsonian manifestations in Gaucher disease carriers demonstrated in the ten families described here are often caused by missense mutations that can result in altered substrate accumulations in specific brain regions and the fibrillary structure and toxic effects of alpha-synuclein aggregates in Parkinson disease. The mechanisms causing the fibrillary structure and toxic effects of alpha-synuclein aggregates and the normal cellular pathways involved in clearing the aggregated material are still being explored.

Table 1: Clinical and neurological features of Gaucher carriers with parkinsonism

<table>
<thead>
<tr>
<th>Pedigree</th>
<th>Sex</th>
<th>Type</th>
<th>Genotype</th>
<th>Relationship to proband</th>
<th>Genotype</th>
<th>Presentation</th>
<th>Age of onset</th>
<th>Age at death</th>
<th>Clinical diagnosis</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F</td>
<td>1</td>
<td>NA</td>
<td>Mother</td>
<td>Obligate carrier</td>
<td>Dementia, tremor</td>
<td>50s</td>
<td>60s</td>
<td>LBD</td>
<td>Poor L-DOPA response</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>1</td>
<td>N370S/N370S</td>
<td>Mother</td>
<td>Obligate carrier</td>
<td>Tremor, rigidity</td>
<td>50s</td>
<td>NA</td>
<td>PD</td>
<td>L-DOPA responsive</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>1</td>
<td>N370S/c.84insG</td>
<td>Father</td>
<td>Obligate carrier</td>
<td>Tremor, rigidity</td>
<td>57</td>
<td>–</td>
<td>PD</td>
<td>Some L-DOPA responsive</td>
</tr>
<tr>
<td>D</td>
<td>F</td>
<td>1</td>
<td>N370S/c.84insG</td>
<td>Paternal uncle</td>
<td>Affected with GD</td>
<td>Tremor, rigidity</td>
<td>63</td>
<td>69</td>
<td>PD</td>
<td>L-DOPA unresponsive, progressive dementia</td>
</tr>
<tr>
<td>E</td>
<td>F</td>
<td>3</td>
<td>L444P/L444P</td>
<td>Paternal grandfather</td>
<td>Obligate carrier (paternal grandmother confirmed non-carrier)</td>
<td>Dementia, tremor</td>
<td>45</td>
<td>55</td>
<td>NA</td>
<td>Progressive dementia, depression</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>1</td>
<td>N370S/c.84insG</td>
<td>Maternal grandmother</td>
<td>L444P/wt</td>
<td>Dementia, tremor, hallucinations</td>
<td>59</td>
<td>–</td>
<td>LBD</td>
<td>Some L-DOPA responsive, progressive dementia</td>
</tr>
<tr>
<td>G</td>
<td>M</td>
<td>3</td>
<td>N370S/RecNcil</td>
<td>Maternal grandfather</td>
<td>RecNcil/wt</td>
<td>Rigidity, masked facies</td>
<td>47</td>
<td>–</td>
<td>PD</td>
<td>L-DOPA responsive, depression, hallucinations with medication</td>
</tr>
<tr>
<td>H</td>
<td>F</td>
<td>1</td>
<td>NA</td>
<td>Mother</td>
<td>Obligate carrier</td>
<td>Tremor, rigidity</td>
<td>47</td>
<td>60s</td>
<td>PD</td>
<td>L-DOPA unresponsive, progressive dementia</td>
</tr>
<tr>
<td>I</td>
<td>M</td>
<td>1</td>
<td>L444P/L444P</td>
<td>Maternal grandfather</td>
<td>NA</td>
<td>Dementia, tremor</td>
<td>53</td>
<td>56</td>
<td>MSA</td>
<td>L-DOPA unresponsive, progressive dementia, autonomic dysfunction</td>
</tr>
<tr>
<td>Fig 1</td>
<td>M</td>
<td>3</td>
<td>L444P/L444P</td>
<td>Father</td>
<td>L444P/wt</td>
<td>Hemitremor, asymmetric arm swing</td>
<td>41</td>
<td>–</td>
<td>Tremor</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paternal grandfather</td>
<td>L444P/wt</td>
<td>Tremor, rigidity</td>
<td>40s</td>
<td>–</td>
<td>PD</td>
<td>L-DOPA responsive</td>
</tr>
</tbody>
</table>

GD, Gaucher disease; LBD, Levy body dementia; L-DOPA, levodopa; MSA, multiple system atrophy; NA, not available; PD, Parkinson disease.
Authors’ affiliations
O Goker-Alpan, M E LaMarca, E Sidransky, Section on Molecular Neurogenetics, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA
O Goker-Alpan, M E LaMarca, E Sidransky, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA
R Schiffmann, Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
R L Nussbaum, A McInerney-Leo, Genetic Diseases Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

Conflict of interest: none declared.

Correspondence to: Dr Ellen Sidransky, Section on Molecular Neurogenetics, 35 Convent Drive MSC 3708, 35/1A213, Bethesda, MD 20892–3708, USA; sidranse@irp.nimh.nih.gov

Revised version received 8 July 2004
Accepted for publication 12 July 2004

REFERENCES

www.jmedgenet.com
Parkinsonism among Gaucher disease carriers

O Goker-Alpan, R Schiffmann, M E LaMarca, R L Nussbaum, A McInerney-Leo and E Sidransky

*J Med Genet* 2004 41: 937-940
doi: 10.1136/jmg.2004.024455

Updated information and services can be found at:
http://jmg.bmj.com/content/41/12/937

These include:

**References**
This article cites 14 articles, 2 of which you can access for free at:
http://jmg.bmj.com/content/41/12/937#ref-list-1

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Metabolic disorders (329)
- Parkinson's disease (19)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/