Microcephaly Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing, 65 Genes

Panel Gene List: AMPD2, ANKLE2, AP4M1, ARGEF2, ASPM, ASXL1, ATR, ATRX, BRAT1, CASK, CDK5RAP2, CDKL5, CENPE, CENPF, CENPJ, CEP135, CEP152, CIT, CREBBP, CTNNB1, DDX3X, DHCR7, DIAPH1, DYRK1A, EFTUD2, EP300, FOXG1*, IER3IP1, KAT6A, KATNB1, KIF11, KIF1A, KMT2D, KNL1, MCPH1, MECP2, MED17, MYCN**, NIPBL, PCNT, PNKP, RAB18, RAB3GAP1, RAB3GAP2, RBBP8, RNASEH2C, RTTN, SEPSECS, SLC25A19, SLC9A6, SNAP29, STAMBP, STIL, TCF4, TRAPPC9, TSEN54, TUBA1A***, TUBB3, TUBGCP4, TUBGCP6, UBE3A, VPS13B, WDR62, ZEB2, ZNF335

* This panel does not include deletion/duplication testing of FOXG1.

** Deletion/duplication of the MYCN gene is performed by MS-MLPA.

*** Only large deletions/duplications may be detected for TUBA1A

Clinical Features:

Microcephaly is defined as a small cranium with an occipito-frontal head circumference (OFC) of more than two standard deviations (SD) below the mean for age, sex, and ethnicity (Ashwal et al., 2009). Microcephaly can be congenital (primary microcephaly) or develop postnatally (secondary microcephaly). Either type can be caused by environmental or genetic factors (Kaindl et al., 2010). Individuals with primary microcephaly have inadequate brain growth during pregnancy, and are born with a significantly small head size with the absence of additional brain malformations (Kaindl et al., 2010; Thornton & Woods, 2009). Individuals with primary microcephaly may also develop mild to severe intellectual disability (ID), seizures, mild short stature, and a narrow sloping forehead due to the reduced cranial size (Verloes et al., 2013). The brain size in cases of secondary microcephaly has the expected size at birth but subsequently fails to grow normally (Woods et al., 2004). Common causes of secondary microcephaly include environmental insults, such as infections or a brain injury. In addition, secondary microcephaly is observed in some metabolic disorders or genetic syndromes, such as Rett or Angelman syndromes, in which a progressive reduction in head circumference is seen in infancy or early childhood (Abuelo et al., 2007). Congenital or postnatal microcephaly can present as an isolated finding in an individual, be associated with other brain malformations such as cerebellar hypoplasia, or be part of an underlying syndrome.

Genetics:

The worldwide incidence of primary microcephaly at birth varies from 1:30,000 to 1: 250,000 live births, depending on the population and the applied SD threshold to define microcephaly (Letard et al., 2018). Microcephaly can be caused by chromosomal abnormalities, inborn errors of metabolism, single gene disorders, trauma and infection. The inheritance patterns can be autosomal dominant, recessive or x-linked. One type of congenital microcephaly that has a genetic etiology is primary autosomal recessive microcephaly (MCPH), which is a rare and heterogeneous disorder characterized by isolated microcephaly with an OFC of < 3 SD at birth that worsens over time (<3-4 SD after 6 months of age) (Verloes et al., 2013; Letard et al., 2018). The incidence of MCPH in consanguineous populations is approximately one in 10,000 and less in non-consanguineous populations.[2] Over ten subtypes of MCPH have been reported and between 25-50% of patients with a strictly characterized MCPH diagnosis have a pathogenic variant in the ASPM gene, associated with MCPH5 (Verloes et

al., 2013). However, many families with MCPH do not have an identifiable variant in one of the seven loci, indicating further genetic heterogeneity (Letard et al., 2018). Syndromic forms of microcephaly are associated with underlying chromosomal aberrations, contiguous gene deletions, and single gene disorders that are inherited in an autosomal dominant, recessive, or X-linked manner (Abuelo et al., 2007). Several of these syndromes have postnatal onset of microcephaly, including Rett syndrome and Ataxia-telangectasia with intellectual disability, whereas other syndromes, such as Cornelia de Lange, Smith-Lemli Opitz, and Seckel, present with congenital microcephaly.

The Microcephaly panel at GeneDx includes sequencing and concurrent deletion/duplication analysis of 65 Mendelian genes. Many of these genes associated with syndromic or non-syndromic microcephaly as reported in the literature and supported by our internal data from whole exome sequencing. The complete list of genes and associated disorders are listed 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). 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. 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. 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. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: FOXG1 gene, no copy number testing, TUBA1A gene, only whole gene deletions or duplications may be detected.

Clinical Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the panel depends on the clinical phenotype. Approximately 15-50% of individuals with microcephaly have been reported to have an underlying genetic etiology (Ashwal et al., 2009). GeneDx has multiple genetic testing options for patients with microcephaly. One option, the Microcephaly Xpanded panel test, interrogates over 800 genes associated with microcephaly. This microcephaly panel is an additional option for those interested in testing for a smaller number of genes that are well-characterized. Specific information about the diagnostic yield for each gene in selected populations is summarized in the following tables

Gene	Disorder(s)	Inheritance	Diagnostic Yield in Selected Population(s)
AMPD2	Pontocerebellar hypoplasia 9 (PCH9); Spastic paraplegia 63 (SPG63)	AR	Rare for PCH9 (Marsh et al., 2017)
ANKLE2	ANKLE2-related disorder	AR	Unknown (Yamamoto et al., 2014)
AP4M1	Spastic paraplegia type 50	AR	Rare (Verkerk et al., 2009; Najmabadi et al., 2011)
ARGEF2	Periventricular heterotopia with microcephaly (ARPHM)	AR	Rare (Tanyalçin et al., 2013; Bahi-Buisson et al., 2013)
ASPM	MCPH 5	AR	25-50% MCPH (Verloes et al., 2013)
ASXL1	Bohring-Opitz syndrome	AD	Rare or unknown (Hoischen et al., 2011)
ATR	Seckel syndrome	AR	Rare or unknown (O'Driscoll et al., 2003)
ATRX	Alpha-Thalassemia intellectual disability syndromes	XL	~25% diagnostic yield in affected individuals with findings suggestive of ATR-X (Badens et al, 2006)
BRAT1	Lethal neonatal rigidity and multifocal seizure syndrome (RMFSL) with expanded phenotypic spectrum (BRAT1-related disorder)	AR	Rare or unknown (Saitsu et al., 2014; Srivastava et al., 2016)
CASK	Intellectual disability and microcephaly with pontine and cerebellar hypoplasia; FG syndrome	XL	~4% in cerebellar hypoplasia and intellectual disability (Najm et al., 2008; Hackett et al., 2010)

RuCDK5RAP2	MCPH 3	AR	<5% of MCPH (Verloes et al., 2013)
CDKL5	Atypical Rett syndrome; XL infantile spasms; Early onset epileptic encephalopathy (EOEE); ID and/or autism spectrum disorder (ASD)	XL	2-8% females with atypical Rett syndrome (Tao et al., 2004; Rosas-Vargas et al., 2008; Archer et al., 2006)
CENPE	MCPH 13; Microcephalic primordial dwarfism	AR	Rare or unknown (Mirzaa et al., 2014)
CENPF	Stromme syndrome	AR	Rare or unknown (Filges et al., 2016)
CENPJ	MCPH 6; Seckel syndrome	AR	<5% MCPH (Verloes et al., 2013); Rare in Seckel syndrome (Al-Dosari et al., 2010)
CEP135	MCPH 8	AR	<5% MCPH; Unknown in Seckel syndrome (Verloes et al., 2013)
CEP152	MCPH 9	AR	<5% MCPH (Verloes et al., 2013)
CIT	MCPH 17	AR	Rare or unknown (Basit et al., 2016; Shaheen et al. 2016)
CREBBP	Rubinstein-Taybi syndrome (RTS)	AD	Estimated to account for 50-60% RTS disorders (Stevens et al., 2014)
CTNNB1	ID	AD	Rare or unknown (Kuechler et al., 2014)
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)
DIAPH1	Seizures, cortical blindness, and microcephaly syndrome (SCBMS)	AR	Rare or unknown for SCBMS (Ercan-Sencicek et al., 2015; Al-Maawali et al., 2016)
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	Rare or unknown (Lines et al., 2014)
EP300	Rubinstein-Taybi syndrome-2	AD	Estimated to account for 3-8% RTS disorders (Stevens et al., 2014)

FOXG1*	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)
IER3IP1	Microcephaly with simplified gyral pattern, epilepsy and permanent neonatal diabetes syndrome (MEDS)	AR	Rare or unknown (DeWit et al., 2006; Poulton et al., 2011)
KAT6A	ID	AD	Rare or unknown (Millan et al., 2016)
KATNB1	KATNB1-related disorder	AR	Rare or unknown (Yigit et al., 2016)
KIF11	KIF11-related disorder	AD	Rare or unknown (Ostegaard et al., 2012)
KIF1A	ID; Neuropathy; Hereditary spastic paraplegia 30	AD/AR	Rare or unknown for neurodevelopmental phenotype (Esmaeeli et al., 2015)
KMT2D	Kabuki syndrome (KS)	AD	Pathogenic variants identified in ~50-75% of individuals with a clinical diagnosis of KS (Adam et al., 2013)
KNL1	MCPH 8	AR	<5% MCPH; Unknown in Seckel syndrome (Verloes et al., 2013)
MCPH1	MCPH 1	AR	<10% of MCPH (Verloes et al., 2013)
MECP2	Rett syndrome	XL	Accounts for ~90% of females with Rett syndrome and ~45% of atypical Rett syndrome (Christodoulou, 2012)
MED17	MED17-related disorder	AR	Rare or unknown (Kaufmann et al., 2010)
MYCN**	Feingold syndrome	AD	~65-75% Feingold syndrome (Marcelis et al., 2008 ; Van Bokhoven et al., 2005 ; Teszas et al., 2006)
NIPBL	Cornelia de Lange syndrome (CdLS)	AD	~37-47% Cornelia de lange syndrome (Pie et al., 2010 ; Selicorni et al., 2007 ; Gillis et al., 2004)
PCNT	Seckel syndrome; Microcephalic osteodysplastic primordial dwarfism (MOPDII)	AR	~30% in Seckel syndrome (Willems et al., 2010) ; 100% in MOPDII (Willems et al., 2010 ; Rauch et al., 2008)
PNKP	PNKP-related disorder	AR	Rare or unknown (Shen et al., 2010; Poulton et al., 2013)
RAB18	Warburg micro syndrome; Martsolf syndrome	AR	~9% of affected individuals (Handley & Sheridan, 2018)

RAB3GAP1	Warburg micro syndrome; Martsolf syndrome	AR	75% of affected individuals (Handley & Sheridan, 2018)
RAB3GAP2	Warburg micro syndrome	AR	~11% of affected individuals (Handley & Sheridan, 2018)
RBBP8	Seckel syndrome	AR	Unknown (Borglum et al., 2001; Qvist et al., 2011)
RNASEH2C	Aicardi-Goutieres Syndrome (AGS)	AR	Accounts for 12% of individuals with AGS (Crow, 2016)
RTTN	RTTN-related disorder	AR	Rare or unknown (Kheradmand et al., 2012)
SEPSECS	SEPSECS-related disorders	AR	Rare or unknown (Agamy et al., 2010; Makrythanasis et al. 2014)
SLC25A19	Amish Lethal Microcephaly	AR	100% in Old Order Amish population (Biesecker et al., 2017), otherwise rare
SLC9A6	Angelman-like syndrome (Christianson)	XL	6% Angelman-like syndrome (Gillfillan et al., 2008); ~1% of X-linked ID (Tarpey et al., 2009)
SNAP29	CEDNIK syndrome (cerebral dysgenesis, neuropathy, ichthyosis, palmoplantar keratoderma syndrome)	AR	Rare or unknown (Hsu et al., 2017)
STAMBP	Neurocutaneous microcephaly-capillary malformation syndrome (MIC-CAP)	AR	Rare or unknown (McDonell et al., 2013)
STIL	MCPH 7	AR	<5% MCPH (Verloes et al., 2013)
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)
TRAPPC9	TRAPPC9-related disorder	AR	Rare or unknown (Mochida et al., 2009; Marangi et al., 2013)
TSEN54	Pontocerebellar hypoplasia type 2 and type 4	AR	60% of PCH (A307S common) (Budde et al., 2008; Namavar et al., 2011)

TUBA1A***	TUBA1A-related disorder	AD	1% of classic lissencephaly; 30% of lissencephaly with cerebellar hypoplasia; ~43% of complex cortical malformations (Kumar et al., 2010; Cushion et al., 2013; Bahi-Buisson et al., 2014)
TUBB3	Complex Cortical Dysplasia, with Other Brain Malformations (CDCBM)	AD	Rare or unknown (Poirier et al., 2010)
TUBGCP4	AR microcephaly and chorioretinopathy 3 (MCCRP3)	AR	Rare or unknown (Scheidecker et al., 2015)
TUBGCP6	AR microcephaly and chorioretinopathy (MCCRP)	AR	Rare or unknown (Martin et al., 2014)
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)
VPS13B (COH1)	Cohen syndrome	AR	Pathogenic sequencing variants identified in ~70% of affected individuals; founder 2bp deletion accts for 75% of pathogenic alleles in Finland (Wang et al., 2016). ~17-40% of patients with Cohen syndrome have only one identifiable pathogenic variant (Kolehmainen et al., 2003; Kolehmainen et al., 2004; Hennies et al., 2004).
WDR62	MCPH 2	AR	<10% MCPH (Verloes et al., 2013)
ZEB2	Mowat-Wilson syndrome	AD	Accounts for ~95% of MWS cases (Adam et al., 2013)
ZNF335	MCPH 10	AR	Rare or unknown (Sato et al., 2016; Verloes et al., 2013)

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