X-Linked Intellectual Disability Panel

Indications for Ordering

Confirm hereditary etiology of suspected intellectual disability (ID)

Test Description

- Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
  - Reported variants confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary test

X-linked Intellectual Disability Panel, Sequencing, 76 Genes 2010225

- Preferred test for individuals with suspected X-linked intellectual disability (XLID) when genomic microarray testing has not identified causal variant(s)

Related tests

X Chromosome Ultra-High Density Microarray 2004434

- Screening test for individuals with
  - Clinical diagnosis/clinical phenotype or
  - Family history of an X-linked condition

Cytogenomic SNP Microarray 2003414

- Preferred first-tier test for individuals with developmental delay, multiple congenital anomalies, or autism

Chromosome Analysis, Peripheral Blood 2002289

- Detect large genomic deletions, duplications, or insertions

X-Chromosome Inactivation Analysis 2006352

- Determine X-chromosome inactivation (XCI) pattern for female carriers of X-linked disorders
- Assess pathogenicity of genetic variant in an X-linked gene
- Does not detect clonality

Fragile X (*FMR1*) with Reflex to Methylation Analysis 2009033

- Diagnose fragile X syndrome
- Screen for carrier status

Disease Overview

Prevalence

- ~11/1,000 children
- ~7/1,000 in adults

Biology

Heterogeneous group of disorders with numerous physical, neurological, and/or metabolic phenotypes

- Share common elements of X-linked inheritance
  - Decreased intellectual functioning
  - Reduced adaptive behavior

Clinical criteria for ID

- Intelligence quotient (IQ) <70
- Limitation in 2 or more adaptive behaviors
  - Communication
  - Self-care
  - Social skills
  - Community use
  - Self-direction
  - Health
  - Safety

Genetics

Genes – see table for genes tested and for gene-specific information

Inheritance – all tested genes have X-linked pattern of inheritance

Mutations

- Mutations in multiple genes for XLID may cause overlapping phenotypes
- Other genetic and/or environmental factors may influence severity of clinical phenotype
- Intrafamilial phenotypic variability may exist
- Germ line and somatic mosaicism documented
- Female carriers may be variably affected

Test Interpretation

Results

- Positive
  - Detection of pathogenic mutation in a male
    - Confirms genetic etiology of ID
  - Detection of a pathogenic mutation in a female
    - Confirms genetic etiology or carrier status for XLID
- Negative
  - No causative mutation detected
    - Reduces, but does not exclude, genetic etiology of ID
- Inconclusive – variants of uncertain clinical significance identified

Limitations

- Not analyzed
  - Mutations in genes not included on the panel
  - Deep intronic and regulatory region mutations
  - Large deletions/duplications
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Lack of a detectable gene mutation does not exclude a diagnosis of hereditary XLID

Gene Symbol	Gene Name	NM #	OMIM #	Condition	Prevalence/Incidence	Mutation Detection Frequency By Test Method
ABCD1	ATP-binding cassette, sub-family D (ALD), member 1	000033	300371	• Adrenoleukodystrophy • Adrenomyeloneuropathy, adult	1/20,000-50,000	~93% by sequencing; ~6% by deletion/duplication analysis
ACSL4 (FACL4)	Acyl-CoA synthetase long-chain family member 4	004458	300157	• XLID, 63	Rare	Majority reported* are sequence variants; large deletions reported
AFF2 (FRAXE)	AF4/FMR2 family, member 2	002025	300806	• XLID, FRAXE type	1-9/million	~50% reported* are sequence variants; large deletions/ duplications reported
AP1S2	Adaptor-related protein complex 1, sigma 2 subunit	003916	300629	• XLID, Fried type	Rare	Majority reported* are sequence variants; large deletions reported
ARHGEF9	Cdc42 guanine nucleotide exchange factor (GEF) 9	015185	300429	• Early infantile epileptic encephalopathy, 8	Rare	~50% reported* are sequence variants; large deletions reported
ARX	Aristaless related homeobox	139058	300382	• XLID, with or without seizures, ARX-related • Early infantile epileptic encephalopathy, 1 • X-linked lissencephaly, 2 • Partington XLID syndrome • Agenesis of corpus callosum with abnormal genitalia	Rare	~75% reported* are sequence variants; large deletions/ duplications reported
ATP7A	ATPase, Cu++ transporting, alpha polypeptide	000052	300011	• Menkes disease • Occipital horn syndrome-linked distal spinal muscular atrophy, 3	Incidence ~1/100,000 (Menkes disease)	~80% by sequencing; ~15% by deletion/duplication analysis
ATRX	Alpha thalassemia/ mental retardation syndrome, X-linked	000489	300032	• X-linked alpha-thalassemia/ID syndrome • XLID/hypotonic facies syndrome	Prevalence <1–9/100,000 live-born males	~95% by sequencing; <5% by deletion/duplication analysis
BCOR	BCL6 co-repressor	017745	300485	• Syndromic microphthalmia, 2	Rare	80% reported* are sequence variants; large deletions reported
BRWD3	Bromodomain and WD repeat domain containing 3	153252	300553	• XLID, 93	Rare	Only sequence variants reported*
CASK	Calcium/calmodulin-dependent serine protein kinase (MAGUK family)	003688	300172	• ID and microcephaly with pontine and cerebellar hypoplasia (MICPCH) • FG syndrome 4 • ID, with or without nystagmus	Unknown *CASK* mutations likely to account for <1% XLID	~50% by sequencing (MICPCH in females); ~50% by deletion/ duplication analysis (MICPCH in females)
CDKL5	Cyclin-dependent kinase-like 5	003159	300203	• Early infantile epileptic encephalopathy, 2 • Angelman-like syndrome	Unknown	~80% reported* are sequence variants; large deletions/ duplications reported
CUL4B	Cullin 4B	003588	300304	• XLID, with short stature, hypogonadism, and abnormal gait	Unknown	Majority reported* are sequence variants; large deletions reported

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DCX	Doublecortin	178153	300121	• X-linked subcortical laminal heterotopia • X-linked lissencephaly	~1/85,000 (Dutch study, 1991, for lissencephaly)	>95% by sequencing; large deletions/duplications reported*
DKC1	Dyskeratosis congenita 1, dyskerin	001363	300126	• X-linked dyskeratosis congenita • Hoyeraal-Hreidarsson syndrome	Rare	Majority reported* are sequence variants; large deletions also reported
DLG3	Discs, large homolog 3 (Drosophila)	021120	300189	• XLID, 90	Rare	75% reported* are sequence variants; large deletions/ duplications reported
DMD	Dystrophin	004006	300377	• Duchenne muscular dystrophy • Becker muscular dystrophy • Dilated cardiomyopathy, 3B	Incidence ~1/3,500 boys	Up to ~35% by sequencing; up to ~65% by deletion/ duplication analysis
FGD1	FYVE, RhoGEF and PH domain containing 1	004463	300546	• X-linked syndromic ID, 16 • Aarskog-Scott syndrome	Unknown; believed to be rare	Majority reported* are sequence variants; large deletions/ duplications reported
FLNA	Filamin A, alpha	001456	300017	• X-linked cardiac valvular dysplasia • Congenital short bowel syndrome • FG syndrome 2 • Frontometaphyseal dysplasia • Periventricular heterotopia • Periventricular heterotopia, ED variant • Neuronal intestinal pseudoobstruction • Melnick-Needles syndrome • Otopalatodigital syndrome, type I • Otopalatodigital syndrome, type II • Terminal osseous dysplasia	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported
FMR1	Fragile X mental retardation 1	002024	309550	• Fragile X syndrome • Fragile X tremor/ataxia syndrome • Premature ovarian failure 1	~16-25/100,000 males, fragile X syndrome	Vast majority of mutations are identified by CGG repeat analysis; <1% by sequencing and deletion/ duplication analysis
FTSJ1	FtsJ RNA methyltransferase homolog 1 (E. coli)	012080	300499	• XLID, 9	Rare	Large deletions detected among the few mutations reported*
GDI1	GDP dissociation inhibitor 1	001493	300104	• XLID, 41	Rare	Large deletions detected among few mutations reported*
GK	Glycerol kinase	000167	300474	• Glycerol kinase deficiency	Rare	Majority reported* are sequence variants; large deletions/ duplications reported
GPC3	Glypican 3	004484	300037	• Simpson-Golabi-Behmel syndrome, type 1	Unknown	~50% of reported* are large deletions
GRIA3	Glutamate receptor, ionotrophic, AMPA 3	000828	305915	• XLID, 94	Unknown	Only a few DNA variants reported*; >50% reported* as large deletions/duplications
HCCS	Holocytochrome c synthase	005333	3000560	• Syndromic microphthalmia, 7	Rare	Only a few DNA variants, including large deletions, reported*
HCFC1	Host cell factor C1 (VP16-accessory protein)	005334	300019	• XLID, 3 (methylmalonic acidemia and homocysteinemia, cblX type)	Rare	Only a few DNA variants reported*; no large deletions/ duplications reported
HPRT1	Hypoxanthine phosphoribosyl-transferase 1	000194	308000	• Lesch-Nyhan syndrome • HPRT-related gout	~1/380,000 (Lesch-Nyhan syndrome)	>90-95% by sequencing; large deletions/duplications reported*
HSD17B10	Hydroxysteroid (17-beta) dehydrogenase 10	004493	300256	• X-linked syndromic ID, 10 • X-linked 17/31, microduplication • 17-beta-hydroxysteroid dehydrogenase X deficiency	Unknown	Only a few DNA variants reported*; no large deletions/ duplications reported

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HUWE1	HECT, UBA, and WWE domain containing 1, E3 ubiquitin protein ligase	031407	300697	• X-linked syndromic ID, Turner type	Unknown	Only a few DNA variants reported*; 75% are large duplications*
IDS	Iduronate 2-sulphatase	000202	300823	• Mucopolysaccharidosis II	1/100,000-170,000 male births	Up to ~91% by sequencing; ~9% by deletion/duplication analysis
IL1RAPL1	Interleukin 1 receptor accessory protein-like 1	014271	300206	• XLID, 21/34	Unknown	Only a few sequence variants reported*; majority reported are large deletions/duplications
IQSEC2	IQ motif and Sec7 domain 2	001111125	300522	• XLID, 1	Rare	Only a few sequence variants reported*; no large deletions/duplications reported
KDM5C	Lysine (K)-specific demethylase 5C	004187	314690	• X-linked syndromic ID, Claes-Jensen type	Unknown	Only sequence variants reported*; no large deletions/ duplications reported
L1CAM	L1 cell adhesion molecule	000425	308840	• Partial agenesis of corpus callosum • CRASH syndrome • MASA syndrome • Hydrocephalus due to aqueductal stenosis • Hydrocephalus with congenital idiopathic intestinal pseudoobstruction • Hydrocephalus with Hirschsprung disease	1/30,000 (hydrocephalus due to aqueductal stenosis)	Majority reported* are sequence variants; large deletions/ duplications reported
LAMP2	Lysosomal-associated membrane protein 2	002294	309060	• Danon disease/glycogen storage disease type IIb	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported
MBTPS2	Membrane-bound transcription factor peptidase, site 2	015884	300294	• IFAP syndrome with or without BRESHECK syndrome • X-linked keratosis follicularis spinulosa decalvans	Unknown	Only sequence variants reported*; large deletions/ duplications reported
MECP2	Methyl CpG binding protein 2 (Rett syndrome)	004992	300005	• Angelman syndrome • Severe neonatal encephalopathy • X-linked syndromic intellectual disability, Lubs type • X-linked syndromic ID, 13 • Rett syndrome • Rett syndrome, preserved speech variant	Prevalence 1/8,500 in females by age 15, Rett syndrome	~80% by sequencing (Rett syndrome); ~8% by deletion/ duplication analysis (Rett syndrome)
MED12	Mediator complex subunit 12	005120	300188	• Lujan-Fryns syndrome • X-linked Ohdo syndrome • Opitz-Kaveggia syndrome	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported
MID1	Midline 1 (Opitz/BBB syndrome)	000381	300552	• Opitz GBBB syndrome, type I	1/50,000-100,000	Majority reported* are sequence variants; large deletions/ duplications reported
NDP	Norrie disease (pseudoglioma)	000266	300658	• X-linked exudative vitreoretinopathy • Norrie disease	Unknown	Majority reported* are sequence variants; large deletions/duplications reported
NDUFA1	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa	004541	300078	• Mitochondrial complex I deficiency	Unknown	Only a few sequence variants reported*; no large deletions/ duplications reported
NHS	Nance-Horan syndrome (congenital cataracts and dental anomalies)	198270	300457	• Nance-Horan syndrome • X-linked cataract 40	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported

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NLGN4X	Neuroligin 4, X-linked	020742	300427	• XLID	Unknown	~50% reported*are sequence variants; ~50% are large deletions/duplications*
NSDHL	NAD(P)H dependent steroid dehydrogenase-like	015922	300275	• CHILD syndrome • CK syndrome	Rare	~90% by sequencing (CHILD syndrome); ~10% by deletion/ duplication analysis (CHILD syndrome)
OCRL	Oculocerebrorenal syndrome of Lowe	000276	300535	• Dent disease 2 • Lowe syndrome	estimated – a few/100,000-1/500,000	~95% by sequencing; ~5% by deletion/duplication analysis
OFD1	Oral-facial-digital syndrome 1	003611	300170	• Joubert syndrome 10 • Oral-facial-digital syndrome 1 (OFDS1) • Simpson-Golabi-Behmel syndrome, type 2	Estimated 1/50,000-250,000 live female births (OFDS1) Predominantly prenatally lethal in males (OFDS1)	~80% by sequencing (females); ~5% by deletion/duplication analysis (females)
OPHN1	Oligophrenin 1	002547	300127	• XLID, with cerebellar hypoplasia and distinctive facial appearance	Rare	~50% by sequencing; ~50% by deletion/duplication analysis
OTC	Ornithine carbamoyltransferase	000531	300461	• Ornithine transcarbamylase deficiency	Prevalence 1/40,000-80,000	~80% by sequencing; ~10% by deletion/duplication analysis
PAK3	p21 protein (Cdc42/Rac)-activated kinase 3	002578	300142	• XLID, 30/47	Rare	Only a few sequence variants reported*; no large deletions/ duplications reported
PCDH19	Protocadherin 19	001184880	300460	• Early epileptic encephalopathy, 9	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported
PDHA1	Pyruvate dehydrogenase (lipoamide) alpha 1	000284	300502	• X-linked Leigh syndrome • Pyruvate dehydrogenase E1-alpha deficiency	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported
PGK1	Phosphoglycerate kinase 1	000291	311800	• Phosphoglycerate kinase 1 deficiency	Unknown	No large deletions/duplications reported*
PHF6	PHD finger protein 6	032458	300414	• Borjeson-Forssman-Lehmann syndrome	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported
PHF8	PHD finger protein 8	015107	300560	• XLID syndrome, Siderius type	Unknown	Only a few sequence variants reported*; no large deletions/ duplications reported
PLP1	Proteolipid protein 1	000533	300401	• Pelizaeus-Merzbacher disease (PMD) • X-linked spastic paraplegia 2	~ 1/200,000-500,000	> 30% by deletion/duplication analysis
PORCN	Porcupine homologue (Drosophila)	203475	300651	• Focal dermal hypoplasia	Rare	~85% by sequencing; ~15% by deletion/duplication analysis
PQBP1	Polyglutamine binding protein 1	005710	300463	• Renpenning syndrome	Rare	Only a few sequence variants reported*; large deletions/ duplications reported
PRPS1	Phosphoribosyl pyrophosphate synthetase 1	002764	311850	• Arts syndrome • X-linked recessive Charcot-Marie-Tooth disease, 5 • X-linked deafness, 1 • PRPS-related gout • Phosphoribosylpyrophosphate synthetase superactivity	Rare	Only sequence variants reported*
PTCHD1	Patched domain containing 1	173495	300828	• Syndrome not characterized	Unknown	>50% reported* are large deletions*
RAB39B	RAB39B, member RAS oncogene family	171998	300774	• XLID, 72	Rare	Only a few sequence variants reported*; no large deletions/ duplications reported
RPS6KA3 (RSK2)	Ribosomal protein S6 kinase, 90 kDa, polypeptide 3	004586	300075	• Coffin-Lowry syndrome • XLID, 19	Incidence 1/50,000-1/100,000 (Coffin-Lowry syndrome)	Majority reported* are sequence variants; large deletions/ duplications reported

Gene Symbol	Gene Name	NM #	OMIM #	Condition	Prevalence/Incidence	Mutation Detection Frequency By Test Method
SLC16A2 (MCT8)	Solute carrier family 16, member 2 (thyroid hormone transporter)	006517	300095	• Allan-Herndon-Dudley syndrome	Unknown	Majority reported* are sequence variants; large deletions/ duplications reported
SLC6A8	Solute carrier family 6 (neurotransmitter transporter), member 8	005629	300036	• Cerebral creatine deficiency syndrome 1	SLC6A8 mutations likely to account for ~2% XLID	Majority reported* are sequence variants; large deletions/ duplications reported
SLC9A6	Solute carrier family 9, subfamily A (NHE6, cation proton antiporter 6), member 6	006359	300231	• X-linked syndromic ID, Christianson type	Unknown	Only a few DNA variants reported*, including large deletions
SMC1A	Structural maintenance of chromosomes 1A	006306	300040	• Cornelia de Lange syndrome 2	Unknown	Duplication reported* in an individual with developmental and neurobehavioral abnormalities
SMS	Spermine synthase	004595	300105	• XLID, Snyder-Robinson type	Rare	Only a few sequence variants reported*; no large deletions/duplications reported
SOX3	SRY (sex determining region Y)-box 3	005634	313430	• XLID, with isolated growth hormone deficiency • X-linked panhypopituitarism	Unknown	Only a few DNA variants reported*
SYN1	Synapsin I	133499	313440	• X-linked epilepsy with variable learning disabilities and behavior disorders	Unknown	Only a few sequence variants reported*; no large deletions/ duplications reported
SYP	Synaptophysin	003179	313475	• XLID, 96	Unknown	Only a few sequence variants reported*; no large deletions/ duplications reported
TIMM8A	Translocase of inner mitochondrial membrane 8 homolog A (yeast)	004085	300356	• Jensen syndrome • Mohr-Tranebjaerg syndrome • X-linked progressive deafness, 1	Unknown	Only a few DNA variants reported*, including large deletions
TSPAN7	Tetraspanin 7	004615	300096	• XLID, 58	Rare	Only a few DNA variants reported, including large duplications*
UBE2A	Ubiquitin-conjugating enzyme E2A	003336	312180	• X-linked syndromic ID, Nascimento type	Rare	Only a few DNA variants reported*; ~50% reported* as large deletions*
UPF3B	UPF3 regulator of nonsense transcripts homolog B (yeast)	080632	300298	• X-linked syndromic ID, 14	Rare	Only a few DNA variants reported*, including large deletions
ZDHHC9	Zinc finger, DHHC-type containing 9	016032	300646	• X-linked syndromic ID, Raymond type	Rare	Only a few DNA variants reported, including large deletions*
ZNF711	Zinc finger protein 711	021998	314990	• XLID, 97	Rare	No large deletions/duplications reported*
*Reported in Human Gene Mutation Database (HGMD)						