# 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

Rh Antigen (*RhD*) Genotyping 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


- Advent ND, Reid ME. The Rh blood group system: a review. Blood. 2000;95(2):375-387
- Klein HG, Anstee DJ. Mollison's Blood Transfusion in Clinical Medicine, 12th ed. Wiley-Blackwell. 2013
- Martin JA, Hamilton BE, et al. Births: final data for 2001. Natl Vital Stat Rep. 2002;51(2):1–102