

Hematologically Important Mutations: Glanzmann Thrombasthenia

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INTRODUCTION

Glanzmann thrombasthenia is an autosomal recessive bleeding disorder characterized by a quantitative or qualitative abnormality of platelet GPIIb/IIIa receptors. This life-long bleeding diathesis is characterized by mucocutaneous hemorrhage with easy bruising, menorrhagia, epistaxis, gingival hemorrhage, and intermittent episodes of gastrointestinal bleeding. The dysfunctional GPIIb/IIIa receptor can either be absent or present on the platelet surface, but the platelets of all patients with Glanzmann thrombasthenia are functionally indistinguishable in that they do not aggregate in response to physiologic agonists such as ADP, thrombin, or epinephrine. Excellent reviews of the clinical spectrum of disease and the biochemical characterization of the defect have been published (1,2). A total of 26 GPIIb mutations have been identified, of which 16 are point mutations resulting in missense or nonsense codons; 5 are deletions and insertions, of which 3 are deletions, 1 is a deletion/insertion, and 1 is an insertion; and 5 are RNA splice mutations, of which 4 are within the consensus splice sequence and 1 is a point mutation resulting in the creation of an alternative splice site. Within the 26 GPIIb mutations, 16 have been identified once; an R358H (R327H) and a T→C exon 29 splice donor site mutation have each been identified in two separate kindreds; and one R584X (R553X) mutation has been identified in six different kindreds. A total of 23 GPIIIa mutations have been identified, of which 13 are point mutations resulting in missense or nonsense codons; 7 are deletions/insertions/inversions, of which 5 are deletions, 1 is a deletion and inver-

sion, and 1 is an insertion; and 3 are splice site mutations. Within the 23 GPIIIa mutations, an D145Y (D119Y) mutation and an D145N (D119N) mutation have been identified in separate kindreds, an R240W (R214W) mutation has been identified in two separate kindreds, and an R240Q (R214Q) mutation has been identified in another kindred. Of note, GPIIIa patient number 7 is a heterozygote who does not have the Glanzmann thrombasthenia phenotype; his mutation was identified as a result of an evaluation for thrombocytopenia.

This registry tabulates the known molecular defects in the genes encoding GPIIb and GPIIIa, the known clinical and biochemical information on the patients and the one carrier of Glanzmann thrombasthenia, and mammalian cell expression studies that have been performed to characterize the mutations.

The GPIIb and GPIIIa mutations are identified according to cDNA nucleotide numbers taken from GenBank sequences based on Poncz et al. (3) and Fitzgerald et al. (4). The GenBank accession number for GPIIb is JO2764 and for GPIIIa is JO2703. In the tables, the cDNA nucleotide numbering begins with the A nucleotide of the ATG start codon as +1. To locate these nucleotides in the GenBank and published sequences, one nucleotide must be added to the GPIIb numbering and 20 nucleotides must be added to the GPIIIa numbering. In the tables, the amino acid numbering begins with methionine of the ATG start codon, and both the amino acid numbers including the leader sequence and excluding the leader sequence (in parentheses) are provided. The mutation nomenclature that is used in the tables is based on published recommendations (5,6).

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GPIIb MUTATIONS

No.	Patient and Classification ¹	Genotype	Mutation ² cDNA Nucleotide Number ³	Amino Acid Substitution ⁴
1	KW I	Homozygote	IVS1→IVS9del4.5kb ⁵ resulting in alternative splicing of exon 1	Premature termination within intron 1
2	Arab ⁶ I	Homozygote	IVS3(-3)→418del ⁷ resulting in use of an alternative splice at 425AG in exon 4	A137-Q142del (include C138)
3	Frankfurt I II	Homozygote	620C→T Exon 5	T207I (T176I)
4	LW II	Homozygote	641T→C Exon 6	L214P (L183P)
5	FLD I	Homozygote	818G→A Exon 8	G273D (G242D)
6	FL I	Homozygote	1063G→A Exon 12	E355K (E324K)
7	KJ II	Homozygote	1073G→A Exon 12	
8	Mila-1 II	Homozygote	1073G→A Exon 12	R358H (R327H)
9	LM I	Homozygote	1346G→A Exon 13	G449D (G418D)
10	LeM I	Compound Heterozygote	1366-1371del Exon 13 Unknown	V456delD457del Unknown
11	Gypsy ⁸ I	Homozygote	IVS15(+1)G→A: Alternative splice resulting in 1537-1544del in exon 15	Frameshift and premature termination
12	CW I	Compound Heterozygote	1750C→T: Exon 17 480C→G: Creates an alternative splice site at 476GT in exon 4	R584X (R553X) S160-S192del (include C161 and C177)
13	Chinese 10 I	Compound Heterozygote	1750C→T Exon 17 Unknown	R584X (R553X) Unknown
14	SK I	Compound Heterozygote	1750C→T: Exon 17 IVS25(-3)C→G: Within acceptor splice sequence of exon 26	R584X (R553X) V868-V909del
15	Family L I	Compound Heterozygote	1750C→T Exon 17 Unknown	R584X (R553X) Unknown
16	Family II I	Compound Heterozygote	1750C→T Exon 17 Unknown	R584X (R553X) Unknown

GPIIb CLINICAL AND BIOCHEMICAL INFORMATION

No.	Bleeding Symptoms (BS) ⁹ Bleeding Time (BT) Clot Retraction (CR)	Platelet Surface GPIIb/IIIa (1) and $\alpha_v\beta_3$ (2) Expression	Platelet GPIIb/GPIIIa and Fibrinogen (Fg) Levels	Ref.
1	BS: E, G, Tx BT: Not reported CR: Not reported	1: Not reported 2: ~200% of normal	IIb/IIIa: Undetectable and 1-5% of normal Fg: Not reported	(7)
2	BS: E, G, GI, M, P, T, Tx BT: > 30 minutes CR: Absent	1: < 2% of normal 2: ~200% of normal	IIb/IIIa: < 1% of normal/1-5% of normal Fg: 10-15% of normal	(8-12)
3	BS: T, Tx BT: > 30 minutes CR: Diminished to 10%	1: 24% expression 2: Not reported	IIb/IIIa: Not reported Fg: Not reported	(13)
4	BS: B, E, T, Tx BT: Prolonged CR: Delayed	1: 12% of normal 2: 192% of normal	IIb/IIIa: 30% and 35% of normal Fg: 5% of normal	(14,15)
5	BS: E, Ec, Tx BT: Prolonged CR: Not reported	1: < 2-5% of normal 2: ~200% of normal	IIb/IIIa: Trace of both, proGPIIb only Fg: Not reported	(16)
6	BS: Not reported BT: Not reported CR: Absent	1: Undetectable complexes 2: Not reported	IIb/IIIa: Undetectable/ Trace Fg: Severely reduced	(17)
7	BS: B, T BT: > 20 minutes CR: Some retractability	1: 7-10% of normal 2: Not reported	IIb/IIIa: Trace/reduced Fg: Not reported	(18)
8	BS: B BT: > 15 minutes CR: Decreased	1: ~25% of normal 2: Not reported	IIb/IIIa: Not reported Fg: 1-2% of normal	(19)
9	BS: Not reported BT: Not reported CR: Not reported	1: Undetectable 2: Not reported	IIb/IIIa: Undetectable/ Small amount Fg: Not reported	(20)
10	BS: P BT: Not reported CR: Not reported	1: < 5% of normal 2: Not reported	IIb/IIIa: Not reported Fg: Not reported	(21)
11	BS: Tx BT: Prolonged CR: Absent	1: Decreased 2: Not reported	IIb/IIIa: Undetectable Fg: Undetectable	(22)
12	BS: Ec, P, Tx BT: Not reported CR: Absent	1: < 1% of normal 2: > 200% of normal	IIb/IIIa: Trace of both Fg: Severely reduced	(23)
13	BS: E, G, M, P, Tx BT: Not reported CR: Not reported	1: < 2% of normal 2: ~170% of normal	IIb/IIIa: Trace of both Fg: Severely reduced	(23)
14	BS: E BT: > 15 minutes CR: Not reported	1: Not reported 2: Not reported	IIb/IIIa: ~ 6% and 11% of normal Fg: Not reported	(24,25)
15	BS: E, G BT: > 15 minutes CR: Not reported	1: Not reported 2: Not reported	IIb/IIIa: Undetectable Fg: Not reported	(26,27)
16	BS: Not reported BT: Not reported CR: Not reported	1: Undetectable 2: Not reported	IIb/IIIa: Undetectable Fg: Not reported	(28)

GPIIb MUTATIONS

No.	Patient and Classification ¹	Genotype	Mutation ² cDNA Nucleotide Number ³	Amino Acid Substitution ⁴
17	MO I	Compound Heterozygote	1750C→T Exon 17 Unknown	R584X (R553X) No transcript detected
18	Iranian-Jewish I	Homozygote	2473-2478del and 2473-2503ins creating an alternative acceptor splice site at 2478AG	L817-N826del substituted inframe with 8 new amino acids
19	NR I	Compound Heterozygote	2941C→T: Exon 28 Unknown	Q981X resulting in R948-Q981del No transcript detected
20	CG I/II	Compound Heterozygote	1787T→C: Exon 18 IVS29(+2)T→C: Within splice donor site of exon 29	I596T (I565T) V982-K1020del
21	MC I/II	Compound Heterozygote	IVS29(+2)T→C: Within splice donor site of exon 29 3094insTG: Exon 30	V982-K1020del Frameshift with no termination
22	AP Variant	Compound Heterozygote	3077G→A Exon 30 Unknown	R1026Q (R995Q) Unknown

GPIIIa MUTATIONS

No.	Patient and Classification ¹	Genotype	Mutation ^{2,10} cDNA Nucleotide Number ³	Amino Acid Substitution ⁴
1	Amsterdam I I	Homozygote	IVS2(+1)G→T: Within donor splice site resulting in 80-165del	Frameshift and premature termination
2	Family I I	Homozygote	262C→T Exon 3	R88X (R62X)
3	Pakistan II	Homozygote	428T→G Exon 4	L143W (L117W)
4	Cam Variant	Homozygote	433G→T Exon 4	D145Y (D119Y)
5	NR Variant	Homozygote	433G→A Exon 4	D145N (D119N)
6	BL II	Homozygote	563C→T Exon 4	S188L (S162L)
7	PDJ Carrier ¹¹	Heterozygote	708-709del Exon 5	Frameshift and premature termination
8	Strasbourg I Variant	Homozygote	718C→T Exon 5	R240W (R214W)

GPIIb CLINICAL AND BIOCHEMICAL INFORMATION

No.	Bleeding Symptoms (BS) ⁹ Bleeding Time (BT) Clot Retraction (CR)	Platelet Surface GPIIb/IIIa (1) and $\alpha_v\beta_3$ (2) Expression	Platelet GPIIb/GPIIIa and Fibrinogen (Fg) Levels	Ref.
17	BS: B, M BT: > 20 minutes CR: Impaired to 8%	1: Undetectable 2: Not reported	Ib/IIIa: < 2% of normal/~15% of normal Fg: Not reported	(29,30)
18	BS: Mu BT: Not reported CR: Absent	1: Minimal 2: 60-100% increase	Ib/IIIa: Trace/reduced Fg: Not reported	(31)
19	BS: M BT: > 30 minutes CR: Not reported	1: Undetectable 2: Not reported	Ib/IIIa: Undetectable/~9% of normal Fg: Not reported	(32,33)
20	BS: G, M BT: ~15 minutes CR: Delayed	1: ~5% of normal 2: > 200% of normal	Ib/IIIa: Reduced levels Fg: ~20% of normal	(34,35)
21	BS: G BT: ~15 minutes CR: Delayed	1: <12% of normal 2: ~200% of normal	Ib/IIIa: Reduced levels Fg: ~12% of normal	(34-36)
22	BS: E, G, H, T BT: > 11 minutes CR: Delayed	1: 12-20% of normal 2: Not reported	Ib/IIIa: ~45% of control Fg: Normal	(37,38)

GPIIIa: CLINICAL AND BIOCHEMICAL INFORMATION

No.	Bleeding Symptoms (BS) ⁹ Bleeding Time (BT) Clot Retraction (CR)	Platelet Surface GPIIb/IIIa (1) and $\alpha_v\beta_3$ (2) Expression	Platelet GPIIb/GPIIIa and Fibrinogen (Fg) Levels	Ref.
1	BS: E, G, M, Tx BT: Not reported CR: Not reported	1. Undetectable 2. Not reported	Ib/IIIa: Not reported Fg: Not reported	(39)
2	BS: Not reported BT: Not reported CR: Not reported	1. Undetectable 2. Not reported	Ib/IIIa: Undetectable Fg: Not reported	(28)
3	BS: Not reported BT: Not reported CR: Not reported	1. 10% of normal 2. Not reported	Ib/IIIa: Not reported Fg: Not reported	(40)
4	BS: E, GI, Mu, S, Tx BT: > 20 minutes CR: Absent	1. >20,000/platelet \pm Ca ²⁺ 2. Not reported	Ib/IIIa: Not reported Fg: 1 μ g/10 ⁹ platelets (nl ¹⁴ : 31 μ g/10 ⁹ platelets)	(41,42)
5	BS: B, E, G, M, Tx BT: Not reported CR: Borderline low	1. Not reported 2. Not reported	Ib/IIIa: Normal Fg: Not reported	(43)
6	BS: B, E, G, Mu, Tx BT: Prolonged CR: Normal	1. ~30% of normal -minimal binding anti-GPIIb/IIIa mAb ¹⁵ 2. Not reported	Ib/IIIa: ~30% of normal Fg: Not reported	(44)
7	BS: None BT: Not reported CR: Not reported	1. ~20,000 complexes/platelet 2. Not reported	Ib/IIIa: Not reported Fg: Not reported	(45)
8	BS: B, H BT: > 10 minutes CR: Subnormal	1. 19,400/platelet + Ca ²⁺ ~300/platelet + EDTA 2. Not reported	Ib/IIIa: Normal levels Fg: 36 ng/10 ⁸ platelets (nl: 168 ng/10 ⁸ platelets)	(46,47)

GPIIIa MUTATIONS

No.	Patient and Classification ¹	Genotype	Mutation ^{2,10} cDNA Nucleotide Number ³³	Amino Acid Substitution ⁴
9	CM Variant	Homozygote	718C→T Exon 5	R240W (R214W)
10	ET Variant	Homozygote	719G→A Exon 5	R240Q (R214Q)
11	SH II	Homozygote	725G→A Exon 5	R242Q (R216Q)
12	GT3 I	Compound Heterozygote	IVS5(+1)G→A resulting in 615-777del or 778-804ins IVS1-5Aluinv15kb+IVS1del1kb	Frameshift/premature termination or 9 new amino acid addition No transcript detected
13	LD II	Compound Heterozygote	847delGC: Exon 6 863T→C: Exon 6	Frameshift and premature termination L288P (L262P)
14	Chinese 20 II	Homozygote	1199G→A Exon 9	C400Y (C374Y)
15	CB I	Homozygote	IVS9ins3-4kb	No GPIIIa transcript and normal GPIIb transcript detected
16	RS I	Homozygote Uniparental disomy	1260G→A+1143C→A result in 1126-1265del and IVS9(-5)-IVS9(-1)ins: alternative splice	Restore reading frame creating V376S377
17	RM Variant	Compound Heterozygote	Unknown deletion within exon 11 2248C→T Exon 14	No GPIIIa transcript detected R750X (R724X)
18	I-J ₁ ¹² I	Homozygote	2031-2041del Exon 13	Frameshift and premature termination
19	I-J ₂ ¹³ I	Compound Heterozygote	2031-2041del: Exon 13 IVS9Alu→2163or2166del11.2kb	Both mutations result in a frameshift and premature termination
20	Patient P Variant	Compound Heterozygote	2332T→C Exon 15 Unknown	S778P (S752P) Unknown

GPIIIa: CLINICAL AND BIOCHEMICAL INFORMATION

No.	Bleeding Symptoms (BS) ⁹ Bleeding Time (BT) Clot Retraction (CR)	Platelet Surface GPIIb/IIIa (1) and $\alpha_v\beta_3$ (2) Expression	Platelet GPIIb/GPIIIa and Fibrinogen (Fg) Levels	Ref.
9	BS: E, G, M, Tx BT: > 10 minutes CR: Abnormal	1. 38,900/platelet + Ca ²⁺ 2,540/platelet + EDTA 2. Not reported	I Ib/IIIa: Normal levels Fg: Severely reduced	(48,49)
10	BS: B, E, M BT: Not reported CR: Absent	1. Normal mAb binding+ Ca ²⁺ No mAb binding+ EDTA 2. Not reported	I Ib/IIIa: Normal levels Fg: Marked deficiency	(50,51)
11	BS: Not reported BT: Not reported CR: Not reported	1. 20% GPIIb, <1% GPIIIa, Undetectable GPIIb/IIIa 2. Not reported	I Ib/IIIa: Quantitative defect Fg: Not reported	(52)
12	BS: Mu BT: > 30 minutes CR: Not reported	1. Not reported 2. Not reported	I Ib/IIIa: Undetectable Fg: Not reported	(53-55)
13	BS: B, G, P BT: Not reported CR: Normal	1. 30% of normal, < 5% GPIIb/IIIa complex 2. Not reported	I Ib/IIIa: ~8% of normal GPIIb/IIIa Fg: Not reported	(56)
14	BS: E, M, P, Tx BT: ~9 minutes CR: Abnormal	1. < 15% of normal 2. 15-19% of normal	I Ib/IIIa: ~10% of normal/~30% of normal Fg: ~36% of normal	(57,58)
15	BS: B, M BT: Prolonged CR: Absent	1. Not reported 2. Not reported	I Ib/IIIa: Undetectable Fg: Not reported	(59)
16	BS: E, G, M Tx BT: Not reported CR: Not reported	1. Not reported 2. Undetectable	I Ib/IIIa: Trace GPIIb, Undetectable GPIIIa Fg: Not reported	(60)
17	BS: Not reported BT: Not reported CR: Not reported	1. 50-60% of normal, normal ligand-binding domain 2. Not reported	I Ib/IIIa: Not reported Fg: Not reported	(61)
18	BS: E, G, GI, P, T, Tx BT: > 10 minutes CR: Absent	1. < 2% of normal 2. < 20% of normal	I Ib/IIIa: Undetectable Fg: 10-15% of normal	(8-12)
19	BS: P BT: > 10 minutes CR: Absent	1. < 2% of normal 2. < 20% of normal	I Ib/IIIa: Undetectable Fg: 10-15% of normal	(62)
20	BS: Not reported BT: Prolonged CR: Normal	1. Resting: 44% of normal Stimulated: 56% of normal 2. Not reported	I Ib/IIIa: Moderate quantitative defect Fg: Not reported	(63-65)

GPIIb: TRANSFECTION STUDIES

No. and Patient	Transfected Cells	GPIIb/IIIa Expression	Ligand Binding
1 KW	Not done		
2 Arab	Not done		
3 Frankfurt I	Not done		
4 LW	CHO: Transient transfection	Surface: ~53-62% of normal	Absent: Anti-GPIIb/IIIa mAb Absent: Immobilized Fg
5 FLD	COS: Transient transfection	Surface: Undetectable Intracellular: ProGPIIb only	Not reported
6 FL	COS: Transient transfection	Surface: Undetectable Intracellular: Present	Not reported
7 KJ	COS: Transient transfection	Surface: Greatly reduced Intracellular: ProGPIIb detected	Not reported
8 Mila-1	CHO: Stable cell lines	Surface: ~9% positive cells Intracellular: Reduced levels of proGPIIb and GPIIb	Not reported
9 LM	COS: Transient transfection	Surface: Undetectable, rescue with Gly418Ala substitution Intracellular: ProGPIIb only	Not reported
10 LeM	COS: Transient transfection	Surface: Undetectable Intracellular: Heterodimer processing blocked	Not reported
11 Gypsy	Not done		
12 CW	Not done		
13 Chinese 10	Not done		
14 SK	Not done		
15 Family L	Not done		
16 Family II	Not done		
17 MO	Not done		
18 Iranian- Jewish	COS: Transient transfection	Surface: Not reported Intracellular: Not reported	Undetectable: anti-GPIIb/IIIa mAb binding
19 NR	COS: Transient transfection	Surface: Undetectable Intracellular: ProGPIIb only and EndoH sensitive	Not reported
20 CG	Not done		
21 MC	Not done		
22 AP	Not done		

GPIIIa: TRANSFECTION STUDIES

No. and Patient	Transfected Cells	Surface GPIIb/IIIa Expression	Ligand Binding
1 Amsterdam I	Not done		
2 Family I	Not done		
3 Pakistan I	COS: Transient transfection	Surface: Trace Intracellular: ProGPIIb only, no GPIIb/IIIa mAb binding	Not reported
4 Cam	CHO: Stable cell lines	Normal expression	RGD ¹⁶ +LIBS1 ¹⁷ mAb: Undetectable
5 NR	Not done		
6 BL	COS: Transient transfection	Subunit mAbs: Detectable Moderate trafficking defect	GPIIb/IIIa mAb binding: Undetectable Subunit-specific binding: Detectable
7 PDJ	Not done		
8 Strasbourg I	Not done		
9 CM	Not done		
10 ET	CHO: Stable cell lines	Normal expression	RGD+LIBS1 mAb: Undetectable Immobilized Fg: Undetectable
11 SH	COS: Transient transfection	Reduced expression	GPIIb/IIIa mAb binding: Undetectable
12 GT3	Not done		
13 LD	Not done		
14 Chinese 20	CHO: Transient transfection Stable cell lines	~10% of normal	Immobilized Fg α_{IIb}/β_3 (C374Y): ~80% of normal Soluble Fg α_{IIb} (R995A)/ β_3 (C374Y): Absent
15 CB	Not done		
16 RS	K562: Transient transfection: in vitro splicing		
17 RM	Not done		
18 I-J ₁	Not done		
19 I-J ₂	Not done		
20 Patient P	CHO: Transient transfection Stable cell lines	Normal expression	PAC-1 - α_{IIb} (6B)/ β_3 (S752P): Undetectable PAC-1+LIBS- α_{IIb} (6B)/ β_3 (S752P): Normal Immobilized Fg: Normal

¹ According to George et al., *Blood* 75:1383-1395, 1990

² Mutations are listed according to patient and exon number except in the cases of compound heterozygotes where both identified mutations are listed together. Abbreviations used: del: deletion, ins: insertion, inv: inversion, IVS: intervening sequence.

³ Nucleotide substitutions are designated by the nucleotide number and the (nucleotide→nucleotide) substitution

⁴ Amino acid substitutions are designated by amino acid-codon number-amino acid. The single letter code is used for amino acids: A: alanine, C: cysteine, D: aspartate, E: glutamate, F: phenylalanine, G: glycine, H: histidine, I: isoleucine, K: lysine, L: leucine, M: methionine, N: asparagine, P: proline, Q: glutamine, R: arginine, S: serine, T: threonine, V: valine, W: tryptophane, Y: tyrosine. The amino acid codon excluding the leader sequence is given in parenthesis.

⁵ IVS1→IVS9del4.5kb reads: a 4.5kb deletion occurred between sites located within introns 1 and 9

⁶ Identified in 3 “unrelated” kindreds in Israel

⁷ IVS3(-3)→418del reads: a deletion occurred between the third base from the end of intron 3 (splice acceptor sequence) to nucleotide 418 (within exon 4)

⁸ Study of 52 individuals in the Gypsy population in France resulting in 11 homozygotes, 32 heterozygotes, and 9 unaffected

⁹ B: bruising, E: epistaxis, Ec: ecchymoses, G: gingival, GI: gastrointestinal, H: hematoma, M: menorrhagia, Mu: mucous membrane, P: petechiae/purpura, S: soft tissue, T: tooth extraction, Tx: transfusion

¹⁰ Exon numbering has been modified to include the nucleotides encoding amino acid residues of the leader sequence as exon 1 according to Villa-Garcia et al., *Blood* 83:668-676, 1994 and to increase by one the exon numbers designated by Zimrin et al., *J Biol Chem* 265:8590-8595, 1990

¹¹ The patient was identified by development of thrombocytopenia and deep venous thrombosis postoperatively. Serologically the patient typed homozygous for PI^{A1}, but DNA typed heterozygous for PI^{A1/A2}

¹² Study of 32 patients belonging to 17 kindreds with 29 independent sources of the mutation. The frequency of the I-J₁ mutant allele in the general Iraqi-Jewish population is 0.0043 (6/700 control individuals)

¹³ Three identified Iraqi-Jewish families carry the I-J₂ mutation in which 2 homozygotes for I-J₂ and 4 heterozygotes for I-J₁ and I-J₂ have been identified. The frequency of the I-J₂ mutant allele in the general Iraqi-Jewish population is <0.0007 (0/700 control individuals)

¹⁴ nl: normal

¹⁵ mAb: monoclonal antibody

¹⁶ RGD: arginine-glycine-aspartic acid

¹⁷ LIBS: ligand induced binding site

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