Tay-Sachs Disease

Indication for Ordering

Identify causative *HEXA* gene variant(s) in individuals with abnormal level of beta-hexosaminidase A (HEX A) enzyme

Test Description

- Polymerase chain reaction followed by bidirectional sequencing of all coding regions and intron/exon boundaries of the *HEXA* gene
- Agarose gel electrophoresis for the *HEXA* 7.6kb deletion

Tests to Consider

Typical testing strategy

- HEX A enzymatic activity
  - Initial test to confirm diagnosis in symptomatic individual
  - First-tier test to determine carrier status
- Molecular testing of *HEXA* gene
  - Identify pathogenic variant(s) when HEX A enzyme activity is abnormal
  - Distinguish pseudodeficiency alleles from pathogenic variants
  - *HEXA* common variants panel is recommended for Ashkenazi Jewish ancestry
  - Tay-Sachs disease sequencing and deletion is recommended for all other ethnicities, including French Canadian

Primary tests

Tay-Sachs Disease (*HEXA*) Sequencing and 7.6kb Deletion 2009298

- Confirm pathogenic and pseudodeficiency *HEXA* gene variants in individuals with abnormal levels of HEX A enzyme

Tay-Sachs Disease (*HEXA*), 7 Variants 0051428

- Confirm common pathogenic and pseudodeficiency *HEXA* gene variants in Ashkenazi Jews and French Canadians with abnormal levels of HEX A enzyme
- Included in a panel of tests (Ashkenazi Jewish Diseases, 16 Genes, 0051415) for common disorders/variants for screening individuals of Ashkenazi Jewish descent

Related tests

Hexosaminidase A Percent and Total Hexosaminidase in Plasma with Reflex to Hexosaminidase A Percent and Total Hexosaminidase in Leukocytes 2008129

- Diagnose suspected Tay-Sachs disease
- Identify carriers of Tay-Sachs disease
- Preferred test for males and nonpregnant females
- For individuals who are pregnant, use oral contraceptives, have severe liver or autoimmune disease, or had previously inconclusive HEX A enzyme serum/plasma level, the preferred test is 2008125
- Can detect Sandhoff disease

Hexosaminidase A Percent and Total Hexosaminidase, Plasma or Serum 2008121

- Diagnose suspected Tay-Sachs disease
- Identify carriers of Tay-Sachs disease in males or nonpregnant females
- Not for individuals who are pregnant, use oral contraceptives, or have severe liver or autoimmune disease
- Can detect Sandhoff disease

Hexosaminidase A Percent and Total Hexosaminidase in Leukocytes 2008125

- Preferred initial test to diagnose suspected Tay-Sachs disease
- Identify carriers of Tay-Sachs disease
- Use for individuals who are pregnant, use oral contraceptives, have severe liver or autoimmune disease, or had previously inconclusive HEX A enzyme testing in plasma/serum
- Can detect Sandhoff disease

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence – varies by ethnicity

- 1/3,000 for Ashkenazi Jews and French Canadians
- Other high-risk populations include Louisiana Cajuns and Old Order Amish
- 1/300,000 for the general population

Symptoms

Acute infantile HEX A deficiency

- Onset 3-6 months, with rapid progression and life expectancy <4 years

- Clinical findings
  - Progressive neurodegeneration
  - Hypotonia
  - Decreased attentiveness
  - Increased startle response
  - Cherry-red spot of the macula
  - Seizures
  - Blindness
  - Spasticity
  - Liver disease

Juvenile HEX A deficiency
- Onset between 2-10 years
- Clinical findings
  - Ataxia/incoordination
  - Decline of speech, cognition, motor skills, vision by 10 years
  - Optic neuropathy and retinitis pigmentosa may develop

Adult-onset or chronic HEX A deficiency
- Onset in childhood to adulthood, more slowly progressive
- Clinically variable course
- Adult onset
  - Muscle wasting, weakness, fasciculations, dysarthria
  - Cognitive dysfunction
  - Psychosis in 40%, often the first manifestation
- Chronic
  - Dystonia, choreoathetosis, ataxia, dysarthria
  - Cognitive/verbal skills affected later in the course

Diagnostic issues
- Affected individuals have absent or extremely low HEX A enzymatic activity
- Enzyme level is inversely correlated with disease severity
- Classic infantile disease – 0-5% activity
- Juvenile/chronic or adult-onset forms – <15% activity

Screening issues
- Enzymatic screening cannot distinguish between carriers of Tay-Sachs disease vs. later-onset forms of disease
- Pseudodeficiency alleles are clinically benign variants that have reduced HEX A enzyme activity toward synthetic substrates but have normal activity in vivo
  - Common pseudodeficiency alleles
    - c.739C>T (p.R247W)
    - c.745C>T (p.R249W)
  - Heterozygotes have HEX A activity level in the carrier range
  - Molecular testing is necessary to distinguish pathogenic variants from pseudodeficiency alleles
- B1 variants are rare, pathogenic *HEXA* gene variants with normal catalytic activity toward synthetic substrates but decreased activity in vivo
  - p.Arg178His B1 variant is predominantly found in individuals of Portuguese ethnicity
  - Associated with non-classic disease phenotypes
  - Heterozygotes not detected by enzymatic screening

Genetics

Gene – *HEXA*

Inheritance – autosomal recessive

Variants
- >130 *HEXA* variants have been identified
  - Majority are null alleles that result in no HEX A enzymatic activity
- 7.6kb deletion is the only recurring large deletion
- Commonly detected variants vary by ethnicity
  - Ashkenazi Jews
    - c.1274_1277dupTATC severe variant accounts for 80% of all pathogenic *HEXA* variants
    - c.805G>A (p.G269S) variant is typically associated with adult-onset HEX A deficiency
    - ~2% of individuals with enzyme level in the carrier range have pseudodeficiency alleles
  - French Canadians
    - 7.6kb deletion is the most common pathogenic variant
  - General population
    - ~36% of individuals with enzyme level in the carrier range have pseudodeficiency alleles

Test Interpretation

Tay-Sachs Disease (*HEXA*) Sequencing and 7.6kb Deletion
- Clinical sensitivity/specificity – 99%
- Analytical sensitivity/specificity – >99%

Results
- Positive – one or more pathogenic *HEXA* gene variants detected
  - Heterozygous
    - Individual is at least a carrier of HEX A deficiency
  - Homozygous or compound heterozygous
    - Confirms diagnosis of HEX A deficiency
      - Disease severity depends on the specific variants identified
- Negative – no pathogenic *HEXA* gene variant detected
  - Greatly decreased probability that the individual is affected with, or a carrier of, HEX A deficiency
  - Pseudodeficiency alleles will be reported but are considered clinically insignificant
- Inconclusive – sequence variant(s) of uncertain clinical significance identified

Limitations
- Regulatory region and deep intronic variants will not be detected
- Large deletions/duplications in *HEXA* other than the 7.6kb deletion will not be detected
- Diagnostic errors can occur due to rare sequence variations