Reviewer's report

**Title:** Polymorphisms in the glucocerebrosidase gene and pseudogene urge caution in clinical analysis of Gaucher disease allele L444P (1448C)

**Version:** 2  **Date:** 25 April 2006

**Reviewer:** Ellen sidransky

**Reviewer's report:**

**General**

**Major Comments:**
1. The rationale for this manuscript is not clear. There are well-established databases detailing the sequences for GBA and pseudoGBA available, as well as published lists of polymorphisms in these sequences. The authors apparently did not adequately familiarize themselves with this gene before designing a multiplex mutation detection strategy. They learned through their mistakes, but these discoveries add little to the available literature.
2. The paper does not review the concept of gene:pseudogene recombination in this locus nor do they describe an adequate means to detect recombinant GBA alleles. Thus, the “improved” technique is still inadequate for accurate genotyping.
3. They do not use the standard mutation nomenclature, nor do they clearly differentiate between genomic and cDNA sequence numbering throughout the manuscript. i.e., L444P should be c.1448T>C or g.7319T>C.
4. It is not clear how the DNA could truly be anonymized if identified genotypes were already assigned to a given individual. Did participants provide informed consent?
5. Most of the polymorphisms the authors report as “not reported in the literature” have already been documented (See Martinez-Arias et. al. (2001) Genome Res and Martinez-Arias et. al. (2001) Hum Mut.).
6. The authors’ major hypothesis, that a polymorphism in the primer binding site of the pseudogene would allow co-amplification with the gene, is absolutely obvious to anyone familiar with this gene.

**Minor Comments**
1. Page 5. The amount of residual enzymatic activity with this mutation is actually quite variable.
2. Page 11. The authors must specify if their nucleotide numbers refer to genomic (g.) or cDNA (c.) sequence, GBA or pseudoGBA. The numbering should also be accompanied by the reference sequence from which the numbering was derived (i.e., J03059.1 or J03060.1).
4. Page 12 and Table 3. This is not a meta-analysis, but a literature review. The authors do not note whether the techniques used in each study they summarized would have detected recombinant alleles.
5. The reference sequence used should be identified in the text, not as a footnote in Table 5.
6. Table 5. These changes have been previously published.

What next?: Reject because too small an advance to publish

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**
I declare that I have no competing interest.
Dr. K.Hruska assisted in this review