Cytogenomic SNP Microarray

Indications for Ordering

- Individuals with
  - Developmental delay/intellectual disability (with or without dysmorphic features)
  - Multiple congenital anomalies
  - Autism spectrum disorder (ASD)/pervasive developmental disorder
  - Epilepsy/seizures
  - Heart defects
  - Family history of a chromosome abnormality tested most effectively by array
- Further characterization of a chromosomal abnormality
  - Marker or ring chromosomes
  - Deletions or duplications
  - Unbalanced translocations
  - Apparently balanced de novo rearrangements in individuals with abnormal phenotypes
- Identification of long contiguous stretches of homozygosity (LCSH)

Test Description

- DNA extraction, amplification, purification, labeling, hybridization, washing, array scanning, analysis, and interpretation
- Affymetrix CytoScan HD platform contains >2.6 million copy-number markers, including 750,000 single-nucleotide polymorphism (SNP) probes, to detect copy number changes and LCSH
- Average marker spacing
  - Intragenic – 880 base pairs (bp)
  - Intergenic (nongene backbone) – 1,700 bp
  - Overall (gene and nongene backbone) – 1,100 bp
- Average functional resolution
  - Deletion of 25 consecutive markers
  - Duplication of 50 consecutive markers

Tests to Consider

Primary tests

Cytogenomic SNP Microarray 2003414

- Preferred first-tier test for developmental delay, multiple anomalies, and ASD
- 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

Related tests

Chromosome Analysis, Peripheral Blood, with Reflex to Genomic Microarray 2005763

- Appropriate when there is a significant chance of trisomy
- Chromosome studies will identify
  - Obvious numerical abnormalities
  - Balanced chromosomal rearrangements
  - Large deletions/duplications
- If chromosomes are normal, testing reflexes to microarray

Cytogenomic SNP Microarray with Five-Cell Chromosome Study, Peripheral Blood 2009353

- Cytogenomic SNP Microarray (2003414) will be performed concurrently with a limited five-cell chromosome study
- Useful when chromosome and array tests would otherwise have been ordered concurrently
- May provide information regarding mechanism of gains and losses
- May identify cytogenetically visible rearrangements

Disease Overview

Incidence

- Intellectual disability – 3% in the general population
- Autism spectrum disorder – 1/100

Diagnostic issues

- Many abnormal phenotypes are associated with chromosomal imbalances
- Conventional cytogenetic testing has limited ability to detect
  - Small and cryptic abnormalities
  - LCSH
- SNP microarray testing can detect many of these chromosomal variants
- Identification of specific abnormalities may be helpful in medical management and planning for special needs

Genetics

- Whole genome coverage, including subtelomeric and pericentromeric regions
- Detects >50 known microdeletion/microduplication syndromes
- Detects absence of heterozygosity at thousands of loci throughout the genome

Test Interpretation

Clinical sensitivity

- 10-15% for individuals with
  - Unexplained intellectual disability
  - ASD
  - Multiple congenital abnormalities
- More severe cognitive impairment and associated findings leads to greater likelihood of identifying a causative copy number variant (CNV)

Results

- A written summary and an interpretation of the microarray findings are provided
- Homozygosity >3% of the autosomal genome may be reported
  - Suggests possible increased risk for a recessive condition
- Unrecognized consanguinity of parents of tested individual may be revealed
- **Normal**
  - No clinically significant abnormality was detected
- **Abnormal**
  - Clinically significant CNV was detected
    - Penetrance and expression of the CNV are known to be variable
  - LCSH was noted across a single region or multiple independent regions
  - Suggestive of either uniparental disomy (UPD) or increased risk of recessive condition
- **Clinical significance unknown** – copy number change detected
  - CNV was detected – insufficient evidence was available for unequivocal determination of clinical significance
  - Deletions/duplications that confer carrier status for recessive conditions may have been identified

Limitations

- Does not detect
  - Base pair mutations
  - Very small deletions/duplications
  - Balanced rearrangements (translocations, inversions, and balanced insertions)
  - Imbalances of the mitochondrial genome
- Low-level mosaicism (<25%) may not be detected
- May not be investigated or reported
  - CNVs devoid of relevant gene content or reported as common findings in the general population
  - Duplications <400 kb and deletions <50 kb, depending on genomic content of the imbalance
  - LCSH <8 Mb (telomeric) or <15 Mb (interstitial) on imprinted chromosomes
  - LCSH <10 Mb (telomeric) or <15 Mb (interstitial) on non-imprinted chromosomes
  - LCSH <3% of the autosomal genome