Autism/ID Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing

Panel Gene List: ADNP, AHDC1, ANKRD11, ARID1A, ARID1B, ASXL1, ASXL3, ATRX, AUTS2, CACNA1A, CASK, CDKL5, CHD2, CHD7, CHD8, CLCN4, CNTNAP2, CREBBP, CSNK2A1, CTCF, CTNNB1, CTNND2, 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, KIAA2022, KIF1A, KMT2A, KMT2D, MAP2K1, MBD5, MECP2, MED12, MED13L, MEF2C, MTOR, MYT1L, NALCN, NF1, NR2F1, NRXN1, NSD1, OPHN1, PACS1 (R203 residue only), 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 1-1.5% 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 (CDC, 2014). 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 (Mefford et al., 2012). 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 (Moeschler et al., 2014)

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 (Miller et al., 2010; Schaefer et al., 2013; Ropers 2010; Retterer et al., 2015). 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 (Miller et al., 2010; Schaefer et al., 2013). 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 (Lopez-Rangel et al., 2008).

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. This is a panel targeting a subset of genes with a relatively high diagnostic yield for patients with ASD and/or ID. In contrast, another testing option, the Autism/ID Xpanded test, evaluates over 2,300 genes associated with autism and/or ID (see www.genedx.com/test-catalog/available-tests/autismid-xpanded-panel/ for more information). 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 tests. 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:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). For the PTEN gene, approximately nucleotides c.-700 through c.-1300 in the promoter region are 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 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 are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reported clinically significant variants are confirmed by an appropriate orthogonal method. 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.

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. This test may not 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. The KCNB1, NF1, NR2F1 and SHANK3 genes have gene level resolution; exon level events may not be reported; deletions/duplications involving the 3' end of the TSC2 gene (exons 36-42) may not be identified.

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 (Van Dijck et al., 2016)
AHDC1	Xia-Gibbs syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Yang et al., 2015)
ANKRD11	KBG syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Low et al., 2016)
ARID1A	Coffin-Siris syndrome (CSS)	AD	Estimated to account for 5% of CSS (Schrier Vergano et al., 2016)
ARID1B	CSS; non-syndromic ID	AD	Estimated to account for 37% of CSS (Schrier Vergano et al., 2016)
ASXL1	Bohring-Opitz syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Hoischen et al., 2011)
ASXL3	Bainbridge-Ropers syndrome (BRS)/Bohring-Opitz like syndrome	AD	Diagnostic yield for ASD/ID is low or unknown for BRS (Bainbridge et al., 2013)
ATRX	Alpha-thalassemia X-linked ID (ATR-X) syndrome	XL	~25% diagnostic yield in affected individuals with findings suggestive of ATR-X (Badens et al, 2006)
AUTS2	ASD and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown (Beunders et al., 2016)
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 (Damaj et al., 2015)
CASK	ID and microcephaly with pontine and cerebellar hypoplasia; ID; FG syndrome	XL	Estimated to account for <1% of ID (Moog et al., 2013)

Gene	Disorder(s)	Inheritance	Additional Comments
CDKL5	Atypical Rett syndrome; XL infantile spasms; EOEE; ID and/or ASD	XL	2-8% females atypical Rett syndrome (Tao et al., 2004; Rosas-Vargas et al., 2008)
CHD2	Epilepsy, ASD, and/or ID	AD	Estimated to account for 1% of epileptic encephalopathy (Carvill et al., 2015)
CHD7	CHARGE syndrome	AD	Clinical sensitivity >90% in individuals meeting CHARGE criteria (Lalani et al., 2012)
CHD8	ASD and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown (Bernier et al., 2014)
CLCN4	ID	XL	Diagnostic yield for ID is low or unknown (Palmer et al., 2016)
CNTNAP2	Pitt-Hopkins-like syndrome (PHS); neuropsychiatric disorders	AD/AR	Diagnostic yield for ASD/ID is low or unknown (Zweier et al., 2009)
CREBBP	Rubinstein-Taybi syndrome (RTS)	AD	Estimated to account for 50-60% RTS disorders (Stevens, 2014)
CSNK2A1	ID	AD	Diagnostic yield for ID is low or unknown (Okur et al., 2016)
CTCF	ID	AD	Diagnostic yield for ID is low or unknown (Gregor et al., 2013)
CTNNB1	ID	AD	Diagnostic yield for ID is low or unknown (Kuechler et al., 2014)
CTNND2	ASD and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown (Turner et al., 2015)
DDX3X	ID	XL	Estimated to account for 1-3% of unexplained ID in females (Snijders et al., 2015)
DHCR7	Smith-Lemli-Opitz syndrome (SLOS)	AR	Clinical sensitivity >96% in individuals with suspected SLOS (Nowaczyk et al., 2013)
DNMT3A	Tatton-Brown-Rahman syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Tatton-Brown et al., 2014)

Gene	Disorder(s)	Inheritance	Additional Comments
DYNC1H1	Severe ID with cortical brain malformations; Charcot-Marie-Tooth disease type 2O	AD	~5% of cortical brain malformations (Poirier et al., 2013)
DYRK1A	ID	AD	Accounts for up to 0.5% of individuals with ID and/or autism (van Bon et al., 2015)
EFTUD2	Mandibulofacial dysostosis with microcephaly (MFDM)	AD	Diagnostic yield for ASD/ID is low or unknown (Lines et al., 2014)
EHMT1	Kleefstra syndrome	AD	Microdeletion of 9q34.3, accounts for ~75% of Kleefstra syndrome (Kleefstra et al., 2015)
EP300	Rubinstein-Taybi syndrome-2	AD	Estimated to account for 3-8% RTS disorders (Stevens, 2014)
FOXG1[a]	Congenital variant of Rett syndrome	AD	1% of Rett syndrome overall (Bahl-Buisson et al., 2010); 25% of congenital variant of Rett (Mencarelli et al., 2010)
FOXP1	FOXP1 syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Hamdan et al., 2010)
GATAD2B	ID	AD	Diagnostic yield for ID is low or unknown (Willemsen et al., 2013)
GNAO1	Early infantile epileptic encephalopathy (EIEE); Movement disorder	AD	Diagnostic yield for ASD/ID is low or unknown (Saitsu et al., 2015)
GPC3	Simpson-Golabi-Behmel syndrome type 1 (SGBS1)	XL	Clinical sensitivity of 37-70% in males with suspected SGBS1 (Golabi et al., 2011)
GRIA3	ID	XL	Diagnostic yield for ID is low or unknown (Wu et al., 2007)
GRIN1	Encephalopathy	AD	Diagnostic yield for ASD/ID is low or unknown (Lemke et al., 2016)
GRIN2B	EIEE; ASD and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown (Endele et al., 2010)

Gene	Disorder(s)	Inheritance	Additional Comments
HUWE1	ID	XL	Diagnostic yield for ID is low or unknown (Friez et al., 2016)
IL1RAPL1	ID	XL	Diagnostic yield for ID is low or unknown (Piton et al., 2008)
IQSEC2	ID; Epileptic encephalopathy	XL	Diagnostic yield for ASD/ID is low or unknown (Shoubridge et al., 2010)
ITPR1	Spinocerebellar ataxia (SCA) 15 and SCA29; Gillespie syndrome	AD/AR	1-3% for familial ataxia (Storey 2014); rare for Gillespie (Gerber et al., 2016)
KAT6A	ID	AD	Diagnostic yield for ID is low or unknown (Millan et al., 2016)
KAT6B	Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome; Genitopatellar syndrome	AD	~75% of individuals with SBBYSS have a pathogenic variant in KAT6B (Clayton-Smith et al., 2011); 83-100% of individuals with GPS have a pathogenic variant in KAT6B (Simpson et al., 2012; Campeau et al., 2012)
KCNB1[b]	Epilepsy disorders	AD	Diagnostic yield for ID is low or unknown (de Kovel et al., 2017)
KDM5C	ID	XL	Diagnostic yield for ID is low or unknown (Goncalves et al., 2014)
KDM6A	Kabuki syndrome type 2	XL	Diagnostic yield for ASD/ID is low or unknown (Adam et al., 2013)
KIAA2022	ID	XL	Diagnostic yield for ID is low or unknown (Van Maldergem et al., 2013)
KIF1A	ID; Neuropathy; Hereditary spastic paraplegia 30	AD/AR	Diagnostic yield for ASD/ID is low or unknown (Esmaeeli et al., 2015)
KMT2A	Wiedemann-Steiner syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Jones et al., 2012)
KMT2D	Kabuki syndrome (KS)	AD	Pathogenic variants identified in 50-75% of individuals with a clinical diagnosis of KS (Adam et al., 2013)

Gene	Disorder(s)	Inheritance	Additional Comments
MAP2K1	Rasopathy	AD	Estimated to account for <2% of Noonan syndrome (Allanson & Roberts, 2001)
MBD5	MBD5 haploinsufficiency	AD	Estimated to account for ~1% of ASD (Mullegama et al., 2016)
MECP2	Rett syndrome	XL	Estimated to account for 5% of females with ASD (Schaefer et al., 2013; Christodoulou & Ho, 2012)
MED12	ID; FG syndrome type 1; Lujan syndrome; Ohdo syndrome	XL	Diagnostic yield for ASD/ID is low or unknown (Lyons 2016)
MED13L	ID	AD	Diagnostic yield for ID is low or unknown (Asadollahi et al., 2013)
MEF2C	MEF2C haploinsufficiency	AD	~2% of epileptic encephalopathy (Bienvenu et al., 2013)
MTOR	Epilepsy, ASD, and/or ID	AD	Diagnostic yield for ASD/ID is low or unknown (Lee et al., 2012)
MYT1L	ID	AD	Diagnostic yield for ID is low or unknown (De Rocker et al., 2015)
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 (Chong et al., 2015)
NF1[b]	Neurofibromatosis 1	AD	Features of ASD occur in up to 30% of children with NF1 (Garg et al., 2013). Pathogenic variant identified in over 90% of individuals who fulfill diagnostic criteria for NF1 (Friedman et a., 2014)
NR2F1[b]	Bosch-Boonstra-Schaaf optic atrophy syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Chen et al., 2016)
NRXN1	PHS; neuropsychiatric disorders	AD/AR	Rare in PHS (Zweier et al., 2009)

Gene	Disorder(s)	Inheritance	Additional Comments
NSD1	Sotos syndrome	AD	Clinical sensitivity >40% in individuals with suspected Sotos syndrome (Tatton-Brown et al., 2015)
OPHN1	ID	XL	12% in XL ID with cerebellar hypoplasia; ~1% in XL ID (Zanni et al., 2005)
PACS1[a]	Schuurs-Hoeijmakers syndrome	AD	This test only targets amino acid residue R203 (NM_018026), which is the location of all published pathogenic variants (Schuurs-Hoeijmakers et al., 2016)
PLA2G6	Neurodegeneration with brain iron accumulation types 2A and 2B (NBIA)	AR	Accounts for ~20% of NBIA (Gregory et al., 2017)
POGZ	ASD and/or ID	AD	Estimated to account for <1% of ASD and/or ID (Stessman et al., 2016)
PPP2R5D	ID	AD	Diagnostic yield for ID is low or unknown (Shang et al., 2016)
PQBP1	Renpenning syndrome	XL	~1% of XL ID (Jensen et al., 2011)
PTCHD1	ASD and/or ID	XL	Diagnostic yield for ASD/ID is low or unknown (Chaudhry et al., 2015)
PTEN	PTEN hamartoma tumor syndrome	AD	Estimated to account for 3-20% of individuals with ASD and macrocephaly (Schaefer et al., 2013, Eng 2016)
PTPN11	Rasopathy	AD	Estimated to account for 50% of Noonan syndrome (Allanson et al., 2016)
PURA	PURA haploinsufficiency	AD	Estimated to account for <1% of ID (Reijnders et al., 2017)
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 (Falco et al., 2017)
RIT1	Rasopathy	AD	Estimated to account for 5% of Noonan syndrome (Allanson et al., 2016)

Gene	Disorder(s)	Inheritance	Additional Comments
RPS6KA3	Coffin-Lowry syndrome (CLS)	XL	~25-40% of individuals with suspected clinical diagnosis of CLS have an identifiable pathogenic variant (Rogers & Abidi, 2018)
SATB2[c]	SATB2-associated syndrome	AD	Estimated to account for <1% of ID/DD (Zarate et al., 2017); 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 (Ottman et al., 2010); 20-24% early-onset cryptic epilepsy (Zucca et al., 2008; Harkin et al.., 2007); Association with autism (Weiss et al., 2003; O'Roak et al., 2011; Wang et al., 2016)
SCN2A	SCN2A-related disorder	AD	1-2% of EIEE (Kamiya et al., 2004; Ogiwara et al., 2009); Association with autism or ID (Weiss et al., 2003; Sanders et al., 2012; Gilissen et al., 2014)
SCN8A	SCN8A-related disorder	AD	Frequency of pathogenic variants was ~1% in individuals with EIEE (Larsen et al., 2015; Hammer et al., 2016). SUDEP reported in ~ 10% of cases (Hammer et al., 2016); autistic features noted in some affected individuals (Larsen et al., 2015)
SETBP1	Intellectual disability 29; Schinzel-Giedion midface retraction syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (Coe et al., 2014; Hoischen et al., 2011)
SETD5	SETD5 haploinsufficiency	AD	Loss of function variants cause ID and core phenotype of 3p25.3 microdeletion syndrome (Grozeva et al., 2014; Kuechler et al., 2015)
SHANK3[b]	Phelan-McDermid syndrome	AD	Also known as 22q13.3 deletion syndrome (Phelan et al., 2011); Associated with isolated ID, ASD and seizures (Cochoy et al., 2015;Holder et al., 2016)

Gene	Disorder(s)	Inheritance	Additional Comments
SLC6A1	Myoclonic-atonic epilepsy (Doose syndrome)	AD	Diagnostic yield for ASD/ID is low or unknown (Carvill et al., 2015; Johannesen et al., 2018
SLC6A8[a]	Creatine transporter deficiency	XL	Diagnostic yield in 2% of males with epilepsy and ID (Mercimek-Mahmutoglu et al., 2009); diagnostic yield of 65% of males with biochemical creatine deficiency (Comeaux et al., 2013)
SLC9A6	Angelman-like (Christianson) syndrome	XL	Accounts for ~6% Angelman-like syndrome (Gillfillan et al., 2008); estimated to account for 1% of XL ID (Schroer et al., 2010; Tarpey et al., 2009)
SMARCA2	Nicolaides-Baraitser syndrome; CSS	AD	Estimated to account for 2% of CSS (Schrier Vergano et al., 2016)
SMARCA4	CSS	AD	Estimated to account for 7% of CSS (Schrier Vergano et al., 2016)
SMC1A	Cornelia de Lange syndrome (CdLS)	XL	Estimated to account for 5% of CdLS (Deardorff et al., 2016)
SOS1	Rasopathy	AD	Estimated to account for 10-13% of Noonan syndrome (Allanson et al., 2016)
STXBP1	Encephalopathy with epilepsy	AD	Pathogenic variants associated with ~35% Ohtahara syndrome (Ottman et al., 2010; Stamberger et al. 2016)
SYNGAP1	ID	AD	Diagnostic yield for ID is low or unknown (Hamdan et al., 2009; Mignot et al., 2016)
TBL1XR1	ASD and/or ID; Pierpont syndrome	AD	Diagnostic yield for ASD/ID is low or unknown (O'Roak et al., 2012)
TCF4	Pitt-Hopkins syndrome (PHS)	AD	Accounts for ~36% PHS (de Pontual et al., 2009; Whalen et al., 2012); 2% of Angelman syndrome (de Pontual et al., 2009)

Gene	Disorder(s)	Inheritance	Additional Comments
TRIO	ASD and/or ID	AD	Estimated to account for <1% of ASD and/or ID (Varvagiannis et al., 2017)
TSC1	Tuberous sclerosis complex (TSC)	AD	Estimated to account for 30% of TSC (Northrup et al., 2015)
TSC2[d]	TSC	AD	Estimated to account for 70% of TSC (Northrup et al., 2015)
UBE3A	Angelman syndrome (AS)	AD-imprinted	68% maternally inherited 15q11.2 deletion and 11% UBE3A pathogenic sequencing variants associated with AS (Lossie et al., 2001)
USP9X	ID	XL	Diagnostic yield for ID is low or unknown (Tarpey et al., 2009; Reijnders et al., 2016)
WAC	ID	AD	Estimated to account for <1% of ID (Varvagiannis et al., 2017)
WDR45	Neurodegeneration with brain iron accumulation (NIBA)	XL	Estimated to account for 1-2% of NIBA (Gregory et al., 2014)
ZC4H2	ID	XL	Diagnostic yield for ID is low or unknown (Hirata et al., 2013)
ZEB2	Mowat-Wilson syndrome (MWS)	AD	Accounts for ~95% of MWS cases (Adam et al., 2013)

a Does not include deletion/duplication analysis
b Exon level deletion/duplication events may not be detected
c Translocations account for ~8% of pathogenic variants and may not be detected by this test
d Deletions/duplications including the 3' end of the TSC2 gene (exons 36-42) may not be detected

References:

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