

Análise Filogenética e de Polimorfismos do Gene GBA1: Implicações para a Doença de Gaucher





Juliana de Paula Bernardes^{1*}; Flávio Lichtenstein²; Aparecida Maria Fontes¹

- ¹ Departamento de Genética, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil
- ² CENTD, Centro de Excelência em Descoberta de Novos Alvos, Instituto Butantan, São Paulo, Brasil

*e-mail: julianabernardes@usp.br

INTRODUÇÃO

A Doença de Gaucher (DG) é um distúrbio autossômico recessivo causado por variantes no gene GBA1, que codifica β -glicocerebrosidase (GCase). A deficiência dessa enzima leva ao acúmulo de glicoesfingolípideos, especialmente em macrófagos. Apesar da Terapia de Reposição Enzimática (TRE) ser eficaz, ela é limitada em formas neuronais da DG. Este estudo busca identificar polimorfismos da GCase em primatas próximos a humanos, visando apoiar modificações experimentais futuras para otimizar suas propriedades bioquímicas.

OBJETIVOS

Este estudo tem como objetivo realizar uma análise comparativa e filogenética in silico do polimorfismo da proteína codificada pelo gene GBA1 em humanos e primatas próximos não humanos.

METODOLOGIA

Foram analisadas 72 sequências da proteína GCase de humanos (*Homo sapiens*) e primatas próximos, obtidas dos bancos de dados do NCBI e UniProt. O alinhamento múltiplo de sequências foi realizado com os softwares Clustal Omega e Muscle, e as sequências repetidas foram removidas, resultando num conjunto final de 24 sequências humanas e 48 sequências de espécies de primatas próximos aos humanos de acordo com a árvore filogenética calculada - a qual foi construída com o método BioNJ utilizando a ferramenta SeaView.

RESULTADOS

A análise de polimorfismo dos primatas não humanos identificou 99 resíduos polimórficos, tendo 20 deles H>0,5 (Tabela 2) e distribuindo-se pelos 3 domínios não contínuos da enzima lisossomal, incluindo na região do peptídeo sinal. Tabela 1: Resíduos polimórficos da GCase H<0,5

3 [[F', 60], [L', 7], [-', 5]] F 60 89.6%; L 7 10.4% 9 [[E', 60], ['Q', 7], [-', 5]] E 60 89.6%; Q 7 10.4% 21 [['M', 60], ['V', 7], [-', 5]] M 60 89.6%; V 7 10.4% 66 [['D', 66], ['E', 1], [-', 5]] D 66 98.5%; E 1 1.5% 70 [['F', 60], ['L', 7], [-', 5]] F 60 89.6%; L 7 10.4% 73 [['L', 60], ['P', 7], [-', 5]] L 60 89.6%; P 7 10.4%	0,483
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73 [['L', 60], ['P', 7], ['-', 5]] L 60 89.6%; P 7 10.4%	0,112
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95 [['I', 65], ['M', 7]] 165 90.3%; M 7 9.7%	0,460
97 [['A', 65], ['T', 7]] A 65 90.3%; T 7 9.7%	0,460
109 [['Q', 54], ['K', 2], ['-', 16]] Q 54 96.4%; K 2 3.6%	0,222
	0,258
113 [['K', 55], ['Q', 1], ['-', 16]] K 55 98.2%; Q 1 1.8%	0,129
116 [['K', 55], ['Q', 1], ['-', 16]] K 55 98.2%; Q 1 1.8%	0,129
117 [['V', 55], ['M', 1], ['-', 16]] V 55 98.2%; M 1 1.8%	0,129
123 [['A', 55], ['T', 1], ['-', 16]] A 55 98.2%; T 1 1.8%	0,129
124 [['M', 55], ['V', 1], ['-', 16]] M 55 98.2%; V 1 1.8%	0,129
129 [['A', 54], ['L', 1], ['S', 1], ['-', 16]] A 54 96.4%; L 1 1.8%; S 1 1.8%	0,258
130 [['L', 55], ['l', 1], ['-', 16]] L 55 98.2%; I 1 1.8%	0,129
131 [['N', 55], ['Y', 1], ['-', 16]] N 55 98.2%; Y 1 1.8%	0,129
133 [['L', 55], ['R', 1], ['-', 16]] L 55 98.2%; R 1 1.8%	0,129
138 [['P', 50], ['A', 6], ['-', 16]] P 50 89.3%; A 6 10.7%	0,491
139 [['A', 54], ['T', 1], ['V', 1], ['-', 16]] A 54 96.4%; T 1 1.8%; V 1 1.8%	0,258
141 [['N', 55], ['A', 1], ['-', 16]] N 55 98.2%; A 1 1.8%	0,129
142 [['L', 55], ['S', 1], ['-', 16]] L 55 98.2%; S 1 1.8%	0,129
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157 [['l', 65], ['L', 7]] 165 90.3%; L 7 9.7%	0,460
184 [['H', 65], ['L', 7]] H 65 90.3%; L 7 9.7%	0,460
187 [['S', 71], ['G', 1]] S 71 98.6%; G 1 1.4%	0,106
193 [['T', 65], ['V', 7]] T 65 90.3%; V 7 9.7%	0,460
196 [['K', 71], ['E', 1]] K 71 98.6%; E 1 1.4%	0,106
202 [['R', 65], ['Q', 7]] R 65 90.3%; Q 7 9.7%	0,460
205 [['Q', 65], ['E', 7]] Q 65 90.3%; E 7 9.7%	0,460
206 [['L', 65], ['M', 7]] L 65 90.3%; M 7 9.7%	0,460
209 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4%	0,106
210 [['P', 65], ['H', 7]] P 65 90.3%; H 7 9.7%	0,460
214 [['L', 65], ['F', 7]] L 65 90.3%; F 7 9.7%	0,460
225 [['K', 71], ['N', 1]] K 71 98.6%; N 1 1.4%	0,106
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243 [['I', 65], ['R', 7]] I 65 90.3%; R 7 9.7%	0,460
262 [['H', 65], ['Y', 7]] H 65 90.3%; Y 7 9.7%	0,460
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314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,106
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314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,106
314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,106 0,211 0,106 0,216 0,187
314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,107 0,106 0,107 0,107 0,108
314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,107 0,108 0,108
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 69], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['R', 7]] H 65 90.3%; R 7 9.7% 330 [['K', 65], ['Q', 7]] K 65 90.3%; R 7 9.7% 331 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 332 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 331 [['C', 71], ['R', 1]] C 71 98.6%; R 11.4% 402 [['L', 71], ['M', 1]] T 7 98.6%; M 1 1.4% 422 [['L', 71], ['P', 1]] L 7 1 98.6%; S 1 1.4% 423 [['A', 71], ['S', 1]] A 71 98.6%; S 1 1.4% 424 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 7 1 98.6%; H 1 1.4% 447 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['L', 1]] P 71 98.6%; L 1 1.4% 474 [['G', 71], ['A', 1]] Q 67 93.1%; E 4 5.6%; H 1 1.4% 476 [['V', 70], ['E', 4], ['H', 1]] G 71 98.6%; R 1 1.4% 480 [['K', 71], ['R', 1]] K 7 1 98.6%; R 1 1.4% 480 [['K', 71], ['R', 1]] K 7 1 98.6%; R 1 1.4% 481 [['D', 68], ['P', 2], ['L', 2]] D 68 97.1%; E 1 1.4%; N 1 1.4% 482 [['D', 68], ['P', 2], ['L', 2]] L 68 97.1%; E 1 1.4%; N 1 1.4% 490 [['H', 69], [N', 1], ['L', 2]] M 69 98.6%; N 1 1.4% 491 [['S', 69], ['C', 1], ['L', 2]] H 69 98.6%; N 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,211 0,106 0,211 0,106 0,216 0,216 0,216 0,216 0,108
314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,107 0,108 0,108
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 69], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['R', 7]] H 65 90.3%; R 7 9.7% 330 [['K', 65], ['Q', 7]] K 65 90.3%; R 7 9.7% 331 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 332 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 331 [['C', 71], ['R', 1]] C 71 98.6%; R 11.4% 402 [['L', 71], ['M', 1]] T 7 98.6%; M 1 1.4% 422 [['L', 71], ['P', 1]] L 7 1 98.6%; S 1 1.4% 423 [['A', 71], ['S', 1]] A 71 98.6%; S 1 1.4% 424 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 7 1 98.6%; H 1 1.4% 447 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['L', 1]] P 71 98.6%; L 1 1.4% 474 [['G', 71], ['A', 1]] Q 67 93.1%; E 4 5.6%; H 1 1.4% 476 [['V', 70], ['E', 4], ['H', 1]] G 71 98.6%; R 1 1.4% 480 [['K', 71], ['R', 1]] K 7 1 98.6%; R 1 1.4% 480 [['K', 71], ['R', 1]] K 7 1 98.6%; R 1 1.4% 481 [['D', 68], ['P', 2], ['L', 2]] D 68 97.1%; E 1 1.4%; N 1 1.4% 482 [['D', 68], ['P', 2], ['L', 2]] L 68 97.1%; E 1 1.4%; N 1 1.4% 490 [['H', 69], [N', 1], ['L', 2]] M 69 98.6%; N 1 1.4% 491 [['S', 69], ['C', 1], ['L', 2]] H 69 98.6%; N 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,211 0,106 0,211 0,106 0,216 0,216 0,216 0,216 0,108
314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108
314 [['N', 65], ['G', 7]]	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,216 0,216 0,216 0,216
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 69], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['Q', 7]] H 65 90.3%; R 7 9.7% 332 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 336 [['T', 65], ['D', 7]] N 65 90.3%; Q 7 9.7% 372 [['N', 65], ['D', 7]] N 65 90.3%; Q 7 9.7% 381 [['C', 71], ['R', 1]] C 71 98.6%; R 1 1.4% 408 [['T', 71], ['M', 1]] T 71 98.6%; M 1 1.4% 422 [['L', 71], ['S', 1]] A 71 98.6%; M 1 1.4% 423 [['A', 71], ['S', 1]] A 71 98.6%; S 1 1.4% 426 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 447 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 471 [['Q', 67], ['E', 4], ['H', 1]] G 67 93.1%; E 4 5.6%; H 1 1.4% 474 [['G', 71], ['A', 1]] G 71 98.6%; A 1 1.4% 476 [['V', 70], ['E', 1], ['D', 1]] V 70 97.2%; E 1 1.4%; D 1 1.4% 480 [['K', 71], ['R', 1]] K 71 98.6%; R 1 1.4% 481 [['C', 68], ['E', 1], ['N', 1], ['-', 2]] D 68 97.1%; E 1 1.4%; D 1 1.4% 482 [['D', 68], ['E', 1], ['N', 1], ['-', 2]] L 68 97.1%; E 1 1.4%; D 1 1.4% 493 [['M', 69], ['L', 1], ['-', 2]] H 69 98.6%; D 1 1.4% 494 [['S', 69], ['C', 1], ['-', 2]] A 69 98.6%; C 1 1.4% 495 [['N', 69], ['C', 1], ['-', 2]] A 69 98.6%; C 1 1.4% 497 [['V', 68], ['G', 1], ['-', 2]] V 68 97.1%; F 1 1.4%; P 1 1.4% 503 [['S', 67], ['F', 1], ['-', 2]] V 68 97.1%; F 1 1.4%; P 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,216 0,218
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['L', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 65], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['C', 7]] H 65 90.3%; R 7 9.7% 330 [['K', 65], ['C', 7]] K 65 90.3%; R 7 9.7% 331 [['K', 65], ['A', 7]] T 65 90.3%; A 7 9.7% 332 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 331 [['C', 71], ['R', 1]] C 71 98.6%; R 1 1.4% 408 [['T, 71], ['M', 1]] T 71 98.6%; M 1 1.4% 422 [['A', 71], ['S', 1]] A 71 98.6%; M 1 1.4% 423 [['A', 71], ['S', 1]] P 71 98.6%; S 1 1.4% 424 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 447 [['R', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['L', 1]] P 71 98.6%; A 1 1.4% 471 [['Q', 67], ['E', 4], ['H', 1]] G 71 98.6%; A 1 1.4% 472 [['Y', 70], ['E', 4], ['H', 1]] Y 70 97.2%; E 1 1.4%; D 1 1.4% 480 [['X', 71], ['R', 1]] K 71 98.6%; R 1 1.4% 481 [['Y', 70], ['E', 1], ['D', 1]] D 68 97.1%; E 1 1.4%; D 1 1.4% 482 [['M', 69], ['L', 1], ['-', 2]] D 68 97.1%; E 1 1.4%; N 1 1.4% 490 [['H', 69], ['L', 1], ['-', 2]] H 69 98.6%; L 1 1.4% 491 [['N', 69], ['L', 1], ['-', 2]] M 69 98.6%; L 1 1.4% 492 [['N', 69], ['C', 1], ['-', 2]] M 69 98.6%; C 1 1.4% 493 [['Y', 68], ['P', 1], ['-', 2]] M 69 98.6%; C 1 1.4% 494 [['S', 69], ['C', 1], ['-', 2]] M 69 98.6%; D 1.4% 503 [['Y', 68], ['P', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 504 [['Y', 68], ['P', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 505 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 506 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 507 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 508 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 69], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['Q', 7]] H 65 90.3%; R 7 9.7% 332 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 336 [['T', 65], ['D', 7]] N 65 90.3%; Q 7 9.7% 372 [['N', 65], ['D', 7]] N 65 90.3%; Q 7 9.7% 381 [['C', 71], ['R', 1]] C 71 98.6%; R 1 1.4% 408 [['T', 71], ['M', 1]] T 71 98.6%; M 1 1.4% 422 [['L', 71], ['S', 1]] A 71 98.6%; M 1 1.4% 423 [['A', 71], ['S', 1]] A 71 98.6%; S 1 1.4% 426 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 447 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 471 [['Q', 67], ['E', 4], ['H', 1]] G 67 93.1%; E 4 5.6%; H 1 1.4% 474 [['G', 71], ['A', 1]] G 71 98.6%; A 1 1.4% 476 [['V', 70], ['E', 1], ['D', 1]] V 70 97.2%; E 1 1.4%; D 1 1.4% 480 [['K', 71], ['R', 1]] K 71 98.6%; R 1 1.4% 481 [['C', 68], ['E', 1], ['N', 1], ['-', 2]] D 68 97.1%; E 1 1.4%; D 1 1.4% 482 [['D', 68], ['E', 1], ['N', 1], ['-', 2]] L 68 97.1%; E 1 1.4%; D 1 1.4% 493 [['M', 69], ['L', 1], ['-', 2]] H 69 98.6%; D 1 1.4% 494 [['S', 69], ['C', 1], ['-', 2]] A 69 98.6%; C 1 1.4% 495 [['N', 69], ['C', 1], ['-', 2]] A 69 98.6%; C 1 1.4% 497 [['V', 68], ['G', 1], ['-', 2]] V 68 97.1%; F 1 1.4%; P 1 1.4% 503 [['S', 67], ['F', 1], ['-', 2]] V 68 97.1%; F 1 1.4%; P 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,216 0,218
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['L', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 65], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['C', 7]] H 65 90.3%; R 7 9.7% 330 [['K', 65], ['C', 7]] K 65 90.3%; R 7 9.7% 331 [['K', 65], ['A', 7]] T 65 90.3%; A 7 9.7% 332 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 331 [['C', 71], ['R', 1]] C 71 98.6%; R 1 1.4% 408 [['T, 71], ['M', 1]] T 71 98.6%; M 1 1.4% 422 [['A', 71], ['S', 1]] A 71 98.6%; M 1 1.4% 423 [['A', 71], ['S', 1]] P 71 98.6%; S 1 1.4% 424 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 447 [['R', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['L', 1]] P 71 98.6%; A 1 1.4% 471 [['Q', 67], ['E', 4], ['H', 1]] G 71 98.6%; A 1 1.4% 472 [['Y', 70], ['E', 4], ['H', 1]] Y 70 97.2%; E 1 1.4%; D 1 1.4% 480 [['X', 71], ['R', 1]] K 71 98.6%; R 1 1.4% 481 [['Y', 70], ['E', 1], ['D', 1]] D 68 97.1%; E 1 1.4%; D 1 1.4% 482 [['M', 69], ['L', 1], ['-', 2]] D 68 97.1%; E 1 1.4%; N 1 1.4% 490 [['H', 69], ['L', 1], ['-', 2]] H 69 98.6%; L 1 1.4% 491 [['N', 69], ['L', 1], ['-', 2]] M 69 98.6%; L 1 1.4% 492 [['N', 69], ['C', 1], ['-', 2]] M 69 98.6%; C 1 1.4% 493 [['Y', 68], ['P', 1], ['-', 2]] M 69 98.6%; C 1 1.4% 494 [['S', 69], ['C', 1], ['-', 2]] M 69 98.6%; D 1.4% 503 [['Y', 68], ['P', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 504 [['Y', 68], ['P', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 505 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 506 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 507 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 508 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 2]] M 69 98.6%; P 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 69], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['Q', 7]] K 65 90.3%; R 7 9.7% 332 [['K', 65], ['Q', 7]] K 65 90.3%; R 7 9.7% 336 [['T', 65], ['Q', 7]] N 65 90.3%; Q 7 9.7% 372 [['N', 65], ['D', 7]] N 65 90.3%; Q 7 9.7% 381 [['C', 71], ['R', 1]] C 71 98.6%; R 11.4% 408 [['T', 71], ['P', 1]] L 71 98.6%; R 11.4% 422 [['L', 71], ['P', 1]] L 71 98.6%; F 11.4% 423 [['A', 71], ['S', 1]] P 71 98.6%; R 11.4% 426 [['P', 71], ['R', 1]] P 71 98.6%; R 11.4% 434 [['R', 71], ['L', 1]] R 71 98.6%; R 11.4% 447 [['A', 71], ['L', 1]] P 71 98.6%; R 11.4% 448 [['R', 71], ['L', 1]] P 71 98.6%; R 11.4% 470 [['P', 71], ['L', 1]] P 71 98.6%; I 11.4% 471 [['Q', 67], ['E', 4], ['H', 1]] Q 67 93.1%; E 4 5.6%; H 1 1.4% 470 [['V', 70], ['E', 1], ['D', 1]] V 70 97.2%; E 11.4%; D 11.4% 480 [['R', 71], ['R', 1]] K 71 98.6%; A 1 1.4% 480 [['R', 71], ['R', 1]] K 71 98.6%; A 1 1.4% 481 [['D', 68], ['P', 2], [-', 2]] L 68 97.1%; F 2 2.9% 489 [['M', 69], ['L', 1], [-', 2]] M 6 9 98.6%; L 1 1.4% 490 [['H', 69], ['L', 1], [-', 2]] M 6 9 98.6%; L 1 1.4% 491 [['V', 68], ['P', 1], [-', 2]] Y 68 97.1%; F 1 1.4%; P 1 1.4% 492 [['V', 68], ['P', 1], [-', 2]] Y 68 97.1%; F 1 1.4%; P 1 1.4% 493 [['V', 68], ['P', 1], [-', 2]] Y 68 97.1%; F 1 1.4%; P 1 1.4% 503 [[S', 67], [F', 1], [P', 1], [-', 2]] Y 68 97.1%; F 1 1.4%; P 1 1.4% 516 [[V', 68], ['Y', 1], [-', 3]] D 68 98.6%; A 1 1.4% 517 [[V', 68], [V', 1], [-', 3]] D 68 98.6%; I 1 1.4% 518 [[V', 68], [V', 1], [-', 3]] D 68 98.6%; I 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,109 0,109 0,109
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [[M', 65], ['V', 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['R', 7]] K 65 90.3%; R 7 9.7% 332 [['K', 65], ['Q', 7]] K 65 90.3%; R 7 9.7% 336 [['T', 65], ['A', 7]] T 65 90.3%; A 7 9.7% 372 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 381 [['C', 71], ['R', 1]] C 71 98.6%; R 1 1.4% 408 [['T', 71], ['P', 1]] L 71 98.6%; R 1 1.4% 422 [['L', 71], ['P', 1]] L 71 98.6%; S 1 1.4% 423 [['A', 71], ['S', 1]] A 71 98.6%; S 1 1.4% 426 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 447 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['L', 1]] P 71 98.6%; H 1 1.4% 471 [['Q', 67], ['E', 4], ['H', 1]] G 67 93.1%; E 4 5.6%; H 1 1.4% 472 [['V', 70], ['E', 1], ['D', 1]] V 70 97.2%; E 11.4%; D 1 1.4% 482 [['D', 68], ['E', 1], ['N', 1], ['-', 2]] D 68 97.1%; E 1 1.4%; N 1 1.4% 482 [['D', 68], ['P', 2], ['-', 2]] L 68 97.1%; P 2 2.9% 489 [['M', 69], ['L', 1], ['-', 2]] M 69 98.6%; L 1 1.4% 490 [['H', 69], ['N', 1], ['-', 2]] M 69 98.6%; N 1 1.4% 491 [['S', 69], ['C', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 492 [['V', 68], ['P', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 493 [['V', 68], ['P', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 494 [['S', 69], ['C', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 495 [['V', 68], ['P', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 509 [['U', 68], ['V', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 510 [['V', 68], ['V', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 511 [['V', 68], ['V', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 512 [['V', 68], ['V', 1], ['-', 2]] S 69 98.6%; N 1 1.4% 513 [['V', 68], ['V', 1], ['-', 3]] S 67 97.1%; F 1 1.4%; P 1 1.4% 514 [['V', 68], ['V', 1], ['-', 3]] S 68 98.6%; N 1 1.4% 515 [['V', 68], ['V', 1], ['-', 3]] S 68 98.6%; N 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,109 0,109
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [['M', 65], ['N', 7]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['N', 7]] H 65 90.3%; R 7 9.7% 332 [['K', 65], ['O', 7]] K 65 90.3%; R 7 9.7% 336 [['T', 65], ['N', 7]] T 65 90.3%; A 7 9.7% 3372 [['N', 65], ['D', 7]] N 65 90.3%; D 7 9.7% 331 [['C', 71], ['R', 1]] C 71 98.6%; R 1 1.4% 408 [['T, 71], ['N', 1]] T 71 98.6%; M 1 1.4% 422 [['L', 71], ['P', 1]] L 71 98.6%; M 1 1.4% 423 [['A', 71], ['S', 1]] A 71 98.6%; R 1 1.4% 424 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 447 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['L', 1]] P 71 98.6%; A 1 1.4% 471 [['Q', 67], ['E', 4], ['H', 1]] G 67 93.1%; E 4 5.6%; H 1 1.4% 472 [['Y', 70], ['E', 4], ['D', 1]] V 70 97.2%; E 1 1.4%; D 1 1.4% 482 [['N', 70], ['E', 1], ['D', 1]] K 71 98.6%; R 1 1.4% 482 [['N', 70], ['E', 1], ['D', 1]] K 79 98.6%; R 1 1.4% 483 [['L', 68], ['P', 2], [-', 2]] L 68 97.1%; E 1 1.4%; D 1 1.4% 494 [['S', 69], ['L', 1], [-', 2]] M 6 9 98.6%; N 1 1.4% 495 [['M', 69], ['D', 1], [-', 2]] M 6 9 98.6%; N 1 1.4% 496 [['M', 69], ['D', 1], [-', 2]] M 6 9 98.6%; N 1 1.4% 497 [['Y', 68], ['Y', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 498 [['S', 69], ['C', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 499 [['Y', 69], ['Y', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 490 [['H', 69], ['N', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 491 [['Y', 68], ['Y', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 492 [['Y', 68], ['Y', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 493 [['Y', 68], ['Y', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 494 [['Y', 68], ['Y', 1], ['-', 3]] S 6 7 9 7.1%; F 1 1.4%; F 1 1.4% 509 [['Y', 68], ['Y', 1], ['-', 3]] S 6 7 9 7.1%; F 1 1.4%; F 1 1.4% 519 [['Y', 68], ['Y', 1], ['-', 3]] S 6 8 98.6%; A 1 1.4% 519 [['Y', 68], ['Y', 1], ['-', 3]] S 6 8 98.6%; A 1 1.4% 519 [['Y', 68], ['Y', 1], ['-', 3]] S 6 8 98.6%; A 1 1.4% 525 [['G', 62], ['A', 7], ['-', 3]] S 6 8 98.6%; A 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,109 0,109 0,109 0,109
314 [['N', 65], ['G', 7]] N 65 90.3%; G 7 9.7% 318 [['L', 65], ['I', 7]] L 65 90.3%; I 7 9.7% 319 [[M', 65], ['V, 3]] M 69 95.8%; V 3 4.2% 329 [['H', 65], ['R', 7]] H 65 90.3%; R 7 9.7% 332 [['K', 65], ['C', 7]] K 65 90.3%; R 7 9.7% 336 [['T', 65], ['A', 7]] T 65 90.3%; A 7 9.7% 3372 [['N', 65], ['D', 7]] N 65 90.3%; A 7 9.7% 331 [['C', 71], ['R', 1]] C 71 98.6%; R 1 1.4% 408 [['T', 71], ['R', 1]] L 71 98.6%; R 1 1.4% 422 [['L', 71], ['P', 1]] L 71 98.6%; S 1 1.4% 423 [['A', 71], ['S', 1]] A 7 1 98.6%; S 1 1.4% 426 [['P', 71], ['R', 1]] P 71 98.6%; R 1 1.4% 434 [['R', 71], ['H', 1]] R 71 98.6%; H 1 1.4% 447 [['K', 65], ['Q', 7]] K 65 90.3%; Q 7 9.7% 467 [['P', 71], ['L', 1]] P 71 98.6%; H 1 1.4% 471 [['G', 67], ['E', 4], ['H', 1]] G 67 93.1%; E 4 5.6%; H 1 1.4% 474 [['G', 71], ['A', 1]] Y 70 97.2%; E 1 1.4%; D 1 1.4% 480 [['K', 71], ['R', 1]] K 71 98.6%; A 1 1.4% 482 [['D', 68], ['E', 1], ['D', 1]] K 71 98.6%; R 1 1.4% 483 [['U', 68], ['P', 2], ['-', 2]] L 68 97.1%; E 1 1.4%; N 1 1.4% 490 [['H', 69], ['N', 1], ['-', 2]] M 6 9 98.6%; L 1 1.4% 491 [['S', 69], ['C', 1], ['-', 2]] M 6 9 98.6%; N 1 1.4% 492 [['V', 68], ['P', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 493 [['S', 69], ['C', 1], ['-', 2]] S 6 9 98.6%; C 1 1.4% 494 [['S', 69], ['P', 1], ['-', 2]] S 6 9 98.6%; N 1 1.4% 495 [['N', 69], ['P', 1], ['-', 2]] S 6 9 98.6%; N 1 1.4% 509 [['U', 68], ['C', 1], ['-', 2]] S 6 9 98.6%; N 1 1.4% 510 [['V', 68], ['C', 1], ['-', 2]] S 6 9 98.6%; N 1 1.4% 511 [['V', 68], ['C', 1], ['-', 2]] S 6 9 98.6%; N 1 1.4% 512 [['V', 68], ['C', 1], ['-', 2]] S 6 9 98.6%; N 1 1.4% 513 [['D', 68], ['C', 1], ['-', 3]] S 6 7 9 7.1%; F 1 1.4%; P 1 1.4% 514 [['V', 68], ['V', 1], ['-', 3]] S 6 8 98.6%; A 1 1.4% 515 [['V', 68], ['V', 1], ['-', 3]] S 6 8 98.6%; A 1 1.4%	0,460 0,250 0,460 0,460 0,460 0,460 0,106 0,106 0,106 0,106 0,106 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,108 0,109 0,109

Domínio	Posição	Contagem absoluta	Frequência	Entropia
Domínio II	92	[['T', 19], ['L', 7], ['M', 46]]	T 19 26.4%; L 7 9.7%; M 46 63.9%	1,247
Domínio III	208	[['R', 15], ['Q', 50], ['K', 7]]	R 15 20.8%; Q 50 69.4%; K 7 9.7%	1,164
Peptídeo Sinal	19	[['N', 13], ['S', 47], ['H', 7], ['-', 5]]	N 13 19.4%; S 47 70.1%; H 7 10.4%	1,158
Domínio II	94	[['T', 45], ['A', 3], ['P', 24]]	T 45 62.5%; A 3 4.2%; P 24 33.3%	1,143
Peptídeo Sinal	15	[['S', 38], ['L', 29], ['-', 5]]	S 38 56.7%; L 29 43.3%	0,987
Domínio II	485	[['T', 27], ['A', 43], ['-', 2]]	T 27 38.6%; A 43 61.4%	0,962
Domínio I	65	[['L', 24], ['F', 43], ['-', 5]]	L 24 35.8%; F 43 64.2%	0,941
Peptídeo Sinal	16	[['G', 45], ['S', 22], ['-', 5]]	G 45 67.2%; S 22 32.8%	0,913
Domínio II	68	[['L', 21], ['P', 46], ['-', 5]]	L 21 31.3%; P 46 68.7%	0,897
Domínio III	368	[['H', 15], ['R', 57]]	H 15 20.8%; R 57 79.2%	0,738
Domínio II	479	[['Q', 64], ['E', 7], ['K', 1]]	Q 64 88.9%; E 7 9.7%; K 1 1.4%	0,564
Domínio II	111	[['E', 49], ['D', 7], ['-', 16]]	E 49 87.5%; D 7 12.5%	0,544
Domínio III	140	[['Q', 49], ['R', 7], ['-', 16]]	Q 49 87.5%; R 7 12.5%	0,544
Domínio I	441	[['I', 63], ['V', 9]]	I 63 87.5%; V 9 12.5%	0,544
Domínio II	522	[['I', 62], ['L', 6], ['V', 1], ['-', 3]]	I 62 89.9%; L 6 8.7%; V 1 1.4%	0,534
Peptídeo Sinal	20	[['I', 59], ['V', 8], ['-', 5]]	I 59 88.1%; V 8 11.9%	0,528
Peptídeo Sinal	23	[['G', 59], ['A', 8], ['-', 5]]	G 59 88.1%; A 8 11.9%	0,528
Domínio II	484	[['D', 62], ['E', 8], ['-', 2]]	D 62 88.6%; E 8 11.4%	0,513
Domínio II	534	[['R', 63], ['H', 2], ['C', 4], ['-', 3]]	R 63 91.3%; H 2 2.9%; C 4 5.8%	0,506
Domínio II	99	[['H', 64], ['R', 8]]	H 64 88.9%; R 8 11.1%	0,503
Domínio I	446	[['T' 64] ['A' 8]]	T 64 88 9%· Δ 8 11 1%	0.503

Analisando a região de petídeo sinal, somente humanos e Rhinopithecus foram polimórficos dentre as espécies da amostra. Destacamos que no resíduo 20 há uma inversão entre o aminoácido prevalente para de cada espécie (Rhinopithecus V 87.50% e I 12.50%, enquanto em Homo sapiens V 3.70% e I 96.30%). Em relação às posições associadas a variantes patogênicas humanas de alta relevância clínica, a maioria mostrou-se conservada entre os primatas analisados (não polimórficas), como a p.L483P (associada à DG tipos 2 e 3), indicando forte pressão seletiva negativa. Árvore filogenética da calculada a partir

de sequências proteicas da GCase

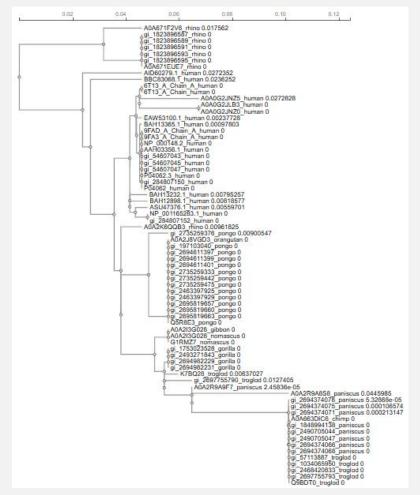


Figura 1: Árvore filogenética das sequências da proteína GCase (GBA1) em humanos (Homo sapiens) e primatas próximos. Observa-se a formação de clados distintos que agrupam sequências de Pongo pygmaeus (orangotango), Rhinopithecus strykeri (rinopiteco), Pan paniscus (bonobo), Pan troglodytes (chimpanzé), Gorilla gorilla (gorila) e Nomascus leucogenys (gibão), refletindo a proximidade evolutiva entre essas espécies e os humanos.

CONCLUSÕES

A análise comparativa do polimorfismo da proteína codificada pelo gene GBA1 em primatas revelou sítios polimórficos nos primatas não humanos distintos dos humanos. A alta conservação de sítios diretamente ligados a formas graves da DG reforça sua criticidade funcional - enquanto a variabilidade observada em outras regiões, como no peptídeo sinal, dissulfeto e região enzimática, podem refletir distintas pressões evolutivas, que resultaram em mutações cujos significados funcionais e enzimáticos serão estudados. Estes achados direcionarão futuros experimentos de engenharia de proteínas, nos quais quimeras com alterações em resíduos específicos poderão ser testadas in vitro para avaliar o impacto na estabilidade da proteína e sua atividade.

PALAVRAS-CHAVE

Doença de Gaucher, GBA1, filogenética, polimorfismo.









