Platelet Antigens (HPA-1 to HPA-6 and HPA-15) Genotyping

Indications for Ordering

Fetal or neonatal testing when
- Parents have had a prior affected pregnancy
- Unexplained intracranial hemorrhage is detected

Maternal and paternal testing when
- Fetus or neonate is suspected to have neonatal alloimmune thrombocytopenia (NAIT)
  - Also referred to as perinatal alloimmune thrombocytopenia (PAT)

Women
- Planning a pregnancy who have a sister with a previously affected pregnancy
- With posttransfusion purpura

Test Description

Multiplex polymerase chain reaction (PCR) followed by allele-specific primer extension using fluorescence to detect human platelet antigen (HPA) alleles
- HPA-1 (*ITGB3*): c.176T>C, p.L59P
- HPA-2 (*GP1BA*) c.482C>T, p.T161M
- HPA-3 (*ITGA2B*): c.2621T>G, p.I874S
- HPA-4 (*ITGB3*): c.506G>A, p.R169Q
- HPA-5 (*ITGA2*): c.1600G>A, p.E534K
- HPA-6 (*ITGB3*): c.1544G>A, p.R515Q
- HPA-15 (*CD109*): c.2108C>A, p.S703Y

Tests to Consider

Primary test

Platelet Antigen Genotyping Panel 0051308
- Use in risk assessment for NAIT
- May be ordered for parental, fetal, or neonatal genotyping

Related tests

- Platelet Antigen 1 Genotyping (HPA-1) 0051309
- Platelet Antigen 2 Genotyping (HPA-2) 0051310
- Platelet Antigen 3 Genotyping (HPA-3) 0051311
- Platelet Antigen 4 Genotyping (HPA-4) 0051490
- Platelet Antigen 5 Genotyping (HPA-5) 0051312
- Platelet Antigen 6 Genotyping (HPA-6) 0051313
- Platelet Antigen 15 Genotyping (HPA-15) 0051314
- Platelet Antibodies, Indirect 0051050

Disease Overview

Incidence – NAIT is the most common cause of severe thrombocytopenia in heathy term neonates and occurs in 1/1,000-5,000 births
- 80% of NAIT in Caucasians is caused by maternal antibodies directed against HPA-1a and ~20% by antibodies directed against HPA-5b
- Posttransfusion purpura occurs in 1/50,000-100,000 transfusions

Symptoms

- Severe thrombocytopenia in an otherwise healthy newborn
- Intracranial hemorrhage – may occur in utero, at birth, or postnatally
  - Fatal in 5-10% of affected neonates
  - May cause intellectual disability, seizures, cerebral palsy, or cortical blindness in up to 25% of survivors
- Widespread petechiae or purpura
- Visceral hemorrhage – often of gastrointestinal or bladder mucosa

Diagnostic issues

- Maternal immunization against fetal platelet alloantigens may result in NAIT
  - NAIT occurs when maternal IgG antibodies, directed toward paternally derived fetal alloantigens on platelets, are transferred across the placenta
- Because prenatal platelet typing is not routinely performed, at-risk women are only identified after having an affected pregnancy
- Recurrence rate is up to 90% and severity may increase in subsequent pregnancies
- Posttransfusion purpura is most common in women who are HPA-1a negative and immunized during a previous pregnancy
- Clinical correlation between antibody titers and NAIT occurrence is not reliable
- Specific paternal platelet antigens are demonstrated to react with alloantibodies in only 50% of cases
  - Genotyping allows for more accurate risk assessment and better pregnancy management

- Testing may be helpful to
  - Screen for neonatal immunization during pregnancy when parents had prior affected pregnancy or when unexplained intracranial hemorrhage is detected
  - Assess risk of NAIT in future pregnancies
  - Assess risk of posttransfusion purpura and thrombocytopenia

Genetics

Gene – HPA genes (*GP1BA, ITGA2B, ITGB3, ITGA2,* and *CD109)*

Variants

~24 different types of platelet-specific alloantigens have been identified

- The more common allele is designated as “a”; the less common allele is known as “b”
  - 2% of Caucasian women are homozygous for HPA-1b
    - These women are at risk for alloimmunization during pregnancy if partner is homozygous HPA-1a or heterozygous HPA-1a/b and contributes the HPA-1a allele to the fetus

Legacy names

- HPA-1: *GPIIIa*
- HPA-2: *GPIba*
- HPA-3: *GPIIb*
- HPA-4:*GPIIIa*
- HPA-5: *GPIa*
- HPA-6: *GPIIIa*
- HPA-15: *CD109*

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity/specificity – variable
- Analytical sensitivity/specificity – 99%

Results

- HPA-a/a homozygous
  - 2 copies of the common “a” allele
- HPA-a/b heterozygous
  - 1 copy of the common “a” allele and 1 copy of the less common “b” allele
- HPA-b/b homozygous
  - 2 copies of the less common “b” allele

Limitations

- HPA genes and variants, other than the ones tested, will not be detected
- Bloody amniotic fluid specimens may give false-negative results due to maternal cell contamination
- Diagnostic errors can occur due to rare sequence variations

References

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