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