

# Hematologically Important Mutations: Gaucher Disease

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Ernest Beutler<sup>1</sup>, Terri Gelbart<sup>2</sup>

A large number of mutations of the glucocerebrosidase gene (*GBA*) have been identified in patients with Gaucher disease, the most common glycolipid storage disorder. Reviews of the various aspects of this disease have been published in the past two years (1-10). A tabulation of the mutations that were known by the end of 1995 has also appeared (11).

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 descendents of a single mutational event, judging from the haplo-

type 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.

**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

<sup>1</sup> Reprint Requests to: Ernest Beutler, M.D., The Scripps Research Institute, Department of Molecular and Experimental Medicine, 10550 North Torrey Pines Road, La Jolla, CA 92037, phone (619)784-8040, fax (619)784-2083, e-mail: beutler@scripps.edu;

<sup>2</sup> The Scripps Research Institute, Department of Molecular and Experimental Medicine, 10550 North Torrey Pines Road, La Jolla, CA 92037.

As recently proposed (12), nucleotide sequences are all numbered from the upstream initiator ATG. 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.

**Table 2.** Seventy-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	(13)
84G→GG	452	2	Frameshift	Null	(14)
IVS2+1g→a*	484	Intron 2	Splice	Null	(15)
160G→T	1080	3	15 Val→Leu	Mild	(16)
203C→del	1124	3	Frameshift	Null	(17)
245C→T	1166	3	43 Thr→Ile	Unknown	(18)
254G→A	1175	3	46 Gly→Glu	Mild	(16)
259C→T*	1180	3	48 Arg→Trp	Mild	(18)
337A→T	1381	4	74 Lys→Stop	Null	(19)
354G→C	1398	4	79 Lys→Asn	Mild	(20)
475C→T*	2476	5	120 Arg→Trp	Unknown	(20)
476G→A	2477	5	120 Arg→Gln	Unknown	(21)
481C→T	2482	5	122 Pro→Ser	Mild	(13)
535G→C†	2536	5	140 Asp→His	Unknown	(22)
586A→C	2587	5	157 Lys→Gln	Severe	(22)
635C→G	2846	6	173 Ser→Stop	Null	(18)
644C→A	2855	6	176 Ala→Asp	Unknown	(17)
649C→T	2860	6	178 Pro→Ser	Severe	(23)
653G→A	2864	6	179 Trp→Stop	Null	(19)
661C→A	2872	6	182 Pro→Thr	Unknown	(17)
680A→G*	2891	6	188 Asn→Ser	Mild	(16)
683G→T	2894	6	189 Gly→Val	Unknown	(24)
721G→A*	2932	6	202 Gly→Arg	Severe	(17)
751T→C	2962	6	212 Tyr→His	Unknown	(13)
754T→A*	2965	6	213 Phe→Ile	Severe	(25)
764T→A	3530	7	216 Phe→Tyr	Mild	(26)
887G→A	3653	7	257 Arg→Gln	Unknown	(17)
914C→del	3680	7	Frameshift	Null	(18)
914C→G	3680	7	266 Pro→Arg	Mild	(27)
970C→T	3736	7	285 Arg→Cys	Unknown	(17)
983C→T	3749	7	289 Pro→Leu	Mild	(28)
1043C→T	4676	8	309 Ala→Val	Unknown	(29)
1053G→T	4686	8	312 Trp→Cys	Mild	(29)
1060G→C	4693	8	315 Asp→His	Unknown	(27)
1070C→A	4703	8	318 Ala→Asp	Unknown	(27)

cDNA Nucleotide Substitution	Genomic Nucleotide	Exon	Amino Acid Substitution	Severity	Reference
1085C→T	4718	8	323 Thr→Ile	Unknown	(28)
1090G→A*	4723	8	325 Gly→Arg	Severe	(30)
1093G→A**	4726	8	326 Glu→Lys	Unknown	(22)
1141T→G	4774	8	342 Cys→Gly	Severe	(30)
1171G→C	4804	8	352 Val→Leu	Unknown	(19)
1192C→T	4825	8	359 Arg→Stop	Null	(31)
1193G→A	4826	8	359 Arg→Gln	Mild	(32)
1208G→C	4841	8	364 Ser→Thr	Mild	(29)
1213A→G	4846	8	366 Ser→Gly	Unknown	(24)
1214G→A	4847	8	366 Ser→Asn	Unknown	(33)
1223C→T	4856	8	369 Thr→Met	Unknown	(20)
1226A→G	5258	9	370 Asn→Ser	Mild	(34)
1246G→A	5278	9	377 Gly→Ser	Mild	(35)
1249T→G	5281	9	378 Trp→Gly	Unknown	(17)
1255G→A	5287	9	380 Asp→Asn	Unknown	(17)
1256A→C	5288	9	380 Asp→Ala	Severe	(36)
1263-1317 del	5296-5350 del	9	Frameshift	Null	(13)
1297G→T	5329	9	394 Val→Leu	Severe	(37)
1304A→C	5335	9	396 Asn→Thr	Mild	(38)
1309G→C	5341	9	398 Val→Leu	Severe	(39)
1312G→A	5344	9	399 Asp→Asn	Severe	(31)
1342G→C*	5374	9	409 Asp→His	Severe	(37)
1343A→T	5375	9	409 Asp→Val	Severe	(37)
1354A→C	5386	9	413 Lys→Gln	Unknown	(24)
1357C→T	5389	9	414 Gln→Stop	Null	(20)
1361C→G	5393	9	415 Pro→Arg	Severe	(40)
1366T→G	5398	9	417 Phe→Val	Unknown	(41)
1370A→G	5402	9	418 Tyr→Cys	Unknown	(42)
1390A→G	5792	10	425 Lys→Glu	Severe	(32)
1413A→G	5815	10	433 Arg→Gly	Unknown	(24)
1447-1466 del, TG ins	5849-5868 del TG ins	10	Frameshift	Null	(43)
1448T→G	5850	10	444 Leu→Arg	Severe	(43)
1448T→C*	5850	10	444 Leu→Pro	Severe	(44)
1504C→T	5906	10	463 Arg→Cys	Unknown	(45)
1505G→A	5907	10	463 Arg→Gln <sup>†</sup>	Null	(46)
IVS10+2t→g	5909	intron 10	Splice	Null	(18)
1549G→A	6045	11	478 Gly→Ser	Unknown	(13)
1589C→T	6085	11	491 Thr→Ile	Severe	(39)
1603C→T	6099	11	496 Arg→Cys	Mild	(32)
1604G→A	6100	11	496 Arg→His	Mild	(13)
Total Gene del	All	All	NA	Null	(47)

\* Mutation represents normal sequence in pseudogene

\*\* Same allele

<sup>†</sup> 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	5' limit	3' limit					
455 <sup>†</sup>	475	(2456)	(2476)	5	475 C→T	120 Arg→Try	Unknown	(29)
				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		
				9	1342 G→C	409 Asp→His		
1317	1343	(5349)	(5375)	10	1448 T→C	444 Leu→Pro	Severe	(30)
				10	1483 G→C	456 Ala→Pro	Severe	(48)
				10	1497 G→C	460 Val→Val		
				10	1497 G→C	460 Val→Val		
1342	1388	(5374)	5689	10	1448 T→C	444 Leu→Pro	Severe	(30) (45)
				10	1483 G→C	456 Ala→Pro		(48)
				10	1497 G→C	460 Val→Val		(49) <sup>‡</sup>

\* 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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