THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panels for Non-specific Intellectual Disability

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). Non-syndromic ID refers to the presence of ID without accompanying additional physical, neurological, and/or metabolic abnormalities.

The prevalence of ID (syndromic and non-syndromic) is estimated to be between 1% - 3%. In general, there is wide variation in the causes of ID: 18 – 44% of cases have exogenous causes (like teratogen exposure or infection) and 17 – 47% have genetic causes (1). X-linked mental retardation (XLMR) affects between 1/600-1/1000 males and a substantial number of females (3). The etiology remains unknown in up to 80% of cases with mild intellectual disability (4). Depending on the underlying etiology, the recurrence risk can vary between the background and 50%. The best approach to the genetic evaluation of a child with ID is to do a careful history, 3-generation family history, and dysmorphologic and neurologic examination. Based on this alone, a geneticist will suspect or establish a diagnosis in as many as two thirds of cases (2). Being able to provide a genetic etiology allows for the opportunity of prenatal diagnosis, guidance with disease management, acceptance of the disability, and connection with other parents and support groups (4).

The distinction between syndromic and non-syndromic ID is not precise. Conditions previously regarded as non-syndromic forms of ID may have additional clinical findings that were not intially recognized or emphasized, thus a range of mutations in a single gene can sometimes confer both syndromic and non-syndromic phenotypes. Our 'non-specific' ID panels include mainly non-syndromic forms of ID, but also include many syndromic forms of ID to account for the above.

Our Autosomal Recessive Non-Specific ID panel includes all of the 49 genes listed below.

Autosomal recessive Non-Specific ID panel								
ADAT3	AP4M1	CLIP1	EZR	KPTN	NDST1	SLC25A1	TRAPPC9	ZNF526
ALDH5A1	AP4S1	CNTNAP2	FBXO31	L2HGDH	NRXN1	SLC6A17	TTI2	
ALG6	ARFGEF2	CRBN	FMN2	LINS	NSUN2	SOBP	TUSC3	
ANK3	C12orf57	D2HGDH	GRIK2	MAN1B1	PCNT	ST3GAL3	VLDLR	
AP4B1	CA8	DDHD2	KCNJ10	MED23	PGAP1	TAF2	VPS13B	
AP4E1	CC2D1A	ERLIN2	KIAA1033	METTL23	PRSS12	TECR	ZC3H14	

Our X-linked Non-Specific ID panel includes all of the 77 genes listed below.

X-linked Non-Specific ID panel								
ACSL4	BRWD3	FLNA	HUWE1	KLF8	NLGN3	PHF6	SHROOM4	TSPAN7
AFF2	CASK	FMR1	IGBP1	MECP2	NLGN4X	PHF8	SLC16A2	UBE2A
AP1S2	CCDC22	FRMPD4	IL1RAPL1	MED12	OFD1	PRPS1	SMC1A	ZDHHC9
ARHGEF6	CDKL5	FTSJ1	IQSEC2	MID1	OPHN1	PTCHD1	SMS	ZNF711
ARHGEF9	CLIC2	GDI1	KDM5C	MID2	PAK3	RAB39B	SRPX2	ZNF81
ARX	CUL4B	GRIA3	KIAA2022	NAA10	PCDH19	RPL10	SYN1	
ATP6AP2	DCX	HCFC1	KIF4A	NHS	PDHA1	RPS6KA3	SYP	
ATRX	DLG3	HPRT1	L1CAM	NSDHL	PLP1	SLC6A8	UPF3B	
BCOR	EIF2S3	HSD17B10	MAOA	OCRL	PQBP1	SLC9A6	ZDHHC15	

In addition, our Non-Specific ID Panel is available, which includes 169 genes in total including all genes listed above implicated in X-linked and autosomal recessive ID, as well as the below autosomal dominant genes

Non-Specific ID panel						
Autosomal Dominant					Autosomal Recessive	X-linked
ADNP	DYNC1H1	GRIN2B	RAI1	SYNGAP1	Including all 49 genes listed above	Including all 77 genes listed above
ARID1A	DYRK1A	IDH2	SCN2A	TCF4		
ARID1B	EHMT1	KIF1A	SETD5	TUBA1A		
CACNG2	EPB41L1	KIRREL3	SHANK2	UBE3A		
CDH15	FOXG1	MBD5	SHANK3	ZEB2		
CTCF	FOXP1	MEF2C	SMARCA4	ZMYND11		
CTNNB1	GATAD2B	NRXN2	SMARCB1	ZNF407		
DEAF1	GRIN1	PACS1	SOX11			
DNMT3A	GRIN2A	PURA	STXBP1			

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interest are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. 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. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Autosomal Recessive Non-Specific ID Panel (49 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2000
CPT codes:	81407
Turn-around time:	8 weeks

X-linked Non-Specific ID Panel (77 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2000
CPT codes:	81470
Turn-around time:	8 weeks

Non-Specific ID Panel (169 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3500
CPT codes:	81407
Turn-around time:	8 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.
Note: We cannot bill insurance for the above tests.

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. Gécz J, Shoubridge C, Corbett M. The genetic landscape of intellectual disability arising from chromosome X. Trends Genet 2009: 25: 308-316.
4. 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.

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