Glucosidase acid beta gene mutations in Egyptian children with Gaucher disease and relation to disease phenotypes

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Original article

Introduction: **More than 200 mutations have been found in patients with Gaucher disease (GD) and some mutations usually have a high frequency in certain populations. Genotype/phenotype correlation in patients with GD has not been established. This study was designed to determine underlying mutations in Egyptian children with GD and to assess their relation to disease phenotypes.**

Methods: **This study comprised 17 patients with GD and 10 healthy controls. Thirteen patients were type 1 GD, 2 type 2, and 2 type 3. DNA was extracted from peripheral blood leukocytes. Exons 9 and 10 were amplified by polymerase chain reaction, and deoxyribonucleic acid sequencing was done with an ABI 310 genetic analyzer.**

Results: **Wild type allele was detected in 95% (19/20) and a normal variant in 5% (1/20) of controls. L444P allele was encountered in 50% (13/26) of the alleles in type 1 patients, H451P in 7.7% (2/26) and recombinant alleles (RecNcil, RecNcil + M450L, RecFs, RecFs + M450L) in 34.6% (9/26). L444P and Rec alleles each occurred in 50% (2/4) of type 2 and 3 patients. A new mutation was seen in this study {g.7336A>C, (M450L)} and 2 mutant alleles were not determined. Type 1 GD patients had L444P/L444P genotype (23.1%) and Rec alleles/L444P (53.8%), while type 2 and 3 GD patients had Rec alleles/ L444P genotypes (100%) with a poor phenotype/genotype correlation.**

Conclusions: **L444P and Rec alleles are common in the studied patients. Novel mutations are continuously detected, adding to the expanding panel of GD mutations. No significant genotype-phenotype association was observed.**

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Key words: **children;**
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Introduction

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder. It is caused by reduction in glucocerebrosidase usually less than 15% of normal that results in the lysosomal storage of a glycolipid named glucosylceramide.[1,2]

The *glucosidase acid beta (GBA)* gene, located on chromosomal locus 1q21, is the only gene known to be associated with GD. It is 7 kb with 11 exons.[3] There is a highly homologous (96% identity) pseudogene (5 kb) located 16 kb downstream to the *GBA* gene.[4] More than 200 gene mutations have been described and some mutations usually have a high frequency in certain populations. So it is essential to know which alleles exist in a certain population and to assess their frequencies to help in genetic counseling, carrier detection and prenatal diagnosis.[5]

The abnormal alleles include exonic missense and nonsense mutations, splice junction mutations, deletions and insertions of one or more nucleotides, and complex alleles resulting from gene conversion or recombination. The most common mutations are N370S, L444P, 84GG, IVS2+1, V394L, D409H, D409V, R463C, R463H, R496H and 55 bp deletion in exon 9. The variable phenotype is probably related to different mutations in the functional glucosidase gene. However, molecular analysis has often shown a poor correlation between genotype and phenotype.[6]

The aim of this study was to determine the underlying mutations in Egyptian children with GD and

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to assess the relations of these mutant alleles to disease phenotypes.

Methods

This study was carried out in the Unit of Genetics, Mansoura University Children's Hospital (MUCH) during the period from May 2004 to May 2007. The study comprised 17 Egyptian patients with GD, 13 males and 4 females with a mean age of 6.09±4.41 years. In addition, 10 healthy children with matched age and sex were enrolled as a control group. The GD patients were recruited from the Hepatology Unit in MUCH (11 patients) and from the Pediatric Hematology Unit, Zagazig University Hospital (6 patients). Diagnosis of patients relied upon demonstration of reduced leucocyte glucosidase acid beta enzyme activity (mean: 0.247±0.125 μmol/g per hour, normal: 1-5 μmol/g per hour),[7] increased chitotriosidase activity in plasma (mean level = 1631±640.2 μmol/L per hour, normal: 4-80 μmol/L per hour),[8] and histologic findings of typical Gaucher cells in bone marrow or liver biopsy in some patients.[9] The patients included 13 with non-neuronopathic GD (type 1), 2 with acute infantile neuronopathic GD (type 2), and 2 with subacute neuronopathic GD (type 3). These patients were not scheduled for enzyme replacement therapy at the time of study. This study was approved by the ethical committee of Mansoura Faculty of Medicine. Informed consents were obtained from legal representatives of all patients and healthy children included in this study.

Clinical and laboratory data at presentation were collected from patient files including age of presentation, family history, growth parameters including weight and height Z scores. Liver and spleen sizes were assessed clinically and by ultrasound. All subjects were assessed for neurological abnormalities by a pediatrician and a pediatric neurologist. Classification of neuronopathic cases into type 2 (infantile) or type 3 was based on the age of onset of neurological signs and symptoms and the rate of disease progression. Patients with an onset before the age of 2 years with a rapidly progressive course and limited psychomotor development were classified as having type 2 GD. Patients with type 3 GD had a late onset and a milder and more slowly progressive course.[10] Laboratory evaluation included complete blood count, liver functions, and skeletal findings of X-ray, dual-energy X-ray absorptiometry and magnetic resonance imaging (MRI).

Fresh blood samples were collected in ethylene diamene tetracetic acid tubes from all subjects for DNA extraction. Samples were either used immediately or frozen for later use. DNA extraction from peripheral blood was done using QIAamp DNA blood mini kit for DNA purification from whole blood and bone marrow aspirates (QIAGEN, Venlo, Netherlands). Complete amplifications of exons 9 and 10 of the *GBA* gene (the most common sites of *GBA* mutations) were done using the Amplitaq Gold polymerase chain reaction master mix (Applied Biosystems- Foster city, CA, USA) using the following primers:

Exon 9: CCAGTGTTGAGCCTTTGTCT, GAGATGATAGGCCTGGTATG

Exon 10: GGTTTCATGGGAGGTACCCC, GAGAGTGTGATCCTGCCAAG

DNA sequencing of exons 9 and 10 of the *GBA* gene for detection of *GBA* gene mutations was done by an Applied Biosystems ABI prism ®310 genetic analyzer, version 2.0. The resulted sequences were compared with their normal counterparts (derived from Genatlas by Universite Rene Descartes-Paris)[11] using a navigator software to detect any base substitution, deletion or insertion.

Statistical analysis

The statistical analysis of data was done using SPSS (Statistical package for social sciences) program version 10. Qualitative data were presented as frequency and proportions, whereas quantitative data were presented as means ± SD. For comparison of qualitative data, Fisher's exact test (when one cell value was less than 5) was used. A *P* value of less than 0.05 was considered statistically significant.

Table 1. Clinical data of Gaucher disease patients at the time of study

Variables	Group 1 (*n*=13) *n* (%)	Group 2 (*n*=4) *n* (%)
Current age (y)		
Mean ± SD	6.6 ± 4.8	4.4 ± 2.2
Range	0.9-13.6	2.3-7.0
Gender		
Male	10 (76.9)	3 (75.0)
Female	3 (23.1)	1 (25.0)
Consanguinity	11 (84.7)	4 (100.0)
Other affected family member	4 (30.8)	0
Growth retardation	10 (76.9)	3 (75.0)
Wt Z-score (mean ± SD)	-1.73 ± 1.34	1.37 ± 0.52
Ht Z-score (mean ± SD)	-2.80 ± 1.79	-2.39 ±1.79
Pallor	12 (92.2)	4 (100.0)
Bleeding tendency	5 (38.5)	0
Hepatomegaly	11 (84.7)	3 (75.0)
Splenectomy	2 (15.4)	1 (25.0)
Splenomegaly	11 (84.7)	3 (75.0)
Skeletal involvement		
Bone pain	3 (23.1)	1 (25.0)
Radiological	4 (30.8)	3 (75.0)
Outcome		
Alive	13 (100.0)	2 (50.0)
Dead	0	2 (50.0)

Group 1: patients with type 1 Gaucher disease; Group 2: neuronopathic patients (types 2 and 3). Wt: weight; Ht: Height.

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Table 2. Laboratory data of the GD patients at the time of study (mean ± SD)

Variables	Group 1 (n=13)	Group 2 (n=4)
Hemoglobin (g/dL)	8.52 ± 1.73	8.75 ± 1.06
Platelets ($\times 10^3$/μL)	148.0 ± 60.99	213.75 ± 123.33
AST (U/L)	24.53 ± 6.42	29.50 ± 4.43
ALT (U/L)	23.0 ± 5.43	24.25 ± 5.37
Alkaline phosphatase (U/L)	461.38 ± 114.16	447.5 ± 100.45
GBA activity (μmol/g/h)	0.256 ± 0.143	0.219 ± 0.088
Chitotrioxidase (μmol/L/h)	1247.0 ± 384.4	928.0 ± 118.2

Group 1: patients with type 1 GD; Group 2: patients with types 2 and 3 GD. GD: Gaucher disease; AST: aspartate transaminase; ALT: alanine transaminase; GBA: acid beta glucosidase.

Table 3. Comparison of allele frequency between Gaucher disease phenotypes

Mutant allele	Type 1 (%)	Type 2 (%)	Type 3 (%)	Total (%)
L444P	13 (50.0)	2 (50.0)	2 (50.0)	17 (50.0)
H451P	2 (7.7)	0	0	2 (5.9)
Rec alleles	9 (34.6)	2 (50.0)	2 (50.0)	13 (38.1)
RecNci1	2 (7.7)	2 (50.0)	1 (25.0)	5 (14.7)
RecNci1+M450L	4 (15.4)	0	1 (25.0)	5 (14.7)
RecFs	2 (7.7)	0	0	2 (5.8)
RecFs+M450L	1 (3.8)	0	0	1 (2.9)
Unknown	2 (7.7)	0	0	2 (5.9)
Total	26	4	4	34

χ^2 (Fisher exact test) = 0.92, P = 0.63.

Table 4. Comparison of genotype frequencies in different types of GD

Genotypes	Type 1 (%)	Type 2 (%)	Type 3 (%)	Total (%)
L444P/L444P	3 (23.1)	0	0	3 (17.6)
Rec alleles/L444P	7 (53.8)	2 (100)	2 (100)	11 (64.8)
RecNci1/L444P	0	2 (100)	1 (50)	3 (17.6)
RecFs/L444P	2 (15.4)	0	0	2 (11.8)
RecNci1+M450L/L444P	4 (30.7)	0	1 (50)	5 (29.4)
RecFs+M450L/L444P	1 (7.7)	0	0	1 (5.9)
H451P/H451P	1 (7.7)	0	0	1 (5.9)
RecNci1/?	2 (15.4)	0	0	2 (11.8)
Total	13	2	2	17

χ^2(Fisher's exact test) = 2.8; P = 0.41. GD: Gaucher disease.

Results

Clinical and laboratory data of the patients are summarized in Tables 1 and 2. Neurological abnormalities included seizure (2 patients), spasticity (2), squint (4), swallowing difficulties (4), and developmental delay (4). Skeletal abnormalities included osteopenia shown by dual-energy X-ray absorptiometry in 7 patients, Erlenmeyer flask deformity shown by X-ray in 4, and marrow infiltration shown by MRI in 2.

In the control group, the wild type allele frequency was 95% (19/20), and a normal allele variant (V460V) was found in 5% (1/20); the wild genotype was present in 90% (9/10). The most frequent mutant allele in the patients was L444P which had a frequency of 50% in each type of GD (13/26 in type 1, 2/4 in type 2, and 2/4 in type 3). Recombinant alleles had a frequency of 38.1% (13/34) [RecNci1 allele 14.7% (5/34), RecNci1+M450L allele 14.7% (5/34), RecFs allele 5.8% (2/34), and RecFS+M450L allele 2.9% (1/34)]. H451P allele had a frequency of 5.8% (2/34) in a homozygous state in only one patient with type 1 GD. Two mutant alleles (5.9%) were not detected in our patients. There was no significant difference between frequencies of different alleles in the three groups (P=0.63) (Table 3).

With regard to genotype frequency in different types of the GD patients, 3 (23.1%) type 1 patients had L444P/L444P genotype, while 7 (53.8%) had Rec alleles/L444P genotype and 1 had H451P/H451P genotype. All type 2 patients and one type 3 patient had RecNci1/L444P genotype. The other type 3 patients had RecNci1+M450L/L444P genotype. There was no significant difference in frequencies of different genotypes between the three groups (P=0.41) (Table 4).

Discussion

This study showed a wild allele frequency of 95% in the controls while only one allele showed substitution of guanine base at g.7368 by cytosine one (g.7368G>C) with no change in amino acid (valine) at position 460 (V460V). This change was reported to be a synonymous single nucleotide polymorphism normally present in the *GBA* gene.[12] On the other hand, the patients in this study showed 6 varieties of mutant alleles: 4 recombinant alleles and 2 single point mutations. The frequency of point mutations comprised 50% (17/34) for missense mutation (g.7319T>G) resulting in substitution of leucine for proline (L444P). Existence of L444P mutant allele at a percentage of 50% is in agreement with the frequency of that allele (42%-45.5%) described in previous studies.[13,14] However, this mutation had lesser frequency (18.5%-25%) in some other populations.[1,9,15] The difference in the frequency of this mutant allele may be due to different sample size or different ethnic background.[16]

Recombinant alleles had a frequency of 38.1% in our patients. However, the frequency of Rec alleles in other studies ranged from 3.5% to 21%.[9,13,17] In addition to different ethnicity and sample size, technical differences may explain this variation.[16] Mutation analysis was done in some studies[9] by screening for the most common mutations only by the mismatched PCR amplification technique, which has inherent limitations as additional mutations may result in under-estimation of the frequency of recombinant alleles.[18]

We detected two novel recombinant alleles

(RecNci1+M450L and RecFs+M450L). Both included a new point mutation in which there was a substitution of the adenosine base at g.7336 by cytosine base (g.7336 A>C) changing the amino acid methionine into leucine at position 450 (M450L). This nucleotide change was not seen in *GBA* polymorphic changes, and none of the controls showed this substitution. This new mutation was in combination with other recombinant mutations (RecNci1 or RecFs). Researchers have discovered several new mutations, adding novel mutations to the expanding panel of *GBA* mutations.[19-21] Although there are many polymorphic variations within several regions in the *GBA* pseudogene,[22] this new mutation (M450L) is not observed in the pseudogene polymorphic changes. Other new Rec alleles were detected by Zhao et al[23] who discovered two new recombinant alleles [(g.7668G>A + deletion g.2113-2114delAG + RecNci1) and (g.7668G>A + g.7678T>C + RecTL)]. In both alleles, a new point mutation (g.7668G>A) was detected. This mutation is not a pseudogene change and also not reported to be a polymorphic change in the *GBA* pseudogene. Zhao and his colleagues[23] suggested that additional pseudogene polymorphic changes could be present. The association of this new point mutation with other Rec alleles makes it difficult to define the pathogenic role of this mutation especially if few exons are sequenced and other mutations exist in others. Thus it would be useful in future studies to screen a large control population for this mutation and to detect its frequency as a single missense mutation.

In the present study, homozygous L444P was detected in 3 patients with type 1 GD while none of the neuronopathic patients had this genotype. Similarly, patients with type 1 GD were reported to have L444P/L444P genotype.[1,13,15] In contrast, other studies showed the association of homozygous L444P with either type 2 or 3[24] or with type 3.[19] The presence of genetic modifiers that can influence and determine the phenotype of patients who carry the same genotype may explain the lack of genotype correlation. Among patients homozygous for L444P, both severely autistic children with seizures and successful college students with few symptoms have been described.[25] However, patients without neurological abnormalities classified as type 1 may develop neuronopathic features later in life and reclassified as type 3.[26]

Recombinant alleles are essentially null alleles as homozygosis for a recombinant allele results in very early lethality, usually in utero or in the first days of life.[27,28] The association of heterozygosis of recombinant alleles with the neuronopathic phenotypes of GD has been described in many reports.[19,29] This association suggests that complex alleles increase the severity of the disease. In our study, all patients with neuronopathic GD were heterozygous for recombinant alleles. All type 2 patients and one patient with type 3 GD had the genotype RecNci1/L444P. The other patient with type 3 GD had the genotype RecNci1+M450L/L444P. These findings agree with the previously mentioned studies. However, 9 of our patients with non-neuronopathic phenotypes had genotypes in which recombinant alleles occur in a heterozygous state. Nevertheless, our findings are in agreement with those of Tayebi and his colleagues,[30] who found recombinant alleles in the following frequencies: 26/310 in 155 patients with type 1 GD, 18/74 in 37 patients with type 2 GD, and 15/96 in 48 patients with type 3 GD.

In our study, there was no significant association between *GBA* alleles or genotype frequencies and different phenotypes of GD. These findings are not different from the corresponding data from other parts of the world. It has become apparent that the same DNA mutations and even the same genotypes are found in patients with different types or clinical presentations of GD.[25,31] In addition, clinically similar patients can have many different genotypes.[19,32] Thus, while the ability to define both genotypes and phenotypes associated with GD has expanded, the correlation between the two still remains elusive. When there are few appropriate generalizations, many exceptions persist, rendering it difficult to use patient genotype to determine the prognosis or need for therapy.

In conclusion, L444P is the most common allele and L444P/Rec alleles are the most common genotypes in studied Egyptian children, which should be considered in genetic counseling and molecular diagnosis. There is no significant association between genotypes and phenotypes. New mutations are still added to the mutation panel of GD.

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