

## Hematologically Important Mutations: Gaucher Disease

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Gaucher Disease is the most common of the glycolipid storage disorders. Recent reviews provide details of the genetics, pathogenesis and treatment of this disorder (1-11).

Mutations of *GBA*, the gene that encodes glucocerebrosidase, cause the disease. Since the sequence of the gene was first published (12) many laboratories have contributed to elucidating the broad spectrum of such mutations. The disease is most common in the Jewish population, and here several mutations, 1226G, 84GG, IVS2(+1), and 1604A predominate. Each of these mutations are probably descendants of a single mutational event, judging from the haplotype in which each exists. We have divided the mutations into three groups, based on their deduced and observed phenotypic effects. This classification is summarized in Table 1. Null alleles are those, such as the single nucleotide insertion of the 84GG mutation, that cannot direct any enzyme production. Severe alleles are those that can produce enzyme, but that, when inherited with a null or another severe allele are usually associated with neuronopathic (Type II or III) disease. Mild alleles are those that are only associated with non-neuronopathic (Type I) disease.

Exactly one year ago we published a tabulation of the 79 mutations known to us at that time. The number of mutations described has continued to increase at a rapid pace, and we now know of 109 mutations that have been described in patients with Gaucher disease. The newly described mutations have been added to the tabulation. Moreover, some mutations that could not previously be classified with respect to severity have now been classified on the basis of new information.

As recently proposed (13), nucleotide sequences are numbered from the upstream initiator ATG using for the cDNA sequence (12,14) and for the genomic sequence (15). To convert the published sequence number to those in the tabulation it is necessary to subtract 93 from the numbers in the publications for the cDNA and 583 from the numbers for the genomic sequence. The amino acid sequence is that of the mature protein, after cleavage of the leader sequence. Table 2 presents single mutations that are associated with Gaucher disease, while Table 3 presents multiple mutations that appear to have arisen as recombination events with the pseudogene 16 Kb downstream from the functional *GBA* gene.

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Table 1. The Expected Clinical Phenotype when Mutations Classified as Null, Severe, and Mild are Combined

		<i>One Allele</i>		
		<b>Null</b>	<b>Severe</b>	<b>Mild</b>
<i>Other Allele</i>	<b>Null</b>	Non-viable	Type II/III	Type I
	<b>Severe</b>	Type II/III	Type II/III	Type I
	<b>Mild</b>	Type I	Type I	Type I

Table 2. One Hundred Six Glucocerebrosidase Mutations not Resulting from Recombination with the Pseudogene

cDNA Nucleotide Substitution	Genomic Nucleotide	Exon	Amino Acid Substitution	Severity	Reference
72C→del	440	2	Frameshift	Null	(16)
84G→GG	452	2	Frameshift	Null	(17)
108G→A	476	2	(-4) Trp→Stop	Null	(18)
IVS2+1g→a*	484	Intron 2	Splice	Null	(19)
121C→CC	1042	3	Frameshift	Null	(20)
160G→T	1080	3	15 Val→Leu	Mild	(21)
203C→del	1124	3	Frameshift	Null	(22)
226T→G	1147	3	37 Phe→Val	Mild	(23)
245C→T	1166	3	43 Thr→Ile	Unknown	(24)
254G→A	1175	3	46 Gly→Glu	Mild	(21)
259C→T*	1180	3	48 Arg→Trp	Mild	(24)
337A→T	1381	4	74 Lys→Stop	Null	(25)
354G→C	1398	4	79 Lys→Asn	Mild	(26)
437C→T	1481	4	107 Ser→Leu	Severe	(27)
455G→A	2456	5	113 Gly→Glu	Unknown	(18)
475C→T*	2476	5	120 Arg→Trp	Severe**	(26)
476G→A	2477	5	120 Arg→Gln	Unknown	(28)
481C→T	2482	5	122 Pro→Ser	Mild	(16)
500T→TT	2501	5	Frameshift	Null	(18)
517A→C	2518	5	134 Thr→Pro	Unknown	(18)
532C→del	2533	5	Frameshift	Null	(29)
535G→C†	2536	5	140 Asp→His	Unknown	(30)
586A→C	2587	5	157 Lys→Gln	Severe	(30)
IVS5+1g→t	2590	intron 5	Splice	Null	(18)
593C→T	2804	6	159 Pro→Leu	Mild	(27)
599T→G	2810	6	161 Ile→Ser	Unknown	(31)

cDNA Nucleotide Substitution	Genomic Nucleotide	Exon	Amino Acid Substitution	Severity	Reference
604C→T	2815	6	163 Arg→Stop	Null	(27)
622C→T	2833	6	169 Gln→Stop	Null	(18)
635C→G	2846	6	173 Ser→Stop	Null	(24)
644C→A	2855	6	176 Ala→Asp	Unknown	(22)
649C→T	2860	6	178 Pro→Ser	Severe	(32)
653G→A	2864	6	179 Trp→Stop	Null	(25)
661C→A	2872	6	182 Pro→Thr	Unknown	(22)
680A→G*	2891	6	188 Asn→Ser	Mild	(21)
683G→T	2894	6	189Gly→Val	Mild**	(33)
689T→G*	2900	6	191 Val→Gly	Unknown	(34)
701G→A	2912	6	195 Gly→Glu	Unknown	(25)
721G→A*	2932	6	202 Gly→Arg	Severe	(22)
751T→C	2962	6	212 Tyr→His	Unknown	(16)
754T→A*	2965	6	213 Phe→Ile	Severe	(35)
764T→A	3530	7	216 Phe→Tyr	Mild	(36)
886C→T	3652	7	257 Arg→Stop	Null	(18)
887G→A	3653	7	257 Arg→Gln	Unknown	(22)
911G→A	3677	7	265 Gly→Asp	Unknown	(31)
914C→del	3680	7	Frameshift	Null	(24)
914C→G	3680	7	266 Pro→Arg	Mild	(37)
929G→A	3695	7	271 Ser→Asn	Mild	(25)
970C→T	3736	7	285 Arg→Cys	Unknown	(22)
983C→T	3749	7	289 Pro→Leu	Mild	(38)
1043C→T	4676	8	309 Ala→Val	Unknown	(39)
1053G→T	4686	8	312 Trp→Cys	Mild	(39)
1054T→C	4687	8	313 Tyr→His	Unknown	(40)
1060G→C	4693	8	315 Asp→His	Unknown	(37)
1070C→A	4703	8	318Ala→Asp	Unknown	(37)
1085C→T	4718	8	323 Thr→Ile	Unknown	(38)
1090G→A*	4723	8	325 Gly→Arg	Severe	(41)
1093G→A†	4726	8	326 Glu→Lys	Unknown	(30)
1098A→AA	4731	8	Frameshift	Null	(40)
1138G→A	4771	8	341 Ala→Thr	Severe	(27)
1141T→G	4774	8	342 Cys→Gly	Severe	(41)
1171G→C	4804	8	352 Val→Leu	Mild**	(25)
1192C→T	4825	8	359 Arg→Stop	Null	(42)
1193G→A	4826	8	359 Arg→Gln	Mild	(43)
1208G→C	4841	8	364 Ser→Thr	Mild	(39)
1213A→G	4846	8	366 Ser→Gly	Severe**	(33)
1214G→A	4847	8	366 Ser→Asn	Unknown	(27)
1223C→T	4856	8	369 Thr→Met	Unknown	(26)
1226A→G	5258	9	370 Asn→Ser	Mild	(44)
1240G→T	5272	9	375 Val→Leu	Mild	(45)

cDNA Nucleotide Substitution	Genomic Nucleotide	Exon	Amino Acid Substitution	Severity	Reference
1246G→A	5278	9	377 Gly→Ser	Mild	(46)
1249T→G	5281	9	378 Trp→Gly	Unknown	(22)
1255G→A	5287	9	380 Asp→Asn	Unknown	(22)
1256A→C	5288	9	380 Asp→Ala	Unknown	(47)
1263-1317 del*	5296-5350 del	9	Frameshift	Null	(16)
1283G→A	5315	9	389 Gly→Glu	Severe	(18)
1289C→T	5321	9	391 Pro→Leu	Unknown	(18)
1292A→T	5324	9	392 Asn→Ile	Severe	(18)
1294T→A	5326	9	393 Trp→Arg	Unknown	(27)
1297G→T	5329	9	394 Val→Leu	Severe	(48)
1304A→C	5335	9	396 Asn→Thr	Mild	(49)
1309G→C	5341	9	398 Val→Leu	Severe	(50)
1312G→A	5344	9	399 Asp→Asn	Severe	(42)
1322T→C	5354	9	402 Ile→Thr	Mild	(45)
1342G→C*	5374	9	409 Asp→His	Severe	(48)
1343A→T	5375	9	409 Asp→Val	Severe	(48)
1348T→A	5380	9	411 Phe→Ile	Unknown	(31)
1351T→C	5383	9	412 Tyr→His	Unknown	(18)
1354A→C	5386	9	413 Lys→Gln	Mild**	(33)
1357C→T	5389	9	414 Gln→Stop	Null	(26)
1361C→G	5393	9	415 Pro→Arg	Severe	(51)
1366T→G	5398	9	417 Phe→Val	Unknown	(52)
1370A→G	5402	9	418 Tyr→Cys	Unknown	(53)
1390A→G	5792	10	425 Lys→Glu	Severe	(43)
1413A→G	5815	10	433 Arg→Gly	Mild**	(33)
1447-1466 del TG ins	5849-5868 del TG ins	10	Frameshift	Null	(54)
1448T→G	5850	10	444 Leu→Arg	Severe	(54)
1448T→C*	5850	10	444 Leu→Pro	Severe	(55)
1451-1452 AC del	5853-5854 del	10	Frameshift	Null	(25)
1504C→T	5906	10	463 Arg→Cys	Unknown	(56)
1505G→A	5907	10	463 Arg→Gln <sup>‡</sup>	Null	(57)
IVS10+2t→g	5909	intron 10	Splice	Null	(24)
1549G→A	6045	11	478 Gly→Ser	Unknown	(16)
1589C→T	6085	11	491 Thr→Ile	Severe	(50)
1603C→T	6099	11	496 Arg→Cys	Mild	(43)
1604G→A	6100	11	496 Arg→His	Mild	(16)
Total Gene del	All	All	NA	Null	(58)

\*Mutation represents normal sequence in pseudogene

\*\* new information can classify severity

†Same allele

‡ Creates an abnormal splice site which results in early termination

Table 3. The Three Combinations of Multiple Mutations (Crossovers or Gene Conversions) that have been Documented in the Glucocerebrosidase Gene

Location of Crossover*				Exons affected	cDNA Substitution	Amino Acid Substitution	Severity	Reference
cDNA	Genomic	5' limit	3' limit					
455 <sup>†</sup>	475	2456	2476	5	475 C→T	120 Arg→Try	Unknown	(39)
				6	667 T→C	184 Try→Arg		
				6	681 T→G	188 Asn→Lys		
754	812	2965	3578	6	689 T→G	191 Val→Gly		
				6	703 T→C	196 Ser→Pro		
				6	721 G→A	202 Gly→Arg		
				6	754 T→A	213 Phe→Ile		
1317	1343	5349	5375	9	1342 G→C	409 Asp→His	Severe	(41)
				10	1448 T→C	444 Leu→Pro		
				10	1483 G→C	456 Ala→Pro		(59)
				10	1497 G→C	460 Val→Val		
1342	1388	5374	5689	10	1448 T→C	444 Leu→Pro	Severe	(41-56)
				10	1483 G→C	456 Ala→Pro		
				10	1497 G→C	460 Val→Val		

\*Due to the extreme homology between the glucocerebrosidase gene and pseudogene the exact point of the crossover cannot always be determined and limits are given at the positions where the two sequences differ.

<sup>†</sup>This crossover event occurs from the glucocerebrosidase gene to the pseudogene and back to the glucocerebrosidase gene.

<sup>‡</sup>fusion gene.

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## REFERENCES

1. Beutler E, Gelbart T. Mutation update: Glucocerebrosidase (Gaucher disease). *Hum Mutat* 8:207-213, 1996.
2. Grabowski GA, Saal HM, Wenstrup RJ, Barton NW. Gaucher disease: A prototype for molecular medicine. *Crit Rev Oncol Hematol* 23:25-55, 1996.
3. Balicki D, Beutler E. Gaucher disease. *Medicine (Baltimore)* 74:305-323, 1995.
4. Beutler E, Grabowski GA: Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill Publishing Company, pp. 2641-2670, 1995.
5. Beutler E, Demina A, Laubscher K, et al. The clinical course of treated and untreated Gaucher disease. A study of 45 patients. *Blood Cells Mol Dis* 21:86-108, 1995.
6. Beutler E. Gaucher disease. *Curr Opin Hematol* 4:19-23, 1997.
7. Beutler E. Gaucher disease. *Adv Genet* 32:17-49, 1995.
8. Elstein D, Zimran A. Recent advances in diagnosis and therapy in Gaucher's disease. *Isr J Med Sci* 31:505-509, 1995.
9. Petrides PE. Morbus Gaucher. Diagnose und Therapie. *Dtsch Med Wochenschr* 120:1177-1182, 1995.
10. Kaminsky P, Belmatoug N, Billette de Villemeur T. Gaucher disease. *Presse Medicale* 25:108-112, 01-27-1996.
11. Sidransky E. New perspectives in type 2 Gaucher disease. *Adv Pediatr* 44:73-107, 1997.
12. Sorge J, West C, Westwood B, Beutler E. Molecular

- cloning and nucleotide sequence of the human glucocerebrosidase gene. *Proc Natl Acad Sci USA* 82:7289-7293, 1985.
13. Beutler E, McKusick VA, Motulsky AG, Scriver CR, Hutchinson F. Mutation nomenclature: Nicknames, systematic names, and unique identifiers. *Hum Mutat* 8:203-206, 1996.
  14. Sorge J, West C, Westwood B, Beutler E. Correction. *Proc Natl Acad Sci USA* 83:3567-3567, 1986.
  15. Horowitz M, Wilder S, Horowitz Z, Reiner O, Gelbart T, Beutler E. The human glucocerebrosidase gene and pseudogene: Structure and evolution. *Genomics* 4:87-96, 1989.
  16. Beutler E, Gelbart T, West C. Identification of six new Gaucher disease mutations. *Genomics* 15:203-205, 1993.
  17. Beutler E, Gelbart T, Kuhl W, Sorge J, West C. Identification of the second common Jewish Gaucher disease mutation makes possible population based screening for the heterozygous state. *Proc Natl Acad Sci USA* 88:10544-10547, 1991.
  18. Cormand B, Grinberg D, Gort L, Chabas A, Vilageliu L. Molecular analysis and clinical findings in the Spanish Gaucher disease population. Putative haplotype of the N370S ancestral chromosome. *Hum Mutat* In press 1998.
  19. Beutler E, Gelbart T, Kuhl W, Zimran A, West C. Mutations in Jewish patients with Gaucher disease. *Blood* 79:1662-1666, 1992.
  20. Choy FYM, Humphries ML, Ferreira P. Novel insertion mutation in a non-Jewish Caucasian type 1 Gaucher disease patient. *Am J Med Genet* 68:211-215, 1997.
  21. Kim J-W, Liou BB, Lai M-Y, Ponce E, Grabowski GA. Gaucher disease: Identification of three new mutations in the Korean and Chinese (Taiwanese) populations. *Hum Mutat* 7:214-218, 1996.
  22. Beutler E, Gelbart T, Demina A. Glucocerebrosidase mutations in Gaucher disease. *Molecular Medicine* 1:82-92, 1994.
  23. Choy FYM, Humphries ML, Shi HP. Identification of two novel and four uncommon missense mutations among Chinese Gaucher disease patients. *Am J Med Genet* 71:172-178, 1997.
  24. Beutler E, Gelbart T, Demina A, Zimran A, LeCoutre P. Five new Gaucher disease mutations. *Blood Cells Mol Dis* 21:20-24, 1995.
  25. Grace ME, Desnick RJ, Pastores GM. Identification and expression of acid beta-glucosidase mutations causing severe type 1 and neurologic type 2 Gaucher disease in non-Jewish patients. *J Clin Invest* 99:2530-2537, 1997.
  26. Beutler E, Gelbart T, Balicki D, et al. Gaucher disease: Four families with previously undescribed mutations. *Proc Assoc Amer Phys* 108:179-184, 1996.
  27. Demina A, Beutler E. Six new Gaucher disease mutations. *Acta Haematol (Basel)* In press 1998.
  28. Graves PN, Grabowski GA, Eisner R, Palese P, Smith FI. Gaucher disease type 1: Cloning and characterization of a cDNA encoding acid  $\beta$ -glucosidase from an Ashkenazi Jewish patient. *DNA* 7:521-528, 1988.
  29. Tayebi N, Cushner SR, Kleijer W, et al. Prenatal lethality of a homozygous null mutation in the human glucocerebrosidase gene. *Am J Med Genet* 73:41-47, 1997.
  30. Eyal N, Firon N, Wilder S, Kolodny EH, Horowitz M. Three unique base pair changes in a family with Gaucher disease. *Hum Genet* 87:328-332, 1991.
  31. Cormand B, Harboe TL, Gort L, et al. Mutation analysis of Gaucher disease patients from Argentina: High prevalence of the RecNciI mutation. *In preparation* 1998.
  32. Choy FYM, Wei C. Identification of a new mutation (P178S) in an African-American patient with type 2 Gaucher disease. *Hum Mutat* 5:345-347, 1995.
  33. Ida H, Rennert OM, Kawame H, Maekawa K, Eto Y. Mutation prevalence among 47 unrelated Japanese patients with Gaucher disease: Identification of four novel mutations. *J Inher Metab Dis* 20:67-73, 1997.
  34. Beutler E, Demina A. *Unpublished* 1998.
  35. Kawame H, Eto Y. A new glucocerebrosidase-gene missense mutation responsible for neuronopathic Gaucher disease in Japanese patients. *Am J Hum Genet* 49:1378-1380, 1991.
  36. Beutler E, Gelbart T. Gaucher disease associated with a unique *KpnI* restriction site: identification of the amino acid substitution. *Ann Hum Genet* 54:149-153, 1990.
  37. Walley AJ, Ellis I, Harris A. Three unrelated Gaucher's disease patients with three novel point mutations in the glucocerebrosidase gene (P266R, D315H and A318D). *Br J Haematol* 91:330-332, 1995.
  38. He G-S, Grace ME, Grabowski GA. Gaucher disease: Four rare missense mutations encoding F213I, F289Y, T323I and R463C in type I variants. *Hum Mutat* 1:423-427, 1992.
  39. Latham TE, Theophilus BDM, Grabowski GA, Smith FI. Heterogeneity of mutations in the acid  $\beta$ -glucosidase gene of Gaucher disease patients. *DNA Cell Biol* 10:15-21, 1991.
  40. Cormand B, Vilageliu L, Balcels S, Gonzalez-Duarte R, Chabas A, Grinberg D. Two novel (1098insA and Y313H) and one rare (R359Q) mutations detected in exon 8 of the beta-glucocerebrosidase gene in Gaucher's disease patients. *Hum Mutat* 7:272-274, 1996.
  41. Eyal N, Wilder S, Horowitz M. Prevalent and rare mutations among Gaucher patients. *Gene* 96:277-283, 1990.
  42. Beutler E, Gelbart T. Two new Gaucher disease

- mutations. *Hum Genet* 93:209-210, 1994.
43. Kawame H, Hasegawa Y, Eto Y, Maekawa K. Rapid identification of mutations in the glucocerebrosidase gene of Gaucher disease patients by analysis of single-strand conformation polymorphisms. *Hum Genet* 90:294-296, 1992.
  44. Tsuji S, Martin BM, Barranger JA, Stubblefield BK, LaMarca ME, Ginns EI. Genetic heterogeneity in type 1 Gaucher disease: Multiple genotypes in Ashkenazic and non-Ashkenazic individuals. *Proc Natl Acad Sci USA* 85:2349-2352, 5708, 1988.
  45. Cormand B, Grinberg D, Gort L, et al. Two new mild homozygous mutations in Gaucher disease patients: Clinical signs and biochemical analyses. *Am J Med Genet* 70:437-443, 1997.
  46. Laubscher KH, Glew RH, Lee RE, Okinaka RT. Use of denaturing gradient gel electrophoresis to identify mutant sequences in the  $\beta$ -glucosidase gene. *Hum Mutat* 3:411-415, 1994.
  47. Walley AJ, Harris A. A novel point mutation (D380A) and a rare deletion (1255del55) in the glucocerebrosidase gene causing Gaucher's disease. *Hum Mol Genet* 2:1737-1738, 1993.
  48. Theophilus BDM, Latham T, Grabowski GA, Smith FI. Comparison of RNase A, chemical cleavage, and GC-clamped denaturing gradient gel electrophoresis for the detection of mutations in exon 9 of the human acid  $\beta$ -glucosidase gene. *Nucleic Acids Res* 17:7707-7722, 1989.
  49. Amaral O, Pinto E, Fortuna M, Lacerda L, Miranda MCS. Type I Gaucher disease: Identification of N396T and prevalence of glucocerebrosidase mutations in the Portuguese. *Hum Mutat* 8:280-281, 1996.
  50. Seeman PJV, Finckh U, Hoepfner J, et al. Two new missense mutations in a non-Jewish Caucasian family with type 3 Gaucher disease. *Neurology* 46:1102-1107, 1996.
  51. Wigderson M, Firon N, Horowitz Z, et al. Characterization of mutations in Gaucher patients by cDNA cloning. *Am J Hum Genet* 44:365-377, 1989.
  52. Choy FYM, Wei C, Applegarth DA, Yong S-L. A new missense mutation in glucocerebrosidase exon 9 of a non-Jewish Caucasian type 1 Gaucher disease patient. *Hum Mol Genet* 3:821-823, 1994.
  53. Tuteja R, Tuteja N, Lilliu F, et al. Y418C: A novel mutation in exon 9 of the glucocerebrosidase gene of a patient with Gaucher disease creates a new Bgl I site. *Hum Genet* 94:314-315, 1994.
  54. Uchiyama A, Tomatsu S, Kondo N, et al. New Gaucher disease mutations in exon 10: A novel L444R mutation produces a new Nci I site the same as L444P. *Hum Mol Genet* 3:1183-1184, 1994.
  55. Tsuji S, Choudary PV, Martin BM, et al. A mutation in the human glucocerebrosidase gene in neuronopathic Gaucher's disease. *N Engl J Med* 316:570-575, 1987.
  56. Hong CM, Ohashi T, Yu XJ, Weiler S, Barranger JA. Sequence of two alleles responsible for Gaucher disease. *DNA Cell Biol* 9:233-241, 1990.
  57. Ohshima T, Sasaki M, Matsuzaka T, Sakuragawa N. A novel splicing abnormality in a Japanese patient with Gaucher's disease. *Hum Mol Genet* 2:1497-1498, 1993.
  58. Beutler E, Gelbart T. Erroneous assignment of Gaucher disease genotype as a consequence of a complete gene deletion. *Hum Mutat* 4:212-216, 1995.
  59. Latham T, Grabowski GA, Theophilus BDM, Smith FI. Complex alleles of the acid  $\beta$ -glucosidase gene in Gaucher disease. *Am J Hum Genet* 47:79-86, 1990.
  60. Zimran A, Sorge J, Gross E, Kubitz M, West C, Beutler E. A glucocerebrosidase fusion gene in Gaucher disease. Implications for the molecular anatomy, pathogenesis and diagnosis of this disorder. *J Clin Invest* 85:219-222, 1990.