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 be seen as isolated clinical findings as well as clinical features of a multi-systemic syndromic diagnosis.

**Our Macrocephaly Sequencing Panel and Macrocephaly Deletion/Duplication Panel include analysis of the 21 genes listed below.**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Features</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRWD3</td>
<td>X-linked intellectual disability</td>
<td>Truncating mutations in the BRWD3 gene have been described in males with nonsyndromic intellectual disability and macrocephaly [3]. Other features include a prominent forehead and large cupped ears.</td>
</tr>
<tr>
<td>CUL4B</td>
<td>X-linked intellectual disability</td>
<td>Mutations in CUL4B have been identified in patients with syndromic X-linked intellectual disability [4]. In addition to relative macrocephaly, clinical features include short stature, hypogonadism and abnormal gait. Carrier females are typically unaffected</td>
</tr>
<tr>
<td>EZH2</td>
<td>Weaver syndrome</td>
<td>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 [5].</td>
</tr>
<tr>
<td>GLI3</td>
<td>Greig cephalopolysyndactyly syndrome</td>
<td>Heterozygous GLI3 mutations and deletions have been identified in patients with Greig cephalopolysyndactyly syndrome [6]. 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.</td>
</tr>
<tr>
<td>GPC3</td>
<td>Simpson-Golabi-Behmel syndrome</td>
<td>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 [7].</td>
</tr>
<tr>
<td>HEPACAM</td>
<td>Megalencephalic leukoencephalopathy with subcortical cysts 2B, remitting, with or without intellectual disability (MLC2B)</td>
<td>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 [8].</td>
</tr>
<tr>
<td>HERC1</td>
<td>Megalencephaly</td>
<td>A homozygous truncating variant in the HERC1 gene has been described in a consanguineous family with megalencephaly, thick corpus callosum and severe intellectual disability [9].</td>
</tr>
</tbody>
</table>
**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 [10].

**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 [11].

**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 [12]. 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 [12].

**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 [13].

**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 [14, 15]. 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 [16, 17].

**PTEN**
PTEN-related disorders

Mutations in PTEN have been identified in up to 27% of patients with autism spectrum disorders and macrocephaly [18]. 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 [19]. 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 [20]. 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 [21].

**RNF135**
Macrocephaly, macrosomia, facial dysmorphism syndrome

Heterozygous mutations in RNF135 were identified in 4 of 245 unrelated individuals with an overgrowth syndrome [22]. The clinical features of these individuals included increased postnatal height and weight, macrocephaly, learning difficulties and dysmorphic facial features.

**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 [23].

**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 [24]. 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 [25].

**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.

**Macrocephaly Sequencing Panel (21 genes sequencing)**

<table>
<thead>
<tr>
<th>Sample specifications:</th>
<th>3 to 10 cc of blood in a purple top (EDTA) tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost:</td>
<td>$3000</td>
</tr>
<tr>
<td>CPT codes:</td>
<td>81407</td>
</tr>
<tr>
<td>Turn-around time:</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

**Note:** We cannot bill insurance for the above test.

**Macrocephaly Deletion/Duplication Panel (21 genes deletion/duplication analysis)**

<table>
<thead>
<tr>
<th>Sample specifications:</th>
<th>3 to 10 cc of blood in a purple top (EDTA) tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost:</td>
<td>$2500</td>
</tr>
<tr>
<td>CPT codes:</td>
<td>81407</td>
</tr>
<tr>
<td>Turn-around time:</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

**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.

**References:**


Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS