THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Intellectual Disability Exome

Intellectual Disability Overview

Intellectual disability (ID), sometimes also referred to as 'mental retardation' and 'cognitive disability', is a lifelong disability that presents in infancy or the early childhood years and is typically measured in three domains: intelligence (IQ), adaptive behavior and systems of support (1). The term 'global developmental delay' is typically reserved for younger children (less than 5 years of age), whereas the term ID is typically applied to older children when IQ testing is valid and reliable (2). Intellectual disability may be observed as part of a syndrome with other phenotypic findings, or may be an isolated finding without accompanying additional physical, neurological, and/or metabolic abnormalities (non-syndromic). Overall, the prevalence of ID is estimated to be between 1% - 3%.

In general, there is wide variation in the causes of ID: 17 – 47% of cases have genetic causes and 18 – 44% have exogenous causes (such as teratogen exposure or infection) (1). The etiology remains unknown in up to 80% of cases with mild intellectual disability (3).

Clinical Utility of Genetic Testing for Intellectual Disability

Genetic testing for intellectual disability can present challenges, due to the large and ever expanding number of genes associated with the disorder, and the wide clinical and genetic heterogeneity that exists. Despite this complexity, determining the molecular basis of intellectual disability using genetic testing can be useful in predicting recurrence risk and disease course. Utilizing exome sequencing technology for the Intellectual Disability Exome test allows us to analyze a large and dynamic gene list that can be updated regularly as new genes are identified. Our Intellectual Disability Exome includes exome analysis of both the patient and both parents (trio analysis), in order to be able to perform segregation studies and identify *de novo* variants upfront, without the need for follow up parental testing.

The Intellectual Disability Exome includes analysis of 1969 genes

The Intellectual Disability Exome involves analysis of exome sequencing data in a predefined set of 1918 genes associated with intellectual disability. These include genes known to be associated with intellectual disability as the only feature, as well as genes associated with certain syndromes for which intellectual disability is a commonly observed feature in affected individuals.

For a complete list of the 1969 genes analyzed, please visit our website at dnatesting.uchicago.edu

Test Analysis

Of the thousands of variants identified by exome sequencing, a list of variants that are located within in a predefined set of 1918 genes that have been associated with intellectual disability is generated. For cases without a clearly pathogenic variant identified in the predefined list of 1918 genes, an additional analysis of previously reported pathogenic variants and truncating variants in known disease genes (present in the HGMD database) will be performed. For variants outside of the predefined list of 1918 genes, only those considered to be the likely cause of the patient's phenotype will be reported. Most variants identified as part of exome sequencing will NOT undergo interpretation by a laboratory staff member. Only those variants considered to be potentially relevant to the patient's condition are reviewed by a team of Board-Certified PhD geneticists, MD geneticists, and genetic counselors who will determine the likelihood of the variant being related to the patient's disorder based on the phenotypic information provided by the ordered clinician.

Parental Analysis

The Intellectual Disability Exome includes exome sequencing of both the patient, and both biological parents. Due to the large number of genes analyzed, testing cannot be performed unless samples on both parents are

received. If parental samples are not available, we recommend consideration of our Non-Specific Intellectual Disability panel, which includes 170 genes associated with intellectual disability.

Test methods

Exome sequencing is performed using the Agilent SureSelect Clinical Research Exome kit that is designed to target the exome with greater coverage of known disease-associated genes. Sequencing is performed using the Illumina technology and reads are aligned to the reference sequence. Approximately 97-98% of exons in the genes of interest are targeted at a minimum depth of 10X in the diagnostic Intellectual Disability Exome. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. In some cases, exome sequencing data may be used to detect larger copy number variations (CNVs) such as whole or partial gene deletions/duplications. The sensitivity of exome sequencing to detect intragenic deletions/duplications >20bp in size is not currently known.

Reporting Results

Typically only likely pathogenic or pathogenic variants that occur in genes within the pre-defined set of genes associated with intellectual disability will be reported. In some cases, variants of unknown significance (VUS) may be reported, if a VUS is identified that is strongly suspected to be associated with the patient's phenotype. However, given the large number of genes on the Intellectual Disability Exome, most VUS identified will not be reported. A list of all variants identified in the pre-defined list of genes will be available upon request. Variants in the additional genes in the exome will not be reported, unless they are identified as part of a secondary analysis of variants in HGMD genes (see "test analysis" section) and considered very highly likely to be the cause of the patient's phenotype, given the phenotypic information provided. Mutations in genes unrelated to the individual's reported phenotype are considered secondary or incidental findings. Secondary or incidental findings will not be interrogated nor reported in the Intellectual Disability Exome. Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Re-analysis

As new gene discoveries and associations are reported in the literature, we can review past cases for findings in these genes. Re-analysis of exome sequencing data is available upon request.

Required Forms

- Intellectual Disability Exome Test Requisition Form
- Completed Intellectual Disability Clinical Checklist
- Completed Intellectual Disability Exome Consent Form

Intellectual Disability Exome (requires a sample from the patient and both biological parents)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$5500
CPT codes:	81415, 81416
Turn-around time:	6 weeks

Note: We do not bill insurance directly for this specific test

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Moeschler JB, Shevell M, Genetics AAoPCo. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics 2006: 117: 2304-2316.
2. Moeschler JB. Genetic evaluation of intellectual disabilities. Semin Pediatr Neurol 2008: 15: 2-9.
3. 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: 2063-2074.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS