Red Blood Cell Antigen Genotyping

Red blood cell (RBC) antigen testing is useful in determining allelic variants that predict RBC antigen phenotypes for patients with recent history of transfusion or with conflicting serologic antibody results due to partial, variant, or weak expression antigens. It is also useful as an aid in management of hemolytic disease of the fetus and newborn (HDFN); for additional information on HDFN testing, refer to the ARUP Consult Hemolytic Disease of the Fetus and Newborn topic.

Featured ARUP Testing

Red Blood Cell Antigen Genotyping 3001053

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

- Use to predict the expression of RBC antigen specificities, aid in the selection of antigen-negative RBCs for transfusion, assess the risk of alloimmune hemolytic disease, or resolve conflicting serologic antibody results.
- Detects 24 variants associated with 35 RBC antigens and phenotypic variants, in addition to the hemoglobin S variant.
- For fetal testing, order Red Blood Cell Antigen Genotyping, Fetal (3016639) using a fetal specimen.

See Related Tests below for antigen-specific genotyping and phenotyping tests.

Disease Overview

Prevalence and/or Incidence

Erythrocyte alloimmunization occurs in up to 58% of patients with sickle cell, up to 35% in other patients who are transfusion-dependent, and in approximately 0.8% of all individuals who are pregnant.

Symptoms

Transfusion reactions or HDFN can occur due to alloimmunization:

- Intravascular hemolysis: hemoglobinuria, jaundice, shock
- Extravascular hemolysis: fever and chills
- HDFN: fetal hemolytic anemia, hepatosplenomegaly, jaundice, erythroblastosis, neurologic damage, hydrops fetalis

Clinical presentation is variable and dependent upon the specific antibody and recipient factors.

Pathophysiology

Extravascular Hemolysis

Removal of antibody-bound RBCs via splenic macrophages

Intravascular Hemolysis

- Rare for non-ABO antibodies
- Donor RBCs are destroyed by the recipient's antibodies while they are still inside blood vessels.
- Hemoglobin released into plasma and excreted in urine; bilirubin accumulates in blood

HDN-Mediated Disease

- Caused by antigen-antibody mediated red-cell hemolysis from previously transferred maternal antibodies
- Examples of antibodies associated with HDFN:
  - Rh (Ant-D, -C, -c, -E, and -e)
  - Kell (Anti-K, -k, -Kp^a, -Kp^b, -Js^a and -Js^b)
  - Duffy (Anti-Fy^a and -Fy^b)
  - MNS (Anti-M, -N, -S, -s, and -U)
  - Kidd (Anti-Jk^a and -Jk^b)
- Anti-D is the most common cause of HDFN, followed by anti-c, anti-K, and anti-E; anti-Jk^a and -Jk^b are rare causes
- Antibodies cross the placenta and cause immune destruction of RBCs in fetus and leads to hydrops fetalis.

Genetics

Refer to the Genes and Variants Tested table below.

Inheritance

Typically codominant for RBC antigens; autosomal recessive for HbS

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity and specificity:
  - >99% for C, c, E, e, K, k, Jk^a, Jk^b, Fy^a, Fy^b, M, N, S, s
  - Unknown for Kp^a, Kp^b, Js^a, Js^b, Lu^a, Lu^b, Di^a, Di^b, Co^a, Co^b, Do^a, Do^b, Jo^a, Hy, LW^a, LW^b, Sc1, Sc2, U, V, VS, HbS
- Analytic sensitivity and specificity:
  - >99% for C, c, E, e, K, k, Jk^a, Jk^b, Fy^a, Fy^b, M, N, S, s
  - Unknown for Kp^a, Kp^b, Js^a, Js^b, Lu^a, Lu^b, Di^a, Di^b, Co^a, Co^b, Do^a, Do^b, Jo^a, Hy, LW^a, LW^b, Sc1, Sc2, U, V, VS, HbS

Results

- Predicted phenotype for each RBC antigen tested will be provided
  - If identified, weak alleles will be reported.
- Possible variant
  - Reported for allele combinations that have not widely been reported in the literature
- Indeterminate
  - Abnormal signal intensities may result in the inability to predict genotype resulting in indeterminate results for all tested antigens and HbS.

Limitations

- Only the variants listed will be interrogated.
- Does not test for Rh D, a major cause of HDFN
- Patients who have had allogeneic hematopoietic stem cell transplants may have inconclusive results.
- Diagnostic/phenotype prediction errors can occur due to:

- Rare variants affecting primer/probe binding
- Molecular events that affect the blood-group antigen expression and phenotypes that are not detected by this assay (ie, certain null phenotypes or other phenotypes with altered expression)

- This assay is not designed to diagnose sickle cell disease.

Genes and Variants Tested

Blood Group	Allele	Antigen (ISBT #)	ISBT Genotype	Variants Tested	Variants Used to Predict Allele	Phenotype Frequency[1,2]
Rh	C	RH2	RHCE*2	c.307C>T; p.Pro103Ser 109bp insertion	c.307T; p.Ser103 109bp insertion	W: 68% AA: 27% A: 93%
	c	RH4	RHCE*4		c.307C; p.Pro103	W: 80% AA: 98% A: 47%
	E	RH3	RHCE*3	c.676G>C; p.Ala226Pro	c.676C; p.Pro226	W: 29% AA: 22% A: 39%
	e	RH5	RHCE*5		c.676G; p.Ala226	W: 98% AA: 98% A: 96%
	V	RH10	RHCE*01.20.01 RHCE*01.20.02 RHCE*01.20.04 RHCE*01.20.05	c.733C>G; p.Leu245Val c.1006G>T; p.Gly336Cys	c.733G; p.Val245	W: 1% AA: 30%
	VS	RH20			c.[733C>G; 1006G>T]; p.[Leu245Val; Gly336Cys]	AA: 26-40% All other populations: <0.01%
Kell	K	KEL1	KEL*01	c.578C>T; p.Thr193Met	c.578T; p.Met193	W: 9% AA: 2% A: Rare Iranian Jews: 12%

Reid, 2012[1]; Dean, 2005[2]

A, Asian; AA, African American; ISBT, International Society for Blood Transfusion (ISBT) Committee on Terminology for Red Cell Surface Antigens; W, White

Reference transcripts: RHCE (NM_020485.5), KEL (NM_000420.2), ACKR1 (NM_002036.3; alt reference NM_001122951.2), SLC14A1 (NM_015865.6), GYPA (NM_002099.7), GYPB (NM_002100.5), BCAM (NM_005581.4), ART4 (NM_021071.2), ICAM4 (NM_001544.4), SLC4A1 (NM_000342.3), AQP1 (NM_198098.3), ERMAP (NM_018538.3)

Blood Group	Allele	Antigen (ISBT #)	ISBT Genotype	Variants Tested	Variants Used to Predict Allele	Phenotype Frequency[1,2]
						Arabs: up to 25%
	k	KEL2	KEL*02		c.578C; p.Thr193	W: 99.8% AA: 100%
	Kp^a	KEL3	KEL*03	c.841C>T; p.Arg281Trp	c.841T; p.Trp281	W: 2% AA: <0.01%
	Kp^b	KEL4	KEL*04		c.841C; p.Arg281	All populations: 100%
	Js^a	KEL6	KEL*06	c.1790T>C; p.Leu597Pro	c.1790C; p.Pro597	W: <0.01% AA: 20%
	Js^b	KEL7	KEL*07		c.1790T; p.Leu597	W: 100% AA: 99%
Duffy	Fy^a	FY1	FY*01	c.125G>A; p.Gly42Asp	c.125G; p.Gly42	W: 66% AA: 10% A: 99% Thai: 97%
	Fy^b	FY2	FY*02		c.125A; p.Asp42	W: 83% AA: 23% A: 18.5% Thai: 31% Chinese: 9.2%
	Fy^b-67C (Fy^b ES)	GATA FY-2	FY*02N.01	c.-67T>C	c.-67T>C	W: rare AA: 68% A: rare
	Fy^x	FY2W	FY*02M	c.265C>T; p.Arg89Cys	c.265C>T; p.Arg89Cys	rare

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Blood Group	Allele	Antigen (ISBT #)	ISBT Genotype	Variants Tested	Variants Used to Predict Allele	Phenotype Frequency[1,2]
Kidd	Jk[a]	JK1	JK*01	c.838G>A; p.Asp280Asn	c.838G; p.Asp280	W: 77% AA: 92% A: 72%
	Jk[b]	JK2	JK*02		c.838A; p.Asn280	W: 74% AA: 49% A: 76%
MNS	M	MNS1	GYPA*01	c.59T>C; p.Leu20Ser	c.59C; p.Ser20	W: 78% A: 74%
	N	MNS2	GYPA*02		c.59T; p.Leu20	W: 72% AA: 75%
	S	MNS3	GYPB*03	c.143C>T; p.Thr48Met	c.143T; p.Met48	W: 55% AA: 31%
	s	MNS4	GYPB*04		c.143C; p.Thr48	W: 89% AA: 93%
	U	MNS5				W: 99.9% AA: 99%
	Silencing S (Uvar)	MNS-3,w5	GYPB*03N.01 GYPB*03N.02 GYPB*03N.03 GYPB*03N.04	c.230C>T; p.Thr77Met or c.270+5G>T	c.230C>T; p.Thr77Met or c.270+5G>T	rare
	Silencing S (Uneg)	MNS-3,-4,-5	Deletion of *GYPB* exons 2-6			rare
Lutheran	Lu[a]	LU1	LU*01	c.230G>A; p.Arg77His	c.230A; p.His77	W: 8% AA: 5%

[illegible][1], [illegible], 2005[2]

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Blood Group	Allele	Antigen (ISBT #)	ISBT Genotype	Variants Tested	Variants Used to Predict Allele	Phenotype Frequency[1,2]
	Lu^b	LU2	LU*02		c.230G; p.Arg77	All populations: 99.8%
Dombrock	Do^a	DO1	DO*01	c. 793G>A; p.Asp265Asn	c.793A; p.Asn265	W: 67% AA: 55% Japanese: 24% Thai: 14%
	Do^b	DO2	DO*02		c.793G; p.Asp265	W: 82% AA: 89%
	Hy	DO4	DO*04	c.323G>T; p.Gly108Val	c.323G; p.Gly108	AA: >99% Most populations: 100%
		DO-4			c.323T; p.Val108	rare
	Jo^a	DO5	DO*05	c.350C>T; p.Thr117Ile	c.350C; p.Thr117	AA: >99% Most populations: 100%
		DO-5			c.350T; p.Ile117	rare
Landsteiner-Wiener (LW)	LW^a	LW5	LW*05	c.299A>G; p.Gln100Arg	c.299G; p.Arg100	All populations: 100%
	LW^b	LW7	LW*07		c.299A; p.Gln100	Most populations: Rare Estonians: 8% Finns: 6% Latvians and Lithuanians:

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Blood Group	Allele	Antigen (ISBT #)	ISBT Genotype	Variants Tested	Variants Used to Predict Allele	Phenotype Frequency[1,2]
						5% Poles and Russians: 2% Other Europeans: <1%
Diego	Di^a	DI1	DI*01	c.2561C>T; p.Pro854Leu	c.2561T; p.Leu854	Most populations: 0.01% South American Indians: 2% -54% Japanese: 12% Chinese: 5% Hispanics: 1% Poles: 0.47%
	Di^b	DI2	DI*02		c.2561C; p.Pro854	Most populations: 100% Native Americans: 99%
Colton	Co^a	CO1	CO*01	c.134C>T; p.Ala45Val	c.134C; p.Ala45	All populations: 99.5%
	Co^b	CO2	CO*02		c.134T, p.Val45	All populations: 10%
Scianna	Sc1	SC1	SC*01	c.169G>A; p.Gly57Arg	c.169G; p.Gly57	All populations: >99%
	Sc2	SC2	SC*02		c.169A; p.Arg57	Europeans: 1%; more

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Blood Group	Allele	Antigen (ISBT #)	ISBT Genotype	Variants Tested	Variants Used to Predict Allele	Phenotype Frequency[1,2]
						common in Mennonites
Hemoglobin S	HbS			HBB c.20A>T; Glu6Val	c.20A>T; Glu6Val	AA: 10%

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References

1. Reid ME, Lomas-Francis C, Olsson ML. *The Blood Group Antigen FactsBook*. 3rd ed. Academic Press; 2012.

2. Dean L. The Kell blood group. In: *Blood Groups and Red Cell Antigens*. National Center for Biotechnology Information (US); 2005. [Accessed: Jun 2019]

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