



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 dysmorphic 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 initially 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 75 genes listed below.

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

In addition, our Non-Specific ID Panel is available, which includes 203 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 Recessive	X-linked
Autosomal Dominant						
ADNP	DCPS	GRIN1	PACS1	SMARCA4	Including all 49 genes listed above	Including all 75 genes listed above
ARID1A	DDX3X	GRIN2A	PPP2R5D	SMARCB1		
AHDC1	DEAF1	GRIN2B	PPT1	SOS1		
ANKRD11	DHCR7	HIVEP2	PTEN	SOX11		
ARID1B	DNMT3A	HNRNPU	PTPN11	STXBP1		
ASXL3	DYNC1H1	HOXA1	PURA	SYNGAP1		
CACNG2	DYRK1A	IDH2	RAI1	TBL1XR1		
BCL11A	EHMT1	KAT6A	RIT1	TCF4		
CDH15	EPB41L1	KIF1A	SATB2	TRIO		
CHD7	FOLR1	MBD5	SCN2A	TUBA1A		
CIC	FOXG1	MED13L	SETBP1	UBE3A		
CLCN4	FOXP1	MED25	SETD5	USP9X		
CNKRS2	FOXP2	MEF2C	SHANK2	ZEB2		
CSNK2A1	GAMT	MYT1L	SHANK3	ZMYND11		
CTCF	GATAD2B	NR2F1	SIN3A	ZNF407		
CTNNB1	GATM	NRXN2	SMARCA2			

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.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Autosomal Recessive Non-Specific ID Panel (49 genes)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
 Cost: \$2000
 CPT codes: 81406
 81407
 Turn-around time: 8 weeks

X-linked Non-Specific ID Panel (75 genes)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
 Cost: \$2000
 CPT codes: 81406
 81407
 Turn-around time: 8 weeks

Non-Specific ID Panel (203 genes)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
 Cost: \$3500
 CPT codes: 81406
 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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