RhEe and RhCc Antigen (RHCE) Genotyping

Indications for Ordering

- Determine fetal genotype when
  - Mother has clinically significant alloantibody level AND
  - Father is phenotypically positive for corresponding Rh antigen or unavailable for testing
- Determine paternal RHCE genotype in phenotypically positive individual when reproductive partner has clinically significant alloantibody

Test Description

Polymerase chain reaction followed by fluorescence monitoring

- RHCE variants tested
  - RhCc antigen genotyping – exons 1 and 2 and intron 2
    - c.48C>G (p.W16C)
    - c.201A>G (p.S67S)
    - c.203A>G (p. N68S)
    - Intron 2 insertion
  - RhEe antigen genotyping – exon 5
    - c.676G>C; p.A226P

Tests to Consider

Primary tests

Assess risk for alloimmune hemolytic disease of the newborn (HDN) due to RHCE gene-related alloimmunization

- RhCc Antigen (RHCE) Genotyping 0050421
- RhEe Antigen (RHCE) Genotyping 0050423

Related tests

Antigen Testing, Rh Phenotype 0013019

- Antigen testing for D, C, E, c, e to assess maternal, paternal, or newborn Rh phenotype status

RhD Gene (RHD) Copy Number 0051368

- Assess risk for alloimmune HDN in fetus or father of pregnancy

Disease Overview

HDN

Incidence

- 6-7/1,000 live births with maternal RhD alloimmunization in the U.S. (Martin, 2002)
- 13% of hydrops fetalis is caused by antigen/antibody-mediated red blood cell (RBC) hemolysis
- RhD antigen causes ~50% of clinically significant maternal alloimmunization cases (Advent, 2000)
  - Anti-c is one of the most common causes of severe HDN after anti-D
  - Anti-C, anti-E, and anti-e are less common causes of HDN
  - When symptoms occur, they are usually mild to moderate (Klein, 2013)

Symptoms of HDN

- Fetal hemolytic anemia
- Jaundice
- Hepatosplenomegaly
- Erythroblastosis
- Hydrops fetalis
- Stillbirth

Physiology

- Transplacentally transferred maternal IgG antibodies attack fetal RBCs in response to foreign, paternally inherited antigens in fetus
- >50 different RBC antigens are known to be associated with maternal alloimmunization and HDN

Genetics

Gene – RHCE

Inheritance – autosomal recessive
**Test Interpretation**

**Analytical sensitivity/specificity** – 98%

**Results**

- **RhCc antigen**
  - Homozygosity for C allele is predictive of RhC positive phenotype and Rhc negative phenotype
  - Cc compound heterozygosity is predictive of RhC and Rhc positive phenotype
  - Homozygosity for c allele is predictive of RhC negative phenotype and Rhc positive phenotype

- **RhEe antigen**
  - Homozygosity for E allele is predictive of RhE negative phenotype and RhE positive phenotype
  - Ee compound heterozygosity is predictive of RhE and RhE positive phenotype
  - Homozygosity for e allele is predictive of RhE negative phenotype and RhE positive phenotype

- Fetus predicted to be unaffected following prenatal genotyping should continue to be monitored by noninvasive means for the development of erythroblastosis or hydrops

**Limitations**

- Bloody amniotic fluid specimens may give false-negative results due to maternal cell contamination
- Genotyping may result in false-negative RhC, Rhc, or RhE predictions due to RHCE-D-CE fusion genes
- Test is occasionally limited in predicting RHCE genotype due to extreme variation in the Rh locus
- Diagnostic errors can occur due to rare sequence variations

**References**