Autism/ID Panel

Panel Gene List: *ADNP, AHDC1, ANKRD11, ARID1A, ARID1B, ASXL1, ASXL3, ATRX, AUTS2, CACNA1A, CACNA1E, CASK, CDKL5, CHD2, CHD7, CHD8, CLCN4, CREBBP, CSNK2A1, CTCF, CTNNB1, DDX3X, DHCR7, DNMT3A, DYNC1H1, DYRK1A, EFTUD2, EHMT1, EP300, FOXG1, FOXP1, GATAD2B, GNAO1, GPC3, GRIA3, GRIN1, GRIN2B, HUWE1, IL1RAPL1, IQSEC2, ITPR1, KAT6A, KAT6B, KCNB1, KDM5C, KDM6A, KIF1A, KMT2A, KMT2D, MAP2K1, MBD5, MECP2, MED12, MED13L, MEF2C, MTOR, MYT1L, NALCN, NEXMIF, NF1, NR2F1, NRXN1, NSD1, OPHN1, PACS1, PLA2G6, POGZ, PPP2R5D, PQBP1, PTCHD1, PTEN, PTPN11, PURA, RAI1, RIT1, RPS6KA3, SATB2, SCN1A, SCN2A, SCN8A, SETBP1, SETD5, SHANK3, SLC6A1, SLC6A8, SLC9A6, SMARCA2, SMARCA4, SMC1A, SOS1, STXBP1, SYNGAP1, TBL1XR1, TCF4, TRIO, TSC1, TSC2, UBE3A, USP9X, WAC, WDR45, ZC4H2, ZEB2*

Clinical Features:

Autism spectrum disorders and intellectual disability (intellectual developmental disorder) are clinically and genetically heterogeneous. Approximately 2.8% of children have an autism spectrum disorder (ASD), characterized by deficits in social interaction, impaired communication, repetitive behavior, and restricted interests and activities beginning in the first few years of life.[1] Autism spectrum disorder includes several clinically defined conditions, of which pervasive developmental disorder-not otherwise specified (PDD-NOS), Asperger syndrome, and autistic disorder ('classic' autism) are the most common. Approximately 1-3% of individuals have intellectual disability (ID), which is typically associated with an IQ of 70 or below and deficits in adaptive functioning, communication, and/or social skills with an onset before 18 years of age.[2] Autism spectrum disorder and ID are often co-morbid disorders; over half of children with autism also have intellectual disability. Young children may also be diagnosed with global development delay (DD), which is defined as significant delay in two or more developmental domains (gross or fine motor, speech/language, cognitive, social/personal, etc.) in children younger than five years. The prevalence is estimated to be 1-3%, similar to that of ID.[3]

Inheritance Pattern/Genetics:

The etiology of ASD is complex, including multiple genetic, epigenetic, and environmental factors. Approximately 20-40% of individuals with ASD and at least 20-30% of individuals with ID have an identifiable genetic cause, often a chromosomal abnormality.[4-7] The cause of ASD and/or ID can be difficult to discern as there are many genes known to cause these neurodevelopmental disorders. It has been suggested that, if a specific underlying genetic syndrome is not suspected (e.g. Fragile X syndrome, Rett syndrome), chromosomal microarray (CMA, also known as array CGH) be considered as a first-tier test for individuals with an ASD or ID.[4-5] In some cases, confirmation of the molecular genetic cause of ASD and/or ID may have implications for treatment, management, and eligibility for needed services.[8]

The Autism/ID Panel at GeneDx includes sequencing and concurrent deletion/duplication analysis of approximately 100 Mendelian genes with relatively high diagnostic yields for individuals with ASD and/or ID. Many of these genes are well-characterized genes associated with syndromic or non-syndromic ASD and/or ID. The complete list of genes and associated disorders are listed in the table below.

Clinical Sensitivity:

GeneDx has multiple genetic testing options for patients with ASD and/or ID. Many patients with autism spectrum disorder experience co-occurring conditions for which guidelines recommend exome sequencing as a first-line test. The American College of Medical Genetics and Genomics recommends exome or genome sequencing as a first-line test for individuals with developmental delay, intellectual disability, and/or congenital anomalies.[9] Additionally, the National Society of Genetic Counselors recommends exome or genome sequencing as a first-line test for all individuals with unexplained epilepsy, and this guideline is endorsed by the American Epilepsy Society.[128] For more information about ordering exome sequencing, see test code 561a *XomeDx*® Trio, https://providers/genedx.com/tests/details/xomedx-trio-882. The Autism/ID Panel targets a subset of genes with a relatively high diagnostic yield for patients with ASD or ID. The genes on the Autism/ID Panel account for >70% of the first 322 positive cases that were identified using the larger Autism/ID *Xpanded*® test. The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included on the panel also depends on the clinical phenotype. Additional information about these genes are provided in the table below.

Test Methods:

Genomic DNA is extracted directly from the submitted specimen or, if applicable, from cultured fibroblasts. The DNA is enriched for the complete coding regions and splice junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data is analyzed to identify sequence variants and most deletions and duplications involving coding exons at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Available evidence for variant classification may change over time and reported variant(s) may be reclassified according to the ACMG/AMP Standards and Guidelines (PMID: 25741868), which may lead to issuing a revised report.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For the *FOXG1*, *PACS1*, and *SLC6A8* genes, sequencing but not deletion/duplication analysis is performed. For the *AHDC1, FOXP1, GRIN1, HUWE1, KDM6A, MBD5, MYT1L, NF1, NR2F1, SHANK3, TCF4, and TSC2* genes, only whole gene deletions or duplications may be detected; and *TSC2* gene, exon level coverage for exons 2-28 and 30-37 only. For *PTEN*, approximately nucleotides c.-700 through c.-1300 in the promoter region are also captured.

Due to inconsistencies between RefSeq and hg19 for the *SHANK3* gene, codons corresponding to amino acids 436-449 of NM_033517 are not analyzed.
The Autism/ID panel does not address genetic disorders due to repeat expansion/contraction, abnormal DNA methylation, and other mechanisms. For example, abnormal methylation of *UBE3A* causing Angelman syndrome would not be detectable by this Autism/ID panel.

Gene	Disorder(s)	Inheritance	Additional Comments
ADNP	Helsmoortel-van der Aa syndrome	AD	Estimated to account for <1% of ASD[10]
AHDC1	Xia-Gibbs syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[11]
ANKRD11	KBG syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[12]
ARID1A	Coffin-Siris syndrome (CSS)	AD	Estimated to account for 5% of CSS[13]
ARID1B	CSS; non-syndromic ID	AD	Estimated to account for 37% of CSS[13]
ASXL1	Bohring-Opitz syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[14]
ASXL3	Bainbridge-Ropers syndrome (BRS)/Bohring-Opitz like syndrome	AD	Diagnostic yield for ASD/ID is low or unknown for BRS[15]
ATRX	Alpha-thalassemia X-linked ID (ATR-X) syndrome	XL	~25% diagnostic yield in affected individuals with findings suggestive of ATR-X[16]
AUTS2	ASD and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown[17]
CACNA1A	Episodic ataxia type 2; Familial hemiplegic migraine; Spinocerebellar ataxia type 6; Early-onset epileptic encephalopathy (EOEE)	AD	Diagnostic yield for ASD/ID is low or unknown[18]
CACNA1E	Developmental and epileptic encephalopathy 69	AD	Rare[31]
CASK	ID and microcephaly with pontine and cerebellar hypoplasia; ID; FG syndrome	XL	Estimated to account for <1% of ID[19]
CDKL5	Atypical Rett syndrome; XL infantile spasms; EOEE; ID and/or ASD	XL	2-8% females atypical Rett syndrome[20-21]
CHD2	Epilepsy, ASD, and/or ID	AD	Estimated to account for 1% of epileptic encephalopathy[22]
CHD7	CHARGE syndrome	AD	Clinical sensitivity >90% in individuals meeting CHARGE criteria[23]
CHD8	ASD and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown[24]
CLCN4	ID	XL	Diagnostic yield for ID is low or unknown[25]

Gene	Disorder(s)	Inheritance	Additional Comments
CREBBP	Rubinstein-Taybi syndrome (RTS)	AD	Estimated to account for 50-60% RTS disorders[27]
CSNK2A1	ID	AD	Diagnostic yield for ID is low or unknown[28]
CTCF	ID	AD	Diagnostic yield for ID is low or unknown[29]
CTNNB1	ID	AD	Diagnostic yield for ID is low or unknown[30]
DDX3X	ID	XL	Estimated to account for 1-3% of unexplained ID in females[32]
DHCR7	Smith-Lemli-Opitz syndrome (SLOS)	AR	Clinical sensitivity >96% in individuals with suspected SLOS[33]
DNMT3A	Tatton-Brown-Rahman syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[34]
DYNC1H1	Severe ID with cortical brain malformations; Charcot-Marie-Tooth disease type 20	AD	~5% of cortical brain malformations[35]
DYRK1A	ID	AD	Accounts for up to 0.5% of individuals with ID and/or autism[36]
EFTUD2	Mandibulofacial dysostosis with microcephaly (MFDM)	AD	Diagnostic yield for ASD/ID is low or unknown[37]
EHMT1	Kleefstra syndrome	AD	Microdeletion of 9q34.3, accounts for ~75% of Kleefstra syndrome[38]
EP300	Rubinstein-Taybi syndrome-2	AD	Estimated to account for 3-8% RTS disorders[27]
FOXG1	Congenital variant of Rett syndrome	AD	1% of Rett syndrome overall[39]; 25% of congenital variant of Rett[40]
FOXP1	FOXP1 syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[41]
GATAD2B	ID	AD	Diagnostic yield for ID is low or unknown[42]
GNAO1	Early infantile epileptic encephalopathy (EIEE); Movement disorder	AD	Diagnostic yield for ASD/ID is low or unknown[43]
GPC3	Simpson-Golabi-Behmel syndrome type 1 (SGBS1)	XL	Clinical sensitivity of 37-70% in males with suspected SGBS1[44]
GRIA3	ID	XL	Diagnostic yield for ID is low or unknown[45]
GRIN1	Encephalopathy	AD	Diagnostic yield for ASD/ID is low or unknown[46]
GRIN2B	EIEE; ASD and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown[47]

Gene	Disorder(s)	Inheritance	Additional Comments
HUWE1	ID	XL	Diagnostic yield for ID is low or unknown[48]
IL1RAPL1	ID	XL	Diagnostic yield for ID is low or unknown[49]
IQSEC2	ID; Epileptic encephalopathy	XL	Diagnostic yield for ASD/ID is low or unknown[50]
ITPR1	Spinocerebellar ataxia (SCA) 15 and SCA29; Gillespie syndrome	AD/AR	1-3% for familial ataxia[51]; rare for Gillespie[52]
KAT6A	ID	AD	Diagnostic yield for ID is low or unknown[53]
KAT6B	Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome; Genitopatellar syndrome	AD	~75% of individuals with SBBYSS have a pathogenic variant in KAT6B[54]; 83-100% of individuals with GPS have a pathogenic variant in KAT6B[55-56]
KCNB1	Epilepsy disorders	AD	Diagnostic yield for ID is low or unknown[57]
KDM5C	ID	XL	Diagnostic yield for ID is low or unknown[58]
KDM6A	Kabuki syndrome type 2	XL	Diagnostic yield for ASD/ID is low or unknown[59]
KIF1A	ID; Neuropathy; Hereditary spastic paraplegia 30	AD/AR	Diagnostic yield for ASD/ID is low or unknown[61]
KMT2A	Wiedemann-Steiner syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[62]
KMT2D	Kabuki syndrome (KS)	AD	Pathogenic variants identified in 50-75% of individuals with a clinical diagnosis of KS[59]
MAP2K1	Rasopathy	AD	Estimated to account for <2% of Noonan syndrome[63]
MBD5	MBD5 haploinsufficiency	AD	Estimated to account for ~1% of ASD[64]
MECP2	Rett syndrome	XL	Estimated to account for 5% of females with ASD[5;65]
MED12	ID; FG syndrome type 1; Lujan syndrome; Ohdo syndrome	XL	Diagnostic yield for ASD/ID is low or unknown[66]
MED13L	ID	AD	Diagnostic yield for ID is low or unknown[67]
MEF2C	MEF2C haploinsufficiency	AD	~2% of epileptic encephalopathy[68]
MTOR	Epilepsy, ASD, and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown[69]
MYT1L	ID	AD	Diagnostic yield for ID is low or unknown[70]

Gene	Disorder(s)	Inheritance	Additional Comments
NALCN	Congenital contractures of the limbs and face with hypotonia and DD syndrome; Infantile hypotonia with psychomotor retardation and characteristic facies	AD/AR	Diagnostic yield for ASD/ID is low or unknown[71]
NEXMIF (KIAA2022)	ID	XL	Diagnostic yield for ID is low or unknown[60]
NF1	Neurofibromatosis 1	AD	Features of ASD occur in up to 30% of children with NF1[72] ;pathogenic variant identified in over 90% of individuals who fulfill diagnostic criteria for NF1[73]
NR2F1	Bosch-Boonstra-Schaaf optic atrophy syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[74]
NRXN1	PHS; neuropsychiatric disorders	AD/AR	Rare in PHS[26]
NSD1	Sotos syndrome	AD	Clinical sensitivity >40% in individuals with suspected Sotos syndrome[75]
OPHN1	ID	XL	12% in XL ID with cerebellar hypoplasia; ~1% in XL ID[76]
PACS1	Schuurs-Hoeijmakers syndrome	AD	This test only targets amino acid residue R203 (NM_018026), which is the location of all published pathogenic variants[77]
PLA2G6	Neurodegeneration with brain iron accumulation types 2A and 2B (NBIA)	AR	Accounts for ~20% of NBIA[78]
POGZ	ASD and/or ID	AD	Estimated to account for <1% of ASD and/or ID[79]
PPP2R5D	ID	AD	Diagnostic yield for ID is low or unknown[80]
PQBP1	Renpenning syndrome	XL	~1% of XL ID[81]
PTCHD1	ASD and/or ID	XL	Diagnostic yield for ASD/ID is low or unknown[82]
PTEN	PTEN hamartoma tumor syndrome	AD	Estimated to account for 3-20% of individuals with ASD and macrocephaly[5;83]
PTPN11	Rasopathy	AD	Estimated to account for 50% of Noonan syndrome[63]
PURA	PURA haploinsufficiency	AD	Estimated to account for <1% of ID[84]
RAI1	Smith-Magenis syndrome (SMS)	AD	~80% of SMS patients have a recurrent deletion encompassing RAI1. Pathogenic RAI1 sequencing variants identified in ~10% of affected individuals[85]

Gene	Disorder(s)	Inheritance	Additional Comments
RIT1	Rasopathy	AD	Estimated to account for 5% of Noonan syndrome[63]
RPS6KA3	Coffin-Lowry syndrome (CLS)	XL	~25-40% of individuals with suspected clinical diagnosis of CLS have an identifiable pathogenic variant[86]
SATB2	SATB2-associated syndrome	AD	Estimated to account for <1% of ID/DD[87]; Translocations that disrupt the SATB2 gene account for ~8% of individuals and may not be detected by the assay
SCN1A	SCN1A-related seizure disorder	AD	70-80% Dravet syndrome[88]; 20-24% early-onset cryptic epilepsy[89-90]; Association with autism[91-92]
SCN2A	SCN2A-related disorder	AD	1-2% of EIEE[93-94]; Association with autism or ID[91;95-96]
SCN8A	SCN8A-related disorder	AD	Frequency of pathogenic variants was ~1% in individuals with EIEE.[97-98] SUDEP reported in ~ 10% of cases[98]; autistic features noted in some affected individuals[97]
SETBP1	Intellectual disability 29; Schinzel-Giedion midface retraction syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[99-100]
SETD5	SETD5 haploinsufficiency	AD	Loss of function variants cause ID and core phenotype of 3p25.3 microdeletion syndrome[101-102]
SHANK3	Phelan-McDermid syndrome	AD	Also known as 22q13.3 deletion syndrome[103] ; Associated with isolated ID, ASD and seizures[104-105]
SLC6A1	Myoclonic-atonic epilepsy (Doose syndrome)	AD	Diagnostic yield for ASD/ID is low or unknown[106-107]
SLC6A8	Creatine transporter deficiency	XL	Diagnostic yield in 2% of males with epilepsy and ID[108]; diagnostic yield of 65% of males with biochemical creatine deficiency[109]
SLC9A6	Angelman-like (Christianson) syndrome	XL	Accounts for ~6% Angelman-like syndrome[110]; estimated to account for 1% of XL ID[111-112]
SMARCA2	Nicolaides-Baraitser syndrome; CSS	AD	Estimated to account for 2% of CSS[13]
SMARCA4	CSS	AD	Estimated to account for 7% of CSS[13]
SMC1A	Cornelia de Lange syndrome (CdLS)	XL	Estimated to account for 5% of CdLS113(Deardorff et al., 2016)

Gene	Disorder(s)	Inheritance	Additional Comments
SOS1	Rasopathy	AD	Estimated to account for 10-13% of Noonan syndrome[63]
STXBP1	Encephalopathy with epilepsy	AD	Pathogenic variants associated with ~35% Ohtahara syndrome[88;114]
SYNGAP1	ID	AD	Diagnostic yield for ID is low or unknown[115-116]
TBL1XR1	ASD and/or ID; Pierpont syndrome	AD	Diagnostic yield for ASD/ID is low or unknown[117]
TCF4	Pitt-Hopkins syndrome (PHS)	AD	Accounts for ~36% PHS[118-119]; 2% of Angelman syndrome[118]
TRIO	ASD and/or ID	AD	Estimated to account for <1% of ASD and/or ID[120]
TSC1	Tuberous sclerosis complex (TSC)	AD	Estimated to account for 30% of TSC[121]
TSC2	TSC	AD	Estimated to account for 70% of TSC[121]
UBE3A	Angelman syndrome (AS)	AD-imprinted	68% maternally inherited 15q11.2 deletion and 11% UBE3A pathogenic sequencing variants associated with AS[122]
USP9X	ID	XL	Diagnostic yield for ID is low or unknown[112;123]
WAC	ID	AD	Estimated to account for <1% of ID[124]
WDR45	Neurodegeneration with brain iron accumulation (NIBA)	XL	Estimated to account for 1-2% of NIBA[125]
ZC4H2	ID	XL	Diagnostic yield for ID is low or unknown[126]
ZEB2	Mowat-Wilson syndrome (MWS)	AD	Accounts for ~95% of MWS cases[127]

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