Autism and Intellectual Disability Comprehensive Panel

Background

Autism spectrum disorders (ASDs) and intellectual disability (ID) represent a neurodevelopmental continuum with significant comorbidity and overlapping etiology.

ASD is classified by varying degrees of social impairment, communication limitations, repetitive behaviors, and/or restricted interests. Symptoms typically present by age 3 and medical diagnoses are made clinically based on severity of symptoms.

Likewise, ID includes comorbidities with ASD and is classified by broad impairment in cognitive and adaptive function with an IQ below 70 and onset before 18. Patients who cannot be accurately assessed using IQ are typically classified by delays in developmental domains. Those with severe global developmental delays (DDs) diagnosed before age 6 are most likely to develop ID.

ASDs, and/or ID may be a feature in various genetic syndromes associated with chromosomal copy number variants (CNVs), fragile X syndrome, and inborn errors of metabolism (IEMs). Literature suggests ~10-15% of individuals with ASD ID have detectable chromosomal abnormalities associated with CNVs and fragile X syndrome, while up to 5% of ASD and up to 8% of ID may be related to potentially treatable IEMs.

Heritability

- ASD: ~90%
- ID: ~50%

Prevalence

- ASD: ~1/68 (1/42 males, 1/189 females)
- ID: ~1/100
- ASD and ID combined incidence: ~1/250

Indications for Ordering

- Comprehensive evaluation of an individual with ASD and/or ID (with or without comorbidities)
- Assist with decisions about treatment and management of an individual with ASD and/or ID
- Confirmation of a clinical diagnosis of ASD and/or ID

Tests to Consider

Primary test

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- Comprehensive genetic evaluation of individuals with ASD and/or ID
- Includes cytogenomic microarray, fragile X methylation analysis, and comprehensive metabolic disorders analysis

Test components (may be ordered separately)

Cytogenomic SNP Microarray 2003414

- Preferred first-tier test for DD, ID, ASD, and multiple anomalies
  - Testing is performed on peripheral blood
- Affymetrix CytoScan HD platform to detect CNV changes such as microdeletions and duplications and long contiguous stretches of homozygosity

Cytogenomic SNP Microarray Buccal Swab 2006267

- Preferred first-tier test for DD, ID, ASD, and multiple anomalies
- Testing is performed on buccal sample

Fragile X (FMR1) with Reflex to Methylation Analysis 2009033

- Preferred test to diagnose fragile X syndrome and carrier screening in individuals with a positive family history
- If fragile X testing detects a CGG repeat of 55 or greater by polymerase chain reaction and capillary electrophoresis, methylation analysis will be added

Autism and Intellectual Disability Metabolic Panel 2014312

- Evaluate for ASD, DD, and/or ID in individuals who have had negative *FMR1* (fragile X) and cytogenomic SNP microarray testing

Acylcarnitine Quantitative Profile, Plasma 0040033

- Quantitative tandem mass spectrometry

Amino Acids Quantitative by LC-MS/MS, Plasma 2009389

- Quantitative liquid chromatography/tandem mass spectrometry

Creatine Disorders Panel, Serum or Plasma 2002328
AND Creatine Disorders Panel, Urine 2002333

- Order these two tests simultaneously for proper result interpretation
- Liquid chromatography/tandem mass spectrometry

Mucopolysaccharides Screen, Urine 0081352

- Spectrophotometry and electrophoresis

Organic Acids, Urine 0098389

- Gas chromatography/mass spectrometry

Test Limitations

- Autism and intellectual disability panel testing limitations:
  - Other etiologies of ASD and ID, such as single gene disorders, may not be identified
  - Uninformative results may occur due to variants of uncertain clinical significance
  - Results may not predict disorder severity
- Cytogenomic SNP microarray limitations:
  - Testing does not detect
    - Base-pair mutations
    - Very small deletions/duplications
    - Balanced rearrangements (translocations, inversions, balanced insertions)
    - Imbalances of the mitochondrial genome
    - Low-level mosaicism (<25%)
  - For further review, see Additional Technical Information for Cytogenomic SNP Microarray 2003414
- Fragile X testing limitations:
  - Estimated size is not provided for full mutations with >200 repeats
  - Rare mutations in *FMR*1 unrelated to trinucleotide expansion will not be detected
  - Diagnostic errors can occur due to rare sequence variations
  - For further review, see Additional Technical Information for Fragile X (*FMR1*) with Reflex to Methylation Analysis 2009033

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