

Autism/ID Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing, 104 Genes

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, 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 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, nucleotides c.-700 through c.-1300 in the promoter region are not captured and only the R203 residue is analyzed for the PACS1 gene. 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) |
| 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) |

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| 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) |
| DYNC1H1 | Severe ID with cortical brain malformations; Charcot-Marie-Tooth disease type 2O | AD | ~5% of cortical brain malformations (Poirier et al., 2013) |

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| 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) |
| 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) |

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| 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) |
| 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) |

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| 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 al., 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) |
| 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) |

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| 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 ^d | 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) |
| RPS6KA3 | Coffin-Lowry syndrome (CLS) | XL | ~25-40% of individuals with suspected clinical diagnosis of CLS have an identifiable pathogenic variant (Rogers & Abidi, 2018) |

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| SATB2 | 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) |
| SLC6A1 | Myoclonic-atonic epilepsy (Doose syndrome) | AD | Diagnostic yield for ASD/ID is low or unknown (Carvill et al., 2015; Johannesen et al., 2018) |

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| 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) |
| 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) |

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| TSC2 ^c | 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 reported

c Deletions/duplications including the 3' end of the TSC2 gene (exons 36-42) may not be detected

d PTEN promoter region is not analyzed

References:

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