Red Blood Cell Antigen Genotyping

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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).

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
  - Antigens designated as positive (+) are predicted to be expressed and antigens designated as negative (-) are predicted to not be expressed.
  - 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 (i.e., 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	Antigen	Variants Tested	Variants Used to Predict Antigen	Phenotype Frequency[1,2]
Rh	C	c.307C>T; p.Pro103Ser 109bp insertion	c.307T; p.Ser103 109bp insertion	A: 93% AA: 27% W: 68%
	c		c.307C; p.Pro103	A: 47% AA: 98% W: 80%

Blood Group	Antigen	Variants Tested	Variants Used to Predict Antigen	Phenotype Frequency[1,2]
	E	c.676G>C; p.Ala226Pro	c.676C; p.Pro226	A: 39% AA: 22% W: 29%
	e		c.676G; p.Ala226	A: 96% AA: 98% W: 98%
	V	c.733C>G; p.Leu245Val c.1006G>T; p.Gly336Cys	c.733G; p.Val245	AA: 30% W: 1%
	VS		c.[733C>G; 1006G>T]; p.[Leu245Val; Gly336Cys]	AA: 26-40% All other populations: <0.01%
Kell	K	c.578C>T; p.Thr193Met	c.578T; p.Met193	A: Rare AA: 2% Arabs: up to 25% Iranian Jews: 12% W: 9%
	k		c.578C; p.Thr193	AA: 100% W: 99.8%
	Kp^a	c.841C>T; p.Arg281Trp	c.841T; p.Trp281	AA: <0.01% W: 2%
	Kp^b		c.841C; p.Arg281	All populations: 100%
	Js^a	c.1790T>C; p.Leu597Pro	c.1790C; p.Pro597	AA: 20% W: <0.01%
	Js^b		c.1790T; p.Leu597	AA: 99% W: 100%
Duffy	Fy^a	c.125G>A; p.Gly42Asp	c.125G; p.Gly42	A: 99% AA: 10% Thai: 97% W: 66%
	Fy^b		c.125A; p.Asp42	A: 18.5% AA: 23% Chinese: 9.2% Thai: 31% W: 83%
	Fy^b-67C (Fy^b ES)	c.-67T>C	c.-67T>C	A: rare AA: 68% W: rare
	$Fy(b+^w)$	c.265C>T; p.Arg89Cys	c.265C>T; p.Arg89Cys	rare

Blood Group	Antigen	Variants Tested	Variants Used to Predict Antigen	Phenotype Frequency[1,2]
Kidd	Jk[a]	c.838G>A; p.Asp280Asn	c.838G; p.Asp280	A: 72% AA: 92% W: 77%
	Jk[b]		c.838A; p.Asn280	A: 76% AA: 49% W: 74%
MNS	M	c.59T>C; p.Leu20Ser	c.59C; p.Ser20	A: 74% W: 78%
	N		c.59T; p.Leu20	AA: 75% W: 72%
	S	c.143C>T; p.Thr48Met	c.143T; p.Met48	AA: 31% W: 55%
	s		c.143C; p.Thr48	AA: 93% W: 89%
	U			AA: 99% W: 99.9%
	Silencing S (Uvar)	c.230C>T; p.Thr77Met or c.270+5G>T	c.230C>T; p.Thr77Met or c.270+5G>T	rare
	Silencing S (Uneg)			rare
Lutheran	Lu[a]	c.230G>A; p.Arg77His	c.230A; p.His77	AA: 5% W: 8%
	Lu[b]		c.230G; p.Arg77	All populations: 99.8%
Dombrock	Do[a]	c. 793G>A; p.Asp265Asn	c.793A; p.Asn265	AA: 55% Japanese: 24% Thai: 14% W: 67%
	Do[b]		c.793G; p.Asp265	AA: 89% W: 82%
	Hy	c.323G>T; p.Gly108Val	c.323G; p.Gly108	AA: >99% Most populations: 100%
	Hy-		c.323T; p.Val108	rare
	Jo[a]	c.350C>T; p.Thr117Ile	c.350C; p.Thr117	AA: >99% Most populations: 100%
			c.350T; p.Ile117	rare

Blood Group	Antigen	Variants Tested	Variants Used to Predict Antigen	Phenotype Frequency[1,2]
Landsteiner-Wiener (LW)	LW[a]	c.299A>G; p.Gln100Arg	c.299G; p.Arg100	All populations: 100%
	LW[b]		c.299A; p.Gln100	Most populations: Rare Estonians: 8% Finns: 6% Latvians and Lithuanians: 5% Poles and Russians: 2% Other Europeans: <1%
Diego	Di[a]	c.2561C>T; p.Pro854Leu	c.2561T; p.Leu854	Most populations: 0.01% Chinese: 5% Hispanics: 1% Japanese: 12% Poles: 0.47% South American Indians: 2%-54%
	Di[b]		c.2561C; p.Pro854	Most populations: 100% Native Americans: 99%
Colton	Co[a]	c.134C>T; p.Ala45Val	c.134C; p.Ala45	All populations: 99.5%
	Co[b]		c.134T, p.Val45	All populations: 10%
Scianna	Sc1	c.169G>A; p.Gly57Arg	c.169G; p.Gly57	All populations: >99%
	Sc2		c.169A; p.Arg57	Europeans: 1%; more common in Mennonites
Hemoglobin S	HbS	HBB c.20A>T; Glu6Val	c.20A>T; Glu6Val	AA: 10%

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)

A, Asian; AA, African American; W, White

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

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. Accessed Jun 2019.

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