Chido/Rodgers Blood Group System

Number of antigens 9

Polymorphic	WH
High prevalence	Ch1, Ch2, Ch3, Ch4, Ch5, Ch6, Rg1, Rg2

Terminology

ISBT symbol (number)	CH/RG (017)
History	Named after the first antibody producers, Chido and Rodgers. Anti-Ch was reported in 1967, and when anti-Rg was described in 1976 there were obvious similarities between them. Ch and Rg appeared to be RBC antigens and were given blood group system status. However, the antigens were later located on the fourth component of complement (C4), which becomes bound to RBCs from the plasma.

Expression

Soluble form	In plasma or serum
Altered	GPA-deficient RBCs have a weak expression of Ch and Rg antigens

Gene

Chromosome	6p21.32
Name	*CH* (*C4B*); *RG*(*C4A*)
Organization	*C4A* 41 exons distributed over 22 kpb of gDNA *C4B* 41 exons distributed over 22 kbp or 16 kbp of gDNA after loss of a 6.8 kbp intron
Product	C4A complement component (Rg) C4B complement component (Ch)

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00019-3

Database accession numbers

GenBank	NM_001002029 *(CH)*; K02403.1 *(RG)*
Entrez Gene ID	720 *(RG)*; 721 *(CH)*

Molecular basis of Ch/Rg phenotypes

Ch and Rg antigens are not intrinsic to the RBC membrane, but are adsorbed from the plasma. The molecular bases of selected phenotypes are given below.

Chido

The reference allele [Accession number NM_001002029 (mRNA)] encodes Ch1 (CH1), CH2, CH3, CH4, CH5, and CH6. Differences from this allele are given.

Allele encodes	Allotype	Exon	Nucleotide^	Amino acid
Ch+Rg– or CH:1,2,–3,4,5,–6. RG:–1,–2	*C4B*1*	27	3527G>A	Ser1176Asn
Ch+Rg– or CH:1,–2,3,4,5,6 RG:–1,–2	*C4B*2*	25	3218G>A	Gly1073Asp
Ch+Rg+WH+ or CH:–1,–2,–3,4,–5,6 RG:1,–2	*C4B*5*	25, 28	3620C>T; 3629G>T; 3630G>C	Gly1073Asp; Ala1207Val; Arg1210Val

^Nucleotide numbers start with A of ATG, which is 52 bp into the reference sequence. The allele names are from the complement community and not the ISBT.

Rodgers

The reference allele [Accession number K02403.1 (mRNA) for *C4A*3*] encodes Rg1 (RG1) and RG2. Differences from this allele are given.

Allele encodes	Allotype	Nucleotide change^	Amino acid change
Ch+Rg– or CH:–1,–2,3,4,5,6 RG:–1,–2	*C4A*1*	3567A>G; 3660T>C; 3669T>G; 3670C>G	Asp1054Gly; Asn1157Ser; Val1188Ala; Leu1191Arg
Ch–Rg+WH+ or CH:–1,–2,–3,–4,–5,6 RG:1,–2	*C4A*3.WH*	3567A>G	Asn1157Ser

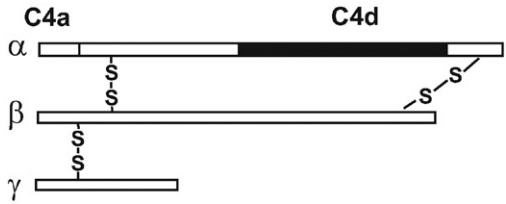
^The site of ATG is not clear. The allele names are from the complement community and not the ISBT.

Carrier molecule

C4A and C4B are glycoproteins which are adsorbed onto the RBC membrane from the plasma. C4A binds preferentially to protein, and C4B to carbohydrate. C4A migrates more quickly in electrophoresis than C4B. C4A and C4B are 99% identical in their amino acid sequences.

Ch and Rg antigens are located in the C4d region of C4B or C4A, respectively. C4d is a tryptic fragment of C4.

C4 molecule (adapted from Daniels)[1].



Amino acid residues associated with CH/RG phenotypes[2]

Allotype	Ch/Rg type	Phenotype	Amino acid residue							
			1054	1101	1102	1105	1106	1157	1188	1191
*C4A*3*	Ch–Rg+	CH/RG:−1,−2,−3, −4,−5,−6,11,12	Asp	Pro	Cys	Leu	Asp	Asn	Val	Leu
*C4A*1*	Ch+Rg–	CH/RG:1,−2,3, −4,5,6,−11,−12	Gly	Pro	Cys	Leu	Asp	Ser	Ala	Arg
*C4A*3*	Ch–Rg+ WH+	CH/RG:−1,−2, −3,−4,−5,6,11,−12	Asp	Pro	Cys	Leu	Asp	Ser	Val	Leu
*C4B*3*	Ch+Rg–	CH/RG:1,2,3, 4,5,6,−11,−12	Gly	Leu	Ser	Ile	His	Ser	Ala	Arg
*C4B*1*	Ch+Rg–	CH/RG:1,2,−3, 4,5,−6,−11,−12	Gly	Leu	Ser	Ile	His	Asn	Ala	Arg
*C4B*2*	Ch+Rg–	CH/RG:1,−2, 3,4,−5,6,−11,−12	Asp	Leu	Ser	Ile	His	Ser	Ala	Arg
*C4B*5*	Ch+Rg+ WH+	CH/RG:−1,−2, −3,4,−5,6,11,−12	Asp	Leu	Ser	Ile	His	Ser	Val	Leu

Function

There are functional differences between C4A and C4B allotypes: C4A is more effective than C4B at solubilizing immune complexes and inhibiting immune precipitation. C4B binds more effectively to the RBC surface (through sialic acid), and thus is more effective at promoting hemolysis. A single amino acid substitution at position 1106 (aspartic acid for histidine) converts the functional activity of C4B to C4A[3], whereas the substitution of cysteine for serine at position 1102 affects hemolytic activity and IgG binding.

Disease association

Inherited low levels of C4 may be a predisposing factor for diseases such as insulin-dependent diabetes and autoimmune chronic active hepatitis. Specific C4 allotypes and null genes have been associated with numerous autoimmune disorders, including Graves' disease and rheumatoid arthritis (for list, see[4]). Lack of C4B (Ch–) gives increased susceptibility to bacterial meningitis in children. Rg– individuals (lack of C4A) have a much greater susceptibility for SLE.

Phenotypes (% occurrence)

Chido phenotype	Most populations	Japanese	Rodgers phenotype	Most populations	Japanese
CH/RG: 1,2,3	88.2	75	CH/RG: 11,12	95	100
CH/RG: 1,−2,3	4.9	24	CH/RG:11,−12	3	0
CH/RG: 1,2,−3	3.1	0	CH/RG: −11,−12	2	0
CH/RG: −1,−2,−3	3.8	1			
CH/RG: −1,2,−3	Rare	0			
CH/RG:1, −2,−3	Rare	0			
Null:	C4-deficient RBCs				

Comments

Antigens of this system are stable in stored serum or plasma. Phenotypes and antibodies of this system are most accurately defined by hemagglutination inhibition tests.
RBCs coated with C4 (+C3) by use of low ionic strength 10% sucrose solution give enhanced reactivity with anti-Ch and anti-Rg.
Sialidase-treated RBCs do not adsorb C4.

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.
[2] Yu, C.Y., et al., 1988. A structural model for the location of the Rodgers and the Chido antigenic determinants and their correlation with the human complement component C4A/C4B isotypes. Immunogenetics 27, 399–405.
[3] Carroll, M.C., et al., 1990. Substitution of a single amino acid (aspartic acid for histidine) converts the functional activity of human complement C4B to C4A. Proc Natl Acad Sci USA 87, 6868–6872.
[4] Moulds, J.M., 1994. Association of blood group antigens with immunologically important proteins. In: Garratty, G. (Ed.), Immunobiology of Transfusion Medicine. Marcel Dekker, Inc., New York, NY, pp. 273–297.

Ch1 Antigen

Terminology

ISBT symbol (number)	CH/RG1 (017001 or 17.1)
Obsolete names	Ch; Ch^a; Chido
History	Named in 1967 after Mrs. Chido, who made “anti-Chido” (considered a nebulous antibody).

Occurrence

Most populations	96%
Japanese	99%

Expression

Cord RBCs	Absent or weak
Altered	Weak on GPA-deficient RBCs

Molecular basis associated with Ch1 antigen

Requires Ala1188 and Arg1191 of C4[1,2]. See System pages.

Effect of enzymes and chemicals on Ch1 antigen on intact RBCs

Ficin/Papain	Sensitive
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
DTT 200 mM	Resistant

In vitro characteristics of alloanti-Ch1

Immunoglobulin class	IgG (mostly IgG2 and IgG4)
Optimal technique	IAT
Neutralization	Antigen-positive serum or plasma

Clinical significance of alloanti-Ch1

Transfusion reaction	Not hemolytic; anaphylactic from plasma products and platelets (few reports)
HDFN	No

Comments

Soluble plasma antigen in donor blood may neutralize patient's antibody. Anti-Ch1 reacts strongly with C4-coated RBCs. Antihuman globulin without anti-IgG4 will not detect anti-Ch1.
Virtually all anti-Ch contain anti-Ch1.
The Ch antigens have been divided (Ch1, Ch2, etc.), but classification is not required for clinical purposes.

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.
[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.

Ch2 Antigen

Terminology

ISBT symbol (number)	CH/RG2 (017002 or 17.2)
History	Defined in 1985, when plasma inhibition studies revealed that there are at least six Chido antigens (Ch1 to Ch6) of high prevalence.

Occurrence

Most populations	Greater than 90%
Japanese	75%

Molecular basis associated with Ch2 antigen

Antigen expression requires presence of Ch4 and Ch5, i.e., Gly1054, Leu1101, Ser1102, Ile1105, and His1106[1,2]. See System pages.

Comments

Anti-Ch2 + anti-Ch4 was detected in a Ch:1,–2,3,–4,5,6 Rg:1, 2 person[3].
Anti-Ch2 + anti-Ch5 was detected in a Ch:1,–2,3,4,–5,6 Rg:1, 2 person[4].

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.
[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.
[3] Fisher, B., et al., 1993. A new allo anti-Ch specificity in a patient with a rare Ch positive phenotype [abstract]. Transf Med 3 (Suppl. 1), 84.
[4] Giles, C.M., et al., 1987. Allo-anti-Chido in a Ch-positive patient. Vox Sang 52, 129–133.

Ch3 Antigen

Terminology

ISBT symbol (number)	CH/RG3 (017003 or 17.3)
History	See Ch2 antigen

Occurrence

Caucasians	93%
Japanese	Greater than 99%

Molecular basis associated with Ch3 antigen

Antigen expression requires presence of Ch1 and Ch6, i.e., Ser1157, Ala1188, and Arg1191[1,2]. See System pages.

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.
[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.

Ch4 Antigen

Terminology

ISBT symbol (number)	CH/RG4 (017004 or 17.4)
History	See Ch2 antigen.

Occurrence

All populations	Greater than 99%

Molecular basis associated with Ch4 antigen

Antigen expression requires presence of Leu1101, Ser1102, Ile1105, and His1106[1,2]. See System pages. Detected on all C4B allotypes.

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.

[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.

Ch5 Antigen

Terminology

ISBT symbol (number)	CH/RG5 (017005 or 17.5)
History	See Ch2 antigen.

Occurrence

All populations	Greater than 99%

Molecular basis associated with Ch5 antigen

Antigen expression requires Gly1054[1,2]. See System pages.

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.

[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.

Ch6 Antigen

Terminology

ISBT symbol (number)	CH/RG6 (017006 or 17.6)
History	See Ch2 antigen.

Occurrence

All populations	Greater than 99%

Molecular basis associated with Ch6 antigen

Antigen expression requires Ser1157 of C4[1,2]. See System pages.

Comments

Rare specificity, two examples reported.

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.

[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.

WH Antigen

Terminology

ISBT symbol (number)	CH/RG7 (017007 or 17.7)
History	Named after the person who was thought to carry a hybrid of C4A and C4B.

Occurrence

Caucasians	15%

Molecular basis associated with WH antigen

Associated with Ch:6, Rg:1,−2 phenotype. Antigen expression requires Ser1157, Val1188, and Leu1191[1,2,3]. See System pages.

In one individual (WH), a single amino acid substitution encoded by the C4A*3 gene at codon 1157 gives rise to Asp in the wild type being replaced by Ser in WH type[1,3].

Comments

Rare specificity, two examples reported[4].

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.
[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.
[3] Moulds, J.M., et al., 1995. Revised model for the Chido/Rogers blood group based on DNA sequencing [abstract]. Transfusion 35 (Suppl.), 53S.
[4] Giles, C.M., Jones, J.W., 1987. A new antigenic determinant for C4 of relatively low frequency. Immunogenetics 26, 392–394.

Rg1 Antigen

Terminology

ISBT symbol (number)	CH/RG11 (017011 or 17.11)
Other names	Rodgers; Rg; Rg^a
History	"Generic" anti-Rg reported in 1976 and named after antibody maker. All anti-Rg contain anti-Rg1 (strongest component) and anti-Rg2.

Occurrence

All populations	Greater than 98%

Expression

Cord RBCs	Absent or weak

Molecular basis associated with Rg1 antigen

Antigen expression requires Val1188 and Leu1191[1,2]. See System pages.

Effect of enzymes and chemicals on Rg1 antigen on intact RBCs

Ficin/Papain	Sensitive
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
DTT 200 mM	Resistant

In vitro characteristics of alloanti-Rg1

Immunoglobulin class	IgG
Optimal technique	IAT
Neutralization	Antigen-positive serum or plasma

Clinical significance of alloanti-Rg1

Transfusion reaction	Not hemolytic; anaphylactic from plasma products and platelets (few reports)
HDFN	No

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.
[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.

Rg2 Antigen

Terminology

ISBT symbol (number)	CH/RG12 (017012 or 17.12)
History	See Rg1 antigen.

Occurrence

Most populations	95%

Molecular basis associated with Rg2 antigen

Antigen expression requires Asp1157, Val1188, and Leu1191[1,2]. See System pages.

Comments

All anti-Rg contain anti-Rg1 (strongest component) and anti-Rg2.

References

[1] Daniels, G., 1995. Blood group antigens as markers of complement and complement regulatory molecules. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 397–419.
[2] Giles, C.M., 1988. Antigenic determinants of human C4, Rodgers and Chido. Exp Clin Immunogenet 5, 99–114.