Kell Antigen (*KEL*) Genotyping

Indications for Ordering

- Determine fetal genotype when
  - Mother has clinically significant alloantibody **AND**
  - Father is either heterozygous for *KEL1* (K) allele or is unavailable for testing
- Determine paternal *KEL1* (K) genotype in phenotypically positive individual when reproductive partner is K negative by RBC antigen typing
- Assess risk for hemolytic transfusion reaction

Test Description

Polymerase chain reaction and fluorescent monitoring using hybridization probes to detect the c.578C>T (p.Thr193Met) variant

Tests to Consider

Primary test

Kell K/k Antigen (*KEL*) Genotyping 0051644

- Assess risk for alloimmune hemolytic disease of the newborn (HDN) or hemolytic transfusion reaction
- May be ordered for parental or fetal genotyping

Related test

Kell Antigen Typing – Patient 2007731

- Initial screen for K antigen status

Disease Overview

Incidence

- K positive (Moise, 2008; Dean, 2005)
  - Up to 25% in Arabs
  - 9% in Caucasians
  - 2% in African Americans
  - K homozygosity is rare
- ~4% of K negative (k/k) mothers will deliver a K positive baby with potential HDN (Moise, 2008)

Symptoms

- HDN
  - Symptoms may be seen as early as 20 weeks gestation
  - Fetal hemolytic anemia – may be severe
  - Jaundice
  - Hepatosplenomegaly
  - Erythroblastosis
  - Hydrops fetalis
- Hemolytic transfusion reaction
  - Intravascular coagulopathy
  - Renal failure
  - Uncontrolled bleeding

Physiology

- Kell blood group system is complex
- Kell locus is highly polymorphic
  - 25 Kell antigens are known
- K and k differ by a single amino acid
  - The k antigen is more common in most populations
  - The K antigen is more likely to trigger an immune reaction
- *KEL1* (K) allele
  - Presence predicts a Kell positive phenotype
  - Maternal anti-K antibodies can cause severe HDN when mother is K negative (k/k) and fetus is K positive (K/k)
  - Anti-K antibodies in blood transfusion recipient can cause severe hemolytic transfusion reaction if donor is K positive (K/K or K/k)
- *KEL2* (k) allele
  - Common allele
  - Anti-k antibodies are a rare cause of HDN or hemolytic transfusion reaction

Mechanism

- Transplacentally transferred maternal antibodies attack fetal red blood cells (RBCs) in response to foreign, paternally inherited antigens
- Transfused RBCs combine with recipient's antibodies and lead to increased destruction of RBCs
- >50% of HDN cases are due to maternal anti-K antibodies from
  - Multiple blood transfusions
  - Previous pregnancy with a K positive fetus
- Alloimmunization due to K antigen should be considered after ABO and Rh incompatibilities have been ruled out
  - Anti-K is responsible for up to 30% of antibody-mediated severe fetal anemias

Genetics

Gene – *KEL*

Inheritance – autosomal dominant

Variant – c.578C>T (p.Thr193Met)

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – 99% (Daniels, 2005)
- Analytical sensitivity/specificity – 99%

Results

- Kell negative (k/k)
  - *KEL1* allele, c.578C>T (p.Thr193Met), not detected
    - Predicts K negative phenotype
- Kell positive (K/K or K/k)
  - One or two copies of *KEL1* allele, c.578C>T (p.Thr193Met), detected
    - Predicts K positive phenotype
  - Paternal homozygous (K/K) result
    - Negates need for fetal *KEL* testing, as all offspring will be K positive

Limitations

- Tests only for *KEL1* (K) and *KEL2* (k) alleles
- Diagnostic errors can occur due to rare sequence variations
- Bloody amniotic fluid specimen may give false-negative result due to maternal cell contamination

References

- Daniels G. The molecular genetics of blood group polymorphism. Transpl Immunol. 2005;14(3-4):143-153
- Dean L. Blood Groups and Red Cell Antigens [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2005. Chapter 8, The Kell blood group (www.ncbi.nlm.nih.gov/books/NBK2270/)
- Moise KJ. Fetal anemia due to non-Rhesus-D red-cell alloimmunization. Semin Fetal Neonatal Med. 2008;13(4):207-214