Names for RHAG (ISBT 030) Blood Group Alleles

Intro

General description:	The RHAG blood group system consists of three antigens carried on a multipass membrane glycoprotein called RhAG (Rh-associated glycoprotein; aka CD241). It consists of 409 amino acids and both amino and carboxyl termini are predicted to be intracellular. It is predicted to sit in the membrane in a tri-molecular complex with either RhD or RhCE in a 2:1 ratio. (1; PMID 16281947)
Gene name:	*RHAG*
Number of exons:	10
Initiation codon:	Within exon 1
Stop codon:	Within exon 10
Entrez Gene ID:	6005
LRG:	LRG_822
LRG sequence:	NG_011704.1 (genomic) NM_000324.2 (transcript)
Reference allele:	*RHAG*01* (shaded)
Reference allele *RHAG*01* encodes:	RHAG1, RHAG3
Antithetical antigens:	n.a.
Additional information	RHAG3 assigned provisionally. Assignment of null (N) and mod (M) alleles has been made according to the phenotypic expression of RhD and RhCE antigens. † The breakpoints for the deleted *RHAG* allele(s), *RHAG*01N.15* (PMID: 25069376 (25); PMID: 28470789 (26)) have not been determined and are assumed to be the same until proven different. At that time, a new allele number will be assigned to distinguish the alleles from each other.

Phenotype	Allele name	Nucleotide change	Exon	Predicted amino acid change	(Reference No.) PMID	Accession number	rs number
RHAG:1 or Duclos+	*RHAG*01*						
RHAG:−1 or Duclos−	*RHAG*01.−01*	c.316C>G	2	p.Gln106Glu	(2) PMID: 19744193	n.a.	rs1180686517
RHAG:2 or Ol(a+) Variant also weakens RhAG expression (3)	*RHAG*01.02*	c.680C>T	5	p.Ser227Leu	(2) PMID: 19744193 (3) Abstract	n.a.	rs902283342
RHAG:−3 or DSLK−	*RHAG*01.−03*	c.490A>C	3	p.Lys164Gln	(2) PMID: 19744193	n.a.	rs144305805
RHAG:4	obsolete as of 2018, PMID: 30421425						
Weak phenotypes							
Rhmod	*RHAG*01M.01*	c.1183delA	9	p.Asn395Thrfs*68	(4) PMID: 11961248	n.a.	n.a.
Rhmod	*RHAG*01M.02*	c.3G>T	1	p.Arg2_Met8del	(5) PMID: 9915949	n.a.	rs121918588
Rhmod	*RHAG*01M.03*	c.236G>A	2	p.Ser79Asn	(7) PMID: 8563755	n.a.	rs121918586
Rhmod	*RHAG*01M.04*	c.269G>T	2	p.Gly90Val	(8) Abstract	n.a.	n.a.
Rhmod	*RHAG*01M.05*	c.398T>C	3	p.Leu133Pro	(3) Abstract	n.a.	n.a.
Rhmod	*RHAG*01M.06*	c.560G>A	4	p.Gly187Asp	(8) Abstract	n.a.	n.a.
Rhmod	*RHAG*01M.07*	c.1195G>T	9	p.Asp399Tyr	(9) PMID: 10895258	n.a.	n.a.
Rhmod	*RHAG*01M.08*	c.182T>G	2	p.Ile61Arg	(10) PMID: 18931342	n.a.	rs863225469
Rhmod	*RHAG*01M.09*	c.194T>C	2	p.Phe65Ser	(10) PMID: 18931342	n.a.	rs863225468
Rhmod	*RHAG*01M.10*	c.572G>A	4	p.Arg191Gln	(11) Abstract	n.a.	rs550840907
Rhmod	*RHAG*01M.11*	c.241G>C	2	p.Gly81Arg	(12) PMID: 27079312	HF934040	n.a.
Rhmod	*RHAG*01M.12*	c.920C>T	6	p.Ser307 Phe	(13) PMID: 32378229	n.a.	n.a.

Phenotype	Allele name	Nucleotide change	Exon	Predicted amino acid change	(Reference No.) PMID	Accession number	rs number
Rhmod	*RHAG*01M.13*	c.514A>G	4	p.Met172Val	(31) Abstract	n.a.	rs759281201
Rhmod	*RHAG*01M.14*	c.[572G>A;707A>C]	4 5	p.[Arg191Gln;Gln236Arg]	(37) PMID: 31032541	MH397221	rs550840907 rs777825752
Null phenotypes							
Rhnull	*RHAG*01N.01*	c.154_157delinsGA	2	p.Pro52Aspfs*57	(7) PMID: 8563755	n.a.	rs387906519
Rhnull	*RHAG*01N.02*	c.1086delA	8	p.Ala363Leufs*15	(7) PMID: 8563755	n.a.	rs1562011389
Rhnull	*RHAG*01N.03*	c.157+1G>A	Intron 1	Aberrant splicing	(14) PMID: 9746795; (15) PMID: 10394146	n.a.	rs1166675172
Rhnull	*RHAG*01N.04*	c.945+1G>A	Intron 6	Aberrant splicing	(16) Abstract; (17) PMID: 30990901	n.a.	n.a.
Rhnull	*RHAG*01N.05*	c.946-1G>A	Intron 6	Aberrant splicing	(14) PMID: 9746795	n.a.	rs1562012697
Rhnull	*RHAG*01N.06*	c.946-1G>T	Intron 6	Aberrant splicing	(18) PMID: 9759472	n.a.	n.a.
Rhnull	*RHAG*01N.07*	c.1067+1G>A	Intron 7	Aberrant splicing	(19) PMID: 9442063	n.a.	rs1562012617
Rhnull	*RHAG*01N.08*	c.808G>A; c.838G>A	6	p.Val270Ile; p.Gly280Arg	(6) PMID: 10467273	n.a.	rs16879498; rs104893987
Rhnull	*RHAG*01N.09*	c.836G>A	6	p.Gly279Glu	(20) PMID: 9454778; (21) PMID: 9716608	n.a.	rs121918587
Rhnull	*RHAG*01N.10*	c.1094T>G	8	p.Leu365Arg	(16) Abstract	n.a.	n.a.
Rhnull	*RHAG*01N.11*	c.1139G>T	9	p.Gly380Val; Aberrant splicing	(6) PMID: 10467273	n.a.	rs121918589
Rhnull	*RHAG*01N.12*	c.353C>T	3	p.Ala118Glu	(22) Abstract	n.a.	n.a.
Rhnull	*RHAG*01N.13*	c.1003G>A	7	p.Gly335Ser	(23) PMID: 25296744	n.a.	rs976240588
Rhnull	*RHAG*01N.14*	c.946-2A>G	Intron 6	Aberrant splicing	(24) Abstract	n.a.	rs754264275
Rhnull	*RHAG*01N.15†*	c.(?_-62)_(*638_?)del; Gene deletion	43840	p.0	(25) PMID: 25069376; (26) PMID: 28470789†	n.a.	n.a.

Phenotype	Allele name	Nucleotide change	Exon	Predicted amino acid change	(Reference No.) PMID	Accession number	rs number
Rhnull	*RHAG*01N.16*	c.310C>T	2	p.Gln104Ter	(27) PMID: 26175207	n.a.	rs1240511011
Rhnull	*RHAG*01N.17*	c.640+3del14	Intron 4	Aberrant splicing	(12) PMID: 27079312	HG971762	n.a.
Rhnull	*RHAG*01N.18*	c.790C>T	5	p.Arg264X	(28) ISBT Science Series, 2016;11:51-7.	AB938314.1	rs1397420527
Rhnull	*RHAG*01N.19*	c.543delT	4	p.Phe181Leufs*5	(29) Abstract	n.a.	n.a.
Rhnull	*RHAG*01N.20*	c.672C>A	5	p.Ser224Arg	(30) PMID: 21682734	n.a.	n.a.
Rhnull	*RHAG*01N.21*	c.571C>T	4	p.Arg191Ter	(32) Abstract	n.a.	rs758540029
Rhnull	*RHAG*01N.22*	c.540C>A	4	p.Tyr180Ter	(34) PMID: 28063760	n.a.	n.a.
Rhnull	*RHAG*01N.23*	c.532delG	4	p.178Glyfs185	(35) PMID: 29266289	KY094063	n.a.
Rhnull	*RHAG*01N.24*	c.12delA	1	p.Phe5fs	(36) Abstract	n.a.	n.a.
Rhnull	*RHAG*01N.25*	c.236G > A	2	pSer79Asn	(38) PMID: 29508504	GQ477180	rs121918586

References

1. PMID: 16281947 Conroy MJ, Bullough PA, Merrick M, Avent ND. Modelling the human rhesus proteins: implications for structure and function. Br J Haematol. 2005 Nov;131(4):543-51.

2. PMID: 19744193 Tilley L, Green C, Poole J, Gaskell A, Ridgwell K, Burton NM, Uchikawa M, Tsuneyama H, Ogasawara K, Akkøk CA, Daniels G. A new blood group system, RHAG: three antigens resulting from amino acid substitutions in the Rh-associated glycoprotein. Vox Sang. 2010 Feb;98(2):151-9.

3. Abstract Tsuneyama H, Ogasawara K, Uchikawa M, Yabe R, Nakajima K. Identification of Two New Mutations in the RhAG Gene of Japanese with Rhmod Phenotype. Transfusion 2008;48 (Suppl.):194-5.

4. PMID: 11961248 Kamesaki T, Iwamoto S, Kajii E, Takahashi J, Kimura K, Nakade T, Tani Y. A new mutation detected in RhAG of a Japanese family with Rh(mod) syndrome may form a longer RhAG protein. Transfusion. 2002 Mar;42(3):383-4.

5. PMID: 9915949 Huang C, Cheng GJ, Reid ME, Chen Y. Rhmod syndrome: a family study of the translation-initiator mutation in the Rh50 glycoprotein gene. Am J Hum Genet. 1999 Jan;64(1):108-17.

6. PMID: 10467273 Huang CH, Cheng G, Liu Z, Chen Y, Reid ME, Halverson G, Okubo Y. Molecular basis for Rh(null) syndrome: identification of three new missense mutations in the Rh50 glycoprotein gene. Am J Hematol. 1999 Sep;62(1):25-32.

7. PMID: 8563755 Cherif-Zahar B, Raynal V, Gane P, Mattei MG, Bailly P, Gibbs B, Colin Y, Cartron JP. Candidate gene acting as a suppressor of the RH locus in most cases of Rh-deficiency. Nat Genet. 1996 Feb;12(2):168-73.

8. Abstract Scharberg A, Tsuneyama H, Ogasawara K, Uchikawa M, Keller HH, Panter K, Senne J, Penz S, Richter E, Bugert P. Rhmod phenotype caused by double heterozygosity for two new alleles of the RHAG gene. Vox Sanguinis 2006; 91 (Suppl. 3) 129A

9. PMID: 10895258 Cartron JP. RH blood group system and molecular basis of Rh-deficiency. Baillieres Best Pract Res Clin Haematol. 1999 Dec;12(4):655-89.

10. PMID: 18931342 Bruce LJ, Guizouarn H, Burton NM, Gabillat N, Poole J, Flatt JF, Brady RL, Borgese F, Delaunay J, Stewart GW. The monovalent cation leak in overhydrated stomatocytic red blood cells results from amino acid substitutions in the Rh-associated glycoprotein. Blood. 2009 Feb 5;113(6):1350-7.

11. Abstract Tsuneyama H, Isa K, Ogasawara K, Yabe R, Uchikawa M, Minami M. Identification of a Mutation in the RHAG Gene of Japanese with Weak D Phenotype. Transfusion 2013-Vol. 53 Supplement 167A

12. PMID: 27079312 Polin H, Pelc-Klopotowska M, Danzer M, Suessner S, Gabriel C, Wilflingseder J, Żmudzin A, Orzińska A, Guz K, Michalewska B, Brojer E. Compound heterozygosity of two novel RHAG alleles leads to a considerable disruption of the Rh complex. Transfusion. 2016 Apr;56(4):950-5.

13. PMID: 32378229 Mufarrege N, Franco N, Trucco Boggione C, Arnoni C, de PaulaVendrame T, Bartoli S, Ensinck A, Principi C, Lujan Brajovich M, Mattaloni S, Riquelme B, Biondi C, Castilho L, Cotorruelo C. Extensive clinical, serologic and molecular studies lead to the first reported Rhmod phenotype in Argentina. Transfusion. 2020 May 6.

14. PMID: 9746795 Chérif-Zahar B, Matassi G, Raynal V, Gane P, Delaunay J, Arrizabalaga B, Cartron JP. Rh-deficiency of the regulator type caused by splicing mutations in the human RH50 gene. Blood. 1998 Oct 1;92(7):2535-40.

15. PMID: 10394146 Cowley NM, Saul A, Cartron J, Hyland CA. A single point mutation at a splice site generates a silent RH50 gene in a composite heterozygous RHnull blood donor. Vox Sang. 1999;76(4):247-8.

16. Abstract Tsuneyama H, Ogasawara K, Uchikawa M, Ishikawa Y, Satake M, Nakajima K, Yabe R, Kasai E, Izumi N, Fuse I. Identification of two new mutations in the RHAG gene of Japanese with Rhnull phenotype. Transfusion 2005; 45:130

17. PMID: 30990901 Ushiki T, Tsuneyama H, Masuko M, Kozakai T, Kasami T, Tanaka T, Uchikawa M, Kitajima T, Kasai E, Komata T, Katagiri T, Kamimura M, Sato K, Fuse I, Ogasawara K, Nakata K. Rhnull phenotype caused by a novel RHAG mutation, c.945+1G>A, in the Japanese population. Transfusion. 2019 Aug;59(8):2519-2522.

18. PMID: 9759472 Kawano M, Iwamoto S, Okuda H, Fukuda S, Hasegawa N, Kajii E. A splicing mutation of the RHAG gene associated with the Rhnull phenotype. Ann Hum Genet. 1998 Mar;62(Pt 2):107-13.

19. PMID: 9442063 Huang CH. The human Rh50 glycoprotein gene. Structural organization and associated splicing defect resulting in Rh(null) disease. J Biol Chem. 1998 Jan 23;273(4):2207-13.

20. PMID: 9454778 Hyland CA, Chérif-Zahar B, Cowley N, Raynal V, Parkes J, Saul A, Cartron JP. A novel single missense mutation identified along the RH50 gene in a composite heterozygous Rhnull blood donor of the regulator type. Blood. 1998 Feb 15;91(4):1458-63.

21. PMID: 9716608 Huang CH, Liu Z, Cheng G, Chen Y. Rh50 glycoprotein gene and rhnull disease: a silent splice donor is trans to a Gly279-->Glu missense mutation in the conserved transmembrane segment. Blood. 1998 Sep 1;92(5):1776-84.

22. Abstract Grimsley S, Poole J, Thornton N, Bullock T, Burton N, Marouf S, Soeker R, Daniels G. Novel Mutations in RHAG Causing Two New Examples of the Regulator Type of Rhnull. Transfusion Medicine, 2012, 22, Suppl. 1, 21

23. PMID: 25296744 St-Louis M, Éthier C, Perreault J, Lavoie J. A new Rhnull allele in francophone Quebecers. Transfusion. 2015 Jun;55(6 Pt 2):1580-1.

24. Abstract Arsenovic MG, Grimsley S, Sørvoll IH, McNeill A, Titze TL, Husebekk A, Olsson ML, Thornton N, Storry JR. The Rhnull phenotype in a Norwegian family is due to a novel RHAG mutation. Vox Sanguinis (2014) 107 (Suppl 1), 192.

25. PMID: 25069376 Gómez-Torreiro E, Eiras-Martínez A, Rodríguez-Calvo MI, Muñiz-Díaz E, Nogués N, López M, Garaizar A, Ochoa-Garay G. Rh-null phenotype caused by a complete RHAG deletion. Transfusion. 2015 Jan;55(1):197-8.

26. PMID: 28470789 Kulkarni SS, Vasantha K, Gogri H, Parchure D, Madkaikar M, Férec C, Fichou Y. First report of Rhnull individuals in the Indian population and characterization of the underlying molecular mechanisms. Transfusion. 2017 Aug;57(8):1944-1948.

27. PMID: 26175207 Arnoni CP, Muniz JG, Gazito D, Person Rde M, Vendrame TA, Castilho L, Latini FR. Novel RHAG allele encoding the Rh(null) phenotype in Brazil. Transfusion. 2015 Oct;55(10):2521-2.

28. No PMID Tanaka M, Yamasaki H, Watanabe S, Takahashi J, Matsukura H, Tani Y. A novel c.790C>T mutation in RHAG gene encoding the Rhnull phenotype in Japanese. ISBT Science Series, 2016;11:51-7.

29. Abstract C Vrignaud, S Ramelet, J Cartron, T Peyrard. Confirmation of a compound heterozygous status for the RHAG gene in a Rh null subject of the regulator type. Vox Sanguinis (2018) 113 (Suppl. 1), 260

30. PMID: 21682734 Tian L, Song N, Yao ZQ, Huang M, Hou L. A family study of the Chinese Rhnull individual of the regulator type: a novel single missense mutation identified in RHAG gene. Transfusion. 2011 Dec;51(12):2686-9.

31. Abstract Tsuneyama H, Isa K, Osabe T, Onodera T, Yabe R, Ogasawara K, Uchikawa M, Minami M. Two cases of the decreasing expression of Rh17 antigen caused by missense mutation in the RHAG gene. Vox Sanguinis (2014) 107 (Suppl. 1), 168-9

32. Abstract Golovkina LL, Stremoukhova A, Vasiljeva M, Pushkina T, Atroscchenko G, Kalandarov R, Khasigova B, Surin V, Pshenichnikova O, Salomashkina V, Parovichnikova E. ABO*A and RHD variants in Russians. Vox Sanguinis (2017) 112 (Suppl. 1),218

33. PMID: 28470789 Kulkarni SS, Vasantha K, Gogri H, Parchure D, Madkaikar M, Férec C, Fichou Y. First report of Rhnull individuals in the Indian population and characterization of the underlying molecular mechanisms. Transfusion. 2017 Aug;57(8):1944-1948.

34. PMID: 28063760 Hou L, Yan QD, Tian L. A novel nonsense mutation in RHAG gene responsible for Rhnull phenotype in a Chinese individual. Transfus Apher Sci. 2017 Apr;56(2):220-222.

35. PMID: 29266289 Tian L, Xu H, Xiao J, Ying B. A novel nucleotide deletion in RHAG allele identified in a Chinese Rhnull individual. Transfusion. 2018 Mar;58(3):826-827.

36. Abstract — Moores S, Edwards J, Grimsley S, Dzialach E, Thornton N, Bansall R, Latham T, Graham J. Rhnull blood group presenting as an undiagnosed haemolytic anaemia Transfusion Medicine, 2019, 29, Suppl. 2, 36.

37. PMID: 31032541 — Xia RW, Xun CZ, Xiang D, Zhang JM, Yang QX, Zhao FY, Wang C, Zhu ZY, Li Q, Ye LY. A novel double-variant RHAG allele leads to Rhmod phenotype. Transfus Med. 2019 Dec;29(6):460-465.

38. PMID: 29508504 — Mu S, Cui Y, Wang W, Wang L, Xu H, Zhu O, Zhu D. A RHAG point mutation selectively disrupts Rh antigen expression. Transfus Med. 2019 Apr;29(2):121-127.

39. PMID: 30421425 — Storry JR, Clausen FB, Castilho L, Chen Q, Daniels G, Denomme G, Flegel WA, Gassner C, de Haas M, Hyland C, Yanli J, Keller M, Lomas-Francis C, Nogues N, Olsson ML, Peyrard T, van der Schoot E, Tani Y, Thornton N, Wagner F, Weinstock C, Wendel S, Westhoff C, Yahalom V. International Society of Blood Transfusion Working Party on Red Cell Immunogenetics and Blood Group Terminology: Report of the Dubai, Copenhagen and Toronto meetings. Vox Sang. 2019 Jan;114(1):95-102.

Track of changes	**from v5.0 170514**	**to v6.0 30-OCT-2020**
created:	Geoff Daniels	Jill Storry
reviewed:		
General		
Intro	Text changed	It is predicted to sit in the membrane in a tri-molecular complex with either RhD or RhCE in a 2:1 ratio. (1; PMID 16281947)
Intro	LRG ID line added:	LRG_822
Allele Table		
Allele Table	Text change:	RHAG3 assigned provisionally. Assignment of null (N) and mod (M) alleles has been made according to the phenotypic expression of RhD and RhCE antigens.
	Line moved to Intro:	
Allele Table	Text change:	
Allele Table	Antigen/allele renamed:	*RHAG*-01* → *RHAG*01.-01*
Allele Table	Antigen/allele renamed:	*RHAG*02* → *RHAG*01.02*
Allele Table	Antigen/allele renamed:	*RHAG*-03* → *RHAG*01.-03*
Allele Table	Antigen/allele added:	RHAG:4 → Deleted. RHAG:4 was made obsolete 2018 (39)
Allele Table	Antigen/allele	Corrected to p.Arg264X after review of the original paper and the Ensembl database
	p.Arg263X	
Allele Table	Antigen/allele added:	*RHAG*01M.13, RHAG*01M.14*
		*RHAG*01N.19 to RHAG*01N.25*
References	References 1-8 updated	References found for all alleles and collated
End of changes	**from v5.0 170514**	**to v6.0 30-OCT-2020**