Syndromic Macrocephaly/Overgrowth Syndromes Panel Sequence Analysis and Exon-Level Deletion/Duplication Testing of 29 Genes

Panel Gene List: AKT3, BRWD3, CCND2, CHD8, CUL4B, DNMT3A, EZH2, GLI3, GPC3, HEPACAM, HERC1, MED12, MTOR, NFIA, NFIX, NSD1, OFD1, PHF6, PIK3CA, PIK3R2, PPP2R5D, PTCH1, PTEN*, RAB39B, RNF135, SETD2, SNX14, TBC1D7, UPF3B

Clinical Features:

Macrocephaly is defined as an occipitofrontal circumference (OFC) greater than the 98th percentile for age. Macrocephaly may occur for many reasons, including megalencephaly, hydrocephalus, cerebral edema, neoplasia, and structural anomalies. Syndromic forms of macrocephaly are often due to megalencephaly, which is defined as a brain weight/volume ratio greater than the 98th percentile for age due to hyperplasia of the central nervous system parenchyma.[58] Individuals with these forms of syndromic macrocephaly may also exhibit somatic overgrowth. Other features commonly observed in individuals with syndromic macrocephaly include developmental delay, hypotonia, increased risk for neoplasia, dysmorphic features, and birth defects.[58,59,60] In many cases, macrocephaly and/or overgrowth are identified in the neonatal period, although in other cases the onset may be postnatal and not noted until childhood. In some cases, growth parameters may normalize in adulthood.[60]

Because of the significant clinical overlap and phenotypic heterogeneity of disorders causing syndromic macrocephaly, it can be difficult to make a clinical diagnosis, particularly in infancy. Additionally, variants in a single gene may be associated with a broad spectrum of clinical presentations (clinical heterogeneity). Therefore, a multi-gene panel is very useful in helping to establish the etiology of syndromic macrocephaly. A complete list of the disorders included on the Syndromic Macrocephaly/Overgrowth Syndromes Panel is available in the table on the last page of this information sheet.

Inheritance Pattern/Genetics:

The Syndromic Macrocephaly/Overgrowth Syndromes Panel at GeneDx includes sequencing and deletion/duplication analysis of 30 genes. Pathogenic variants in these genes are associated with X-linked or autosomal dominant disorders and typically have a loss-of-function effect. The variant spectrum includes missense, nonsense, splicing, and small insertion or deletion variants, as well as exonic deletions or duplications. Many of these genes encode proteins that play a role in cell growth and division, cell death, chromatin regulation, histone modification, cell migration, and angiogenesis. [61,62]

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 PTEN, approximately nucleotides c.-700 through c.-1300 in the promoter region are also captured. 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; 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. 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	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
AKT3	AD	MPPH2	~30% of MPPH syndrome[1]
BRWD3	XL	X-linked intellectual disability with macrocephaly	Rare [2,3]
CCND2	AD	MPPH3	~30% of MPPH syndrome [1]
CHD8	AD	Neurodevelopmental and autism spectrum disorders	Rare [4,5]
CUL4B	XL	Cabezas syndrome	~3% of X-linked intellectual disability[6,7]
DNMT3A	AD	Tatton-Brown-Rahman syndrome	Rare [4,8,9]
EZH2	AD	Weaver syndrome	5% patients with non-specific overgrowth[10]
GLI3	AD	Grieg cephalopolysyndactyly syndrome (GCPS)	68% GCPS[11,12] 91% PHS[11,12]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
		Pallister-Hall syndrome (PHS)	
GPC3	XL	Simpson-Golabi-Behmel syndrome (SGBS)	56% males with SGBS[13,14,15]
HEPACAM	AD/AR	Megalencephalic leukoencephalopathy with subcortical cysts	Rare [16,17]
HERC1	AR	Macrocephaly, dysmorphic facies, and psychomotor retardation	Rare [18,19,20,21]
MED12	XL	FG syndrome Lujan syndrome	13% males with clinical diagnosis of FG syndrome[24]
MTOR	AD	Smith-Kingsmore syndrome	Rare [4,25]
NFIA	AD	Brain malformations with or without urinary tract defects	Rare [26,27]
NFIX	AD	Sotos syndrome-2 Marshall-Smith syndrome	4% patients with Sotos-like features[28]
NSD1	AD	Sotos syndrome	90-93% of non-Japanese patients with Sotos syndrome[29,30] 63% Japanese patients with Sotos syndrome[31]
OFD1	XL	Joubert syndrome Orofaciodigital syndrome	Rare in JSRD[32,33,34]
PHF6	XL	Borjeson-Forssman-Lehmann syndrome (BFLS)	56% males with BFLS[35]
PIK3CA	AD	megalencephaly-capillary malformation (MCAP) syndrome, CLOVE syndrome, and fibroadipose hyperplasia	~40% of megalencephaly-capillary malformation (MCAP)[36]
PIK3R2	AD	MPPH1	~40% of MPPH syndrome [1]
PPP2R5D	AD	autosomal dominant intellectual disability	Rare [37]
PTCH1	AD	Gorlin syndrome	72% of patients with Gorlin syndrome[38,39]
PTEN	AD	PTEN-related autism and macrocephaly Cowden syndrome (CS) Bannayan-Riley-Ruvalcaba syndrome (BRRS)	2-17% of patients with autism spectrum disorders and macrocephaly[40,41,42,43] 81% of patients with CS[44] 71% of patients with BRRS[45,46]
RAB39B	XL	X-linked intellectual disability	Rare [47,48]
RNF135	AD	Macrocephaly, macrosomia, facial	Rare [49]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
		dysmorphism syndrome	
SETD2	AD	Luscan-Lumish syndrome	Rare [50,51]
SNX14	AR	autosomal recessive spinocerebellar ataxia-20	Rare [52,53]
TBC1D7	AR	Macrocephaly/megalencephaly syndrome	Rare [54,55]
UPF3B	XL	Lujan syndrome FG syndrome Nonsyndromic X-linked intellectual disability	~1% X-linked intellectual disability[56,57]

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