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Next Generation Sequencing Panels for Non-syndromic 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].

Our Autosomal Recessive non-syndromic ID panel includes all of the 20 genes listed below.

Autosomal recessive non-syndromic ID panel				
AP4B1	CA8	ERLIN2	PRSS12	TUSC3
AP4E1	CC2D1A	GRIK2	ST3GAL3	VLDLR
AP4M1	CNTNAP2	MAN1B1	STXBP1	ZC3H14
AP4S1	CRBN	NRXN1	TRAPPC9	ZNF526

Our X-linked non-syndromic ID panel includes all of the 61 genes listed below.

X-linked non-syndromic ID panel				
ACSL4	CUL4B	IQSEC2	PCDH19	SLC9A6
AFF2	DCX	KDM5C	PHF6	SRPX2
AGTR2	DLG3	MAGT1	PHF8	SYN1
AP1S2	FLNA	MECP2	PLP1	SYP
ARHGEF6	FMR1	MED12	PQBP1	TSPAN7
ARHGEF9	FTSJ1	MID1	PRPS1	UBE2A
ARX	GDI1	NHS	PTCHD1	UPF3B
ATP6AP2	GRIA3	NSDHL	RAB39B	ZDHHC9
ATRX	HCCS	OCRL	RPS6KA3	ZNF41
BCOR	HSD17B10	OFD1	SHROOM4	ZNF674
BRWD3	HUWE1	OPHN1	SLC16A2	ZNF711
CASK	IL1RAPL1	PAK3	SLC6A8	ZNF81
CDKL5				

In addition, our Comprehensive non-syndromic ID Panel is available, which includes 93 genes in total including all genes listed above implicated in X-linked and autosomal recessive ID, as well as the below autosomal dominant genes

Comprehensive non-syndromic ID panel				
Autosomal Dominant			Autosomal Recessive	X-linked
CDH15	KIRREL3	SYNGAP1	All 20 AR genes listed above	All 61 X-linked genes listed above
FOXG1	MEF2C	TCF4		
FOXP1	RAI1	UBE3A		
GRIN2B	SOBP	ZEB2		

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are amplified using highly parallelized and multiplexed PCR reactions assembled with the Raindance System. DNA is sequenced 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 novel and/or potentially 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 8 bp.

Autosomal Recessive non-syndromic ID Panel (20 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $3500
CPT codes: 81407
Turn-around time: 8 - 10 weeks

X-linked non-syndromic ID Panel (61 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $4500
CPT codes: 81407
Turn-around time: 8 - 10 weeks

Comprehensive non-syndromic ID Panel (93 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $5500
CPT codes: 81407
Turn-around time: 8 - 10 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.

References:

1. Moeschler JB, *et al*. "Clinical genetic evaluation of the child with mental retardation or developmental delays". (2006) Pediatrics 117: 2304-16.
2. Moeschler JB. "Genetic evaluation of intellectual disabilities". (2008) Semin Pediatr Neurol 15:2-9.
3. Gecz J, et al. "The genetic landscape of intellectual disability arising from chromosome X". (2009) Trends Genet 25:308-16.
4. Rauch A, *et al*. "Diagnostic Yield of Various Genetic Approaches in Patients with Unexplained Developmental Delay or Mental Retardation." (2006) Am. J. Med. Genet A. 140A:2063-2074.

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