THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Macrocephaly

Macrocephaly refers to an abnormally large head, OFC greater than 98th percentile, inclusive of the scalp, cranial bone and intracranial contents. Megalencephaly, brain weight/volume ratio greater than 98th percentile, results from true enlargement of the brain parenchyma [1]. Megalencephaly is typically accompanied by macrocephaly, however macrocephaly can occur in the absence of megalencephaly [2]. Both macrocephaly and megalencephaly can been seen as isolated clinical findings as well as clinical features of a mutli-systemic syndromic diagnosis.

Our Macrocephaly Panel includes analysis of the 36 genes listed below.

Macrocephaly Sequencing Panel				
ASXL2	GLI3	MTOR	PPP2R5D	TCF20
BRWD3	GPC3	NFIA	PTEN	TBC1D7
CHD4	HEPACAM	NFIX	RAB39B	UPF3B
CHD8	HERC1	NONO	RIN2	ZBTB20
CUL4B	KPTN	NSD1	RNF125	
DNMT3A	MED12	OFD1	RNF135	
EED	MITF	PIGA	SEC23B	
EZH2	MLC1	PPP1CB	SETD2	

Gene	Clinical Features	Details
ASXL2	Shashi-Pena syndrome	Shashi *et al.* (2016) found that six patients with developmental delay, macrocephaly, and dysmorphic features were found to have de novo truncating variants in *ASXL2* [3]. Distinguishing features were macrocephaly, absence of growth retardation, and variability in the degree of intellectual disabilities The phenotype also consisted of prominent eyes, arched eyebrows, hypertelorism, a glabellar nevus flammeus, neonatal feeding difficulties and hypotonia.
BRWD3	X-linked intellectual disability	Truncating mutations in the *BRWD3* gene have been described in males with nonsyndromic intellectual disability and macrocephaly [4]. Other features include a prominent forehead and large cupped ears.
CHD4	Sifrim-Hitz-Weiss syndrome	Weiss *et al.*, 2016, identified five individuals with *de novo* missense variants in the *CHD4* gene with intellectual disabilities and distinctive facial dysmorphisms [5]. Additional features noted in these patients included hearing loss, macrocephaly, palatal abnormalities, ventriculomegaly, and hypogonadism.
CHD8	Macrocephaly and autism-spectrum disorder	*De novo* loss of function variants in *CHD8* have been identified in multiple patients with autism spectrum disorder [6, 7]. The majority of these patients also exhibit macrocephaly [7]. Facial dysmorphism is a variable feature.
CUL4B	X-linked intellectual disability	Mutations in *CUL4B* have been identified in patients with syndromic X-linked intellectual disability [8]. In addition to relative macrocephaly, clinical features include short stature, hypogonadism and abnormal gait. Carrier females are typically unaffected
DNMT3A	Tatton-Brown-Rahman syndrome	Among thirteen individuals with *de novo DNMT3A* mutations, Tatton-Brown *et al.* (2014) found an increased head circumference ranging from 1.2 to 5.1 standard deviations above the mean, distinctive facial appearance (including round face, heavy and horizontal eyebrows and narrow palpebral fissures), tall stature and mild to moderate intellectual disability [9]. Subsequently, additional patients with Tatton-Brown-Rahman syndrome due to *de novo* mutations in *DNMT3A* have been identified [10, 11].
EED	Cohen-Gibson syndrome	*De novo*, heterozygous mutations in *EED* have been reported in patients with a phenotype similar to Weaver syndrome, with features including prenatal/postnatal overgrowth, advanced osseous maturation, mild-to-severe intellectual disability, and characteristic craniofacial features which include macrocephaly, and hypertelorism [12-14].
EZH2	Weaver syndrome	Mutations in *EZH2* have been identified in patients with Weaver syndrome. Individuals with Weaver Syndrome are characterized by pre- and postnatal overgrowth with marked macrocephaly, advanced bone age, developmental delay and characteristic facial features [15].

GLI3	Greig cephalopolysyndactyly syndrome	Heterozygous *GLI3* mutations and deletions have been identified in patients with Greig cephalopolysyndactyly syndrome [16]. Greig cephalopolysyndactyly syndrome is characterized by frontal bossing, scaphocephaly and hypertelorism associated with pre/postaxial polydactyly and variable syndactyly. The phenotype can also include craniosynostosis.
GPC3	Simpson-Golabi-Behmel syndrome	Mutations in *GPC3* have been identified in patients with Simpson-Golabi-Behmel syndrome, which is characterized by pre and postnatal overgrowth, coarse facies, congenital heart defects and other congenital anomalies. Carrier females may exhibit minor manifestations. Exonic deletions as well as point mutations have been described [17].
HEPACAM	Megalencephalic leukoencephalopathy with subcortical cysts 2B, remitting, with or without intellectual disability (MLC2B)	Mutations in *HEPACAM* have been identified in MLC2B, which is characterized by infantile-onset macrocephaly and mildly delayed motor development associated with white matter abnormalities on brain MRI. Intellectual disability is identified in less than half of patients. Dominant *HEPACAM* mutations can cause either macrocephaly and mental retardation with or without autism or benign familial macrocephaly [18].
HERC1	Megalencephaly	A homozygous truncating variant in the *HERC1* gene has been described in a consanguineous family with megaencephaly, thick corpus callosum and severe intellectual disability [19].
KPTN	Autosomal recessive intellectual disability	In consanguineous Amish families with intellectual disability, macrocephaly, craniosynostosis and dysmorphic facial features, Baple *et al* (2014) identified a homozygous truncating mutation in the *KPTN* gene [20].
MED12	Opitz-Kaveggia syndrome	Mutations in *MED12* have been identified in patients with Opitz-Kaveggia syndrome. This X-linked intellectual disability syndrome is characterized by dysmorphic features, relative macrocephaly, hypotonia, constipation and characteristic brain MRI imaging. A single missense mutation (p.N1007S) in the *MED12* gene has been identified in a number of families with Opitz-Kaveggia syndrome, although more recently additional mutations have been described [21].
MITF	COMMAD syndrome	Biallelic *MITF* mutations have been identified in two unrelated individuals with coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness, termed COMMAD syndrome [22]. The parents of these individuals, who were each heterozygous for one of the *MITF* mutations, each had features consistent with Waardenburg syndrome type 2A, which is caused by heterozygous mutations in *MITF*.
MLC1	Megalencephalic leukoencephalopathy with subcortical cysts	Biallelic pathogenic variants in *MLC1* are associated with megalencephalic leukoencephalopathy with subcortical cysts (MLC). MLC is characterized by early onset macrocephaly, mild early developmental delays, seizures, gradual onset of ataxia, and typically later onset mild cognitive decline [23].
MTOR	Smith-Kingsmore Syndrome	Heterozygous mutations in *MTOR* are associated with Smith-Kingsmore syndrome, which is characterized by macrocephaly or megalencephaly, seizures, intellectual disabilities and dysmorphic features [24]. The majority of cases are *de novo*; however, gonadal mosaicism has been reported [24, 25].
NFIA	Hypoplastic corpus callosum, craniofacial abnormalities and urinary tract defects	Large deletions involving the whole *NFIA* gene have been associated with findings including macrocephaly, hypoplastic corpus callosum, ventriculomegaly or hydrocephalus, and genitourinary tract defects [26]. Rao *et al* (2014) reported a patient with an intragenic deletion involving exons 4-9 of the NFIA gene in a patient with findings consistent with what has been described for patients with larger deletions of this gene [26].
NFIX	Sotos-like syndrome	Mutations in *NFIX* have been identified in patients with Sotos-like syndrome, an overgrowth syndrome that shows resemblance to Sotos syndrome. Features include postnatal overgrowth, macrocephaly, advanced bone age, long narrow face, high forehead, slender habitus, scoliosis, and intellectual disability[27].
NONO	X-linked intellectual disability	Hemizygous mutations in *NONO* are associated with X-linked intellectual disability-34 [OMIM# 300967], which is characterized by intellectual disability with speech delays, dysmorphic features, cardiac defects, and macrocephaly [28-30]. Some patients have abnormalities of the corpus callosum including dysgenesis of the corpus callosum and thickening of the corpus callosum. The majority of reported variants have been *de novo*; however, maternally inherited variants have been reported [28].
NSD1	Sotos syndrome	Microdeletions and mutations of the *NSD1* gene have been identified in approximately 80% of patients with a clinical diagnosis of Sotos syndrome [31, 32]. Sotos syndrome is characterized by characteristic facial features, developmental delay, and increased height and head circumference.
OFD1	Simpson-Golabi-Behmel syndrome, type 2	A frameshift mutation in *OFD1* has been identified in two families with a severe form of Simpson-Golabi-Behmel syndrome. Males in these families have renal cysts, dysmorphic features, macrocephaly, developmental delay and respiratory problems. Most males died very early in life. Females appear unaffected [33, 34].

PIGA	Simpson-Golabi-Behmel syndrome type 2	Multiple male patients have been identified with a recurrent *PIGA* mutation, c.1234C>T (p.Arg412*), which causes a severe phenotype similar to Simpson-Golabi-Behmel syndrome type 2 [34, 35]. Major clinical findings included macrocephaly and increased birth weight, early onset intractable epileptic encephalopathy with a burst-suppression pattern on EEG, generalized muscular hypotonia, structural brain abnormalities, and joint contractures. Additional features include coarse facial features, widely spaced eyes, a short nose with anteverted nares, gingival overgrowth, a wide mouth, and short limbs with short distal phalanges. Early infantile lethality is typical of males with this pathogenic variant. Carrier females are typically phenotypically normal with the exception of widely spaced eyes [34].
PPP1CB	Noonan syndrome-like disorder	Heterozygous mutations in *PPP1CB* have been reported in patients with Noonan-syndrome like disorder with loose anagen hair, which is characterized by Noonan-like features including macrocephaly or relative macrocephaly, low set ears, developmental delay, and slow growing, sparse, and/or unruly hair [36]. Ma, *et al.*, 2016, identified an additional eight individuals with an overlapping phenotype with *de novo* mutations in *PPP1CB* who additionally had congenital heart disease and skeletal and connective tissue abnormalities in some patients [37].
PPP2R5D	Autosomal dominant intellectual disability	Shang, *et al.*, 2016 identified *de novo* missense variants in seven individuals with intellectual disability, autism spectrum disorder, macrocephaly, and hypotonia. Variable features included ataxia, brain abnormalities, and ophthalmologic abnormalities [38].
PTEN	PTEN-related disorders	Mutations in *PTEN* have been identified in up to 27% of patients with autism spectrum disorders and macrocephaly [39]. Mutations in *PTEN* are also identified in more than 70% of patients with Cowden syndrome (CS). Multiple hamartomas develop in patients affected with CS, and these patients are at increased risk for breast, endometrial and thyroid cancers
RAB39B	X-linked intellectual disability	Truncating mutations in *RAB39B* have been identified in two families with X-linked intellectual disability [40]. All affected males had macrocephaly.
RIN2	Macrocephaly, alopecia, cutis laxa, and scoliosis (MACS) syndrome	Homozygous mutations in *RIN2* have been identified in a few consanguineous families with MACS syndrome [41]. This is a rare autosomal recessive connective tissue disorder characterized by macrocephaly, soft and redundant facial skin, sparse scalp hair, severe joint hyperlaxity and scoliosis.
RNF125	Tenorio syndrome	Autosomal dominant mutations in *RNF125* are associated with Tenorio syndrome, which is characterized by overgrowth, macrocephaly, and intellectual disability [42].
RNF135	Macrocephaly, macrosomia, facial dysmorphism syndrome	Heterozygous mutations in *RNF135* were identified in 4 of 245 unrelated individuals with an overgrowth syndrome [43]. The clinical features of these individuals included increased postnatal height and weight, macrocephaly, learning difficulties and dysmorphic facial features.
SEC23B	Cowden syndrome	In a large pedigree with an autosomal dominant Cowden syndrome phenotype and negative testing for mutations in the *PTEN* gene, Yehia *et al.*, 2015 identified a missense variant in *SEC23B* that segregated with disease in the family. Individuals in this family exhibited macrocephaly in addition to multiple cancers including thyroid, breast, endometrial and skin cancer [44].
SETD2	Sotos-like syndrome	*De novo* mutations in *SETD2* have been described in patients with features similar to Sotos syndrome, including overgrowth, macrocephaly and speech delays [45].
TCF20	Intellectual disability	Schafgen, *et al*, 2016, identified *de novo* nonsense and frameshift variants in *TCF20* in two individuals with intellectual disability and postnatal development of macrocephaly, obesity, and tall stature. Mild intellectual disabilities were also seen [46].
TBC1D7	Macrocephaly / Megaencephaly syndrome	Biallelic mutations in the *TBC1D7* gene are associated with macrocephaly/ megaencephaly that is present at birth or develops in early childhood [47]. Affected individuals also have intellectual disability.
UPF3B	X-linked intellectual disability	Truncating mutations in *UPF3B* were identified in three families with syndromic intellectual disability (two with Lujan–Fryns and one with Opitz-Kaveggia syndrome); and a missense mutation in a highly conserved domain of the protein in a family with non-specific X-linked intellectual disability[48]
ZBTB20	Primrose syndrome	Primrose syndrome is a rare condition characterized by macrocephaly, tall stature, intellectual disability, dysmorphic features, disturbances in glucose metabolism and distal muscle wasting [49]. Alby, *et al.* (2018) found that corpus callosum abnormalities are common in individuals with this condition [50]. Primrose syndrome is caused by *de novo* mutations in the *ZBTB20* gene. Functional studies have demonstrated that causative mutations have a dominant negative impact on gene function [49].

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Macrocephaly Panel (36 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3000
CPT codes:	81406 81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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