X Chromosome Ultra-High Density Microarray

Indications for Ordering

- Screening of individuals for X chromosome microdeletions and microduplications associated with clinically diagnosed X-linked syndromes/clinical phenotypes
- Screening of individuals who have a family history of intellectual disabilities (IDs) or developmental disabilities that fit an X-linked pattern of inheritance
- To further characterize previously identified X chromosome abnormalities
  - Marker and ring chromosomes
  - Deletions and/or duplications
  - Unbalanced rearrangements
  - Apparently balanced de novo rearrangements in individuals with abnormal phenotypes

Test Description

- Microarray-based comparative genomic hybridization
  - X chromosome specific
  - Ultra-high density exonic oligonucleotide based
  - Custom designed
- Copy number changes are calculated based on hybridization signal ratios between individual specimen and controls
- Targets all disease-causing genes located on the X chromosome
  - Detects exonic level deletions/duplications
  - Detects copy number variations within all known X chromosome genes associated with X-linked ID (XLID) and autism
  - Detects small, unique deletions and/or duplications that may not be identified by conventional sequencing-based technologies within genes associated with other X-linked disorders

Tests to Consider

Primary test

X Chromosome Ultra-High Density Microarray 2004434

- Detects exon level losses or gains of DNA on the X chromosome in individuals with
  - Unexplained ID
  - Autism
  - Other X-linked conditions

Related tests

Cytogenomic SNP Microarray 2003414

- Preferred first-tier test for
  - Developmental delay
  - Multiple anomalies
  - Autism
- Testing is performed on peripheral blood

Cytogenomic SNP Microarray Buccal Swab 2006267

- Same test as the Cytogenomic SNP Microarray, except testing is performed on a buccal specimen
- Requires a buccal swab using Oracollect collection kit

Chromosome Analysis, Peripheral Blood 2002289

- Conventional cytogenetic analysis (karyotyping)
- Detects
  - Large additions/duplications
  - Large deletions
  - Balanced and unbalanced translocations and inversions involving all areas of the genome (including the X chromosome)

Other molecular techniques (eg, gene sequencing or other PCR-based assays)

- More sensitive than genomic microarray for detecting many intragenic alterations
  - Point mutations
  - Very small deletions or duplications (single base-pair resolution)
- Highly specific
- Restricted to the genetic site or gene of interest

Disease Overview

Prevalence and/or incidence – varies by disorder

Diagnostic issues

- X chromosome testing is important because many disorders are inherited in an X-linked fashion
- X-linked genetic defects are responsible for up to 30% of inherited IDs
  - Highly heterogeneous condition
  - Syndromic versus nonsyndromic XLID
    - ~2/3 of XLID is nonsyndromic
    - Defined based on the presence or absence of
      - Physical abnormalities
      - Dysmorphic features
      - Abnormal laboratory findings
      - Abnormal brain imaging studies

- Numerous X-linked disorders not involving ID
  - Hearing loss
  - Hemophilia
  - Immunodeficiency disorders
  - Metabolic disorders
  - Myopathies
  - Neuromuscular disorders
  - Skin disorders

Genetics

Genes – all disease-causing genes on the X chromosome

Inheritance

- X-linked recessive
- X-linked dominant

Test Interpretation

Clinical sensitivity/specificity – varies by condition

Results

- Positive – a pathogenic copy number change was identified involving one or more disease-causing genes on the X chromosome
- Negative – no known pathogenic copy number change was identified
- Inconclusive – a copy number change was identified that cannot currently be categorized as either pathogenic or benign

Limitations

- Does not exclude the diagnosis of any disorders represented on the microarray
- Will not detect
  - Numerical X chromosome changes (eg, Klinefelter, Turner, or XXX syndromes)
  - Balanced rearrangements
  - Base-pair changes within genes
  - Genomic imbalances smaller than the resolution of the array
  - Gains or losses within regions of the genome not represented on the array
- May not detect
  - Copy number imbalances for areas of high-sequence similarity
  - Mosaic gains or losses