Autism and Intellectual Disability Comprehensive Panel

Last Literature Review: May 2019 Last Update: May 2024

Autism spectrum disorder (ASD) and intellectual disability (ID) represent a neurodevelopmental continuum with significant comorbidity and overlapping etiologies. ASD is classified by varying degrees of social impairment, communication limitations, repetitive behaviors, and/or restricted interests. Symptoms typically present by age 3. ID is classified by broad impairment in cognitive and adaptive functioning, typically with an IQ below 70, and presents before age 18. A global developmental delay (DD) diagnosis often precedes a diagnosis of ID, as cognitive skill or IQ cannot be reliably assessed prior to age 6. Those with severe DD diagnosed before age 6 are most likely to develop ID.

ASD and IDs are often comorbid and 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 and/or ID have detectable chromosomal abnormalities, CNVs, and fragile X syndrome.

Disease Overview

Indications for Ordering (Testing)

- 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

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

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:

- The genome-wide resolution is approximately 25-50 kb for copy number changes and approximately 3 Mb for regions of homozygosity
- Testing does not detect
  - CNVs below the limit of resolution of this platform
  - Sequence-level variants (mutations) including point mutations and indels

Featured ARUP Testing

Autism and Intellectual Disability Comprehensive Panel 2014314

Method: Tandem Mass Spectrometry/Electrophoresis/Spectrophotometry/Gas Chromatography-Mass Spectrometry/Liquid Chromatography-Tandem Mass Spectrometry/Quantitative Liquid Chromatography-Tandem Mass Spectrometry, Genomic Microarray (Oligo-SNP Array), Polymerase Chain Reaction/Capillary Electrophoresis

- 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

Method: Genomic Microarray (Oligo-SNP Array)

- Preferred first-tier test for DD, ID, ASD, and multiple anomalies
- Testing is performed on peripheral blood
- CytoScan HD platform (Thermo Fisher Scientific) to detect copy number changes, including deletions and duplications as well as copy-neutral regions of homozygosity

Cytogenomic SNP Microarray Buccal Swab 2006267

Method: Genomic Microarray (Oligo-SNP Array)

- 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

Method: Polymerase Chain Reaction (PCR)/Capillary Electrophoresis

- 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 100 or greater by polymerase chain reaction and capillary electrophoresis, methylation analysis will be added

- Low-level mosaicism (generally, less than 20-30%)
- Balanced chromosomal rearrangements (translocations, inversions, and insertions)
- Genomic imbalance in repetitive DNA regions (centromeres, telomeres, segmental duplications, and acrocentric chromosome short arms)
- Mitochondrial DNA alterations

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

Autism and Intellectual Disability Metabolic Panel 2014312

Method: Tandem Mass Spectrometry/Electrophoresis/Spectrophotometry/ Gas Chromatography-Mass Spectrometry/Liquid Chromatography-Tandem Mass Spectrometry

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

Additional Resources

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Publishing; 2013.

Campistol J, Díez-Juan M, Callejón L, et al. Inborn error metabolic screening in individuals with nonsyndromic autism spectrum disorders. *Dev Med Child Neurol*. 2016;58(8):842-847.

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Karam SM, Riegel M, Segal SL, et al. Genetic causes of intellectual disability in a birth cohort: a population-based study. *Am J Med Genet A*. 2015;167(6):1204-1214.

Kaufman L, Ayub M, Vincent JB. The genetic basis of non-syndromic intellectual disability: a review. *J Neurodev Disord*. 2010;2(4):182-209.

Michelson DJ, Shevell MI, Sherr EH , et al. Evidence report: genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2011;77(17):1629-1635.

Rauch A, Hoyer J, Guth S, et al. Diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation. *Am J Med Genet A*. 2006;140(19):2063-2074.

Sandin S, Lichtenstein P, Kuja-Halkola R, et al. The familial risk of autism. *JAMA*. 2014;311(17):1770-1777.

Sempere A, Arias A, Farré G, et al. Study of inborn errors of metabolism in urine from patients with unexplained mental retardation. *J Inherit Metab Dis*. 2010;33(1):1-7.

South ST, Lee C, Lamb AN, et al. ACMG standards and guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. *Genet Med*. 2013;15(11):901-909.

van Karnebeek CDM, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. *Mol Genet Metab*. 2012;105(3):368-381.

Related Information

Alpha-Iduronidase Enzyme Activity in Leukocytes
Creatine Disorders Panel Testing
Laboratory Testing for Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder
Testing for Genetic Syndromes Related to Developmental Delay (DD) and Intellectual Disability (ID)