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Microcephaly Sequencing Panel

Microcephaly is typically defined as an occipitofrontal circumference (OFC) of at least 2 standard deviations below the mean. Microcephaly may be congenital, or can be acquired postnatally (1). Microcephaly can have a genetic etiology, however the finding of microcephaly can also be due to other environmental factors such as teratogens and infection (1). Microcephaly may be observed as an isolated finding, or as part of syndrome (1).

Our Microcephaly Sequencing Panel includes sequence analysis of the 56 genes listed below.

Microcephaly Sequencing Panel						
Congenital Microcephaly					Postnatal Microcephaly	
Syndromic			Autosomal Recessive Primary Microcephaly			
ARFGEF2	KIF11	PCNT	ASPM	CEP152	CDKL5	SLC9A6
ASXL3	LIG4	PNKP	CASC5	MCPH1	DYRK1A	TBC1D20
ATR	NBN	RAD50	CDK5RAP2	PHC1	FOXG1	TCF4
ATRX	NDE1	RBBP8	CDK6	STIL	MECP2	TRAPPC9
CASK	NHEJ1	SLC25A19	CENPJ	WDR62	MED17	TSEN2
CDC6	NIN	STAMBP	CEP135	ZNF335	RAB18	TSEN34
CDT1	ORC1	TRMT10A			RAB3GAP1	TSEN54
CEP63	ORC4	TUBGCP6			RAB3GAP2	UBE3A
IER3IP1	ORC6	ZEB2			SLC2A1	

Congenital Syndromic Microcephaly Genes

Gene	Inheritance	Clinical Features
ARFGEF2 [OMIM#605371]	AR	Missense and frameshift mutations were identified in two Turkish families with autosomal recessive periventricular heterotopia with microcephaly [OMIM#608097] which is characterized by microcephaly, periventricular heterotopia, intellectual disability and recurrent infections (2).
ASXL3 [OMIM 615115]	AD	<i>De novo</i> nonsense or frameshift mutations were identified in ASXL3 in four individuals with IUGR (3/4), microcephaly (3/4), severe developmental delay (4/4), severe feeding difficulty (3/4), dysmorphic features (4/4), ulnar deviation of the hands (3/4), and high arched palate (3/4) (3). These patients had some overlapping features with Bohring-Opitz disease, caused by mutations in ASXL1 [612990].
ATR [OMIM#601215]	AR	A homozygous mutation in ATR was been identified in two consanguineous Pakistani families with Seckel syndrome [OMIM#210600] (4). Seckel syndrome is characterized by severe proportionally short stature with severe microcephaly, a 'bird like' profile including a beak-like protusion of the nose, narrow face, receding lower jaw and micrognathia, and intellectual disability (5).
ATRX [OMIM#300032]	XL	Mutations in ATRX are associated with a wide and clinically heterogeneous spectrum of X-linked mental retardation syndromes (6). Clinical features may include intellectual disability, hypotonia, microcephaly, genital abnormalities, short stature and seizures (6). Affected individuals may have microcytic hypochromic anemia characteristic of alpha-thalassemia, however many do not. Carrier females are typically not affected (6).
CASK [OMIM#300172]	XL	X-linked mental retardation and microcephaly with pontine and cerebellar hypoplasia (MIC-PHC) [OMIM #300749] is associated with <i>de novo</i> CASK mutations, and is characterized by severe or profound intellectual disability, microcephaly, and disproportionate pontine and cerebellar hypoplasia in females (7). Mutations associated with MIC-PHC are believed to be lethal in males, however milder familial mutations may also be observed, which can cause intellectual disability in males.

<i>CDC6</i> [OMIM#602627] <i>CDT1</i> [OMIM#605525] <i>ORC1</i> [OMIM#601902] <i>ORC4</i> [OMIM#603056] <i>ORC6</i> [OMIM#607213]	AR	Meier-Gorlin syndrome (MGS) is a rare disorder characterized by severe intrauterine and postnatal growth retardation, congenital microcephaly, bilateral microtia, and aplasia or hypoplasia of the patellae. Mutations in <i>ORC1</i> have been identified in 4/33 individuals with MGS (8). Mutation analysis of other genes of this pre-replication complex showed mutations in <i>ORC4</i> , <i>ORC6</i> , <i>CDT1</i> and <i>CDC6</i> in 14 individuals from nine families with MGS (9). Guernsey <i>et al</i> identified mutations in <i>ORC1</i> , <i>ORC4</i> and <i>CDT1</i> in 8 individuals from five families with MGS. While most affected individuals described had typical features of MGS, a considerable wide phenotypic variation was observed and no clear genotype-phenotype correlation has been elucidated.
<i>CEP63</i> [OMIM#614728]	AR	A homozygous nonsense mutation was identified in <i>CEP63</i> in a consanguineous family of Pakistani descent with three members with primary microcephaly and proportionate short stature, clinically consistent with mild Seckel syndrome [OMIM#614728] (10).
<i>IER3IP1</i> [OMIM#609382]	AR	Homozygous missense mutations were identified in two unrelated consanguineous families with at least three children affected with a syndrome of primary microcephaly with simplified gyral pattern, severe infantile epileptic encephalopathy, and early-onset diabetes (11).
<i>KIF11</i> [OMIM#148760]	AD	Ostergaard <i>et al.</i> (2012) identified <i>KIF11</i> mutations in individuals from 17 families with autosomal dominant microcephaly and primary lymphedema [OMIM#152950] and/or chorioretinopathy [OMIM#156590] (12). Most individuals had mild to moderate intellectual disabilities. Nonsense, splice site, missense, and frameshift mutations were all observed.
<i>LIG4</i> [OMIM#601837]	AR	Biallelic truncating <i>LIG4</i> mutations have been identified in a series of 11 patients with microcephalic primordial dwarfism (13). The position of truncating mutations has been observed to correlate with phenotypic severity (13). <i>LIG4</i> mutations have been recurrently reported in <i>LIG4</i> syndrome (OMIM#606593), originally identified in a typically-developing 14-year-old with acute lymphoblastic leukemia (14). Bone marrow failure has occurred in 70% of patients reported to date (13). Other patients with <i>LIG4</i> syndrome are described as having immunodeficiency, developmental delay, Seckel or "bird-like" facies, microcephaly, and growth restriction (15).
<i>MED17</i> [OMIM#603810]	AR	A homozygous missense mutation was identified in 5 infants from 4 Jewish families with postnatal progressive microcephaly and severe developmental retardation associated with cerebral and cerebellar atrophy (16).
<i>NDE1</i> [OMIM#609449]	AR	Mutations in <i>NDE1</i> have been reported in children with severe congenital microcephaly, with brains smaller than 10 SD below the mean, simplified gyri, and profound intellectual disability (17). Homozygous mutations have been reported in one Turkish, two Saudi and two Pakistani consanguineous families.
<i>NBN (NBS1)</i> [OMIM#602667]	AR	<i>Nibrin</i> (abbreviation <i>NBN</i> , previously <i>NBS1</i>) is mutated in Nijmegen breakage syndrome, an autosomal recessive disorder characterized by microcephaly, intellectual disability, growth restriction, immunodeficiency, and predisposition to cancer (18). The majority of patients are homozygous for the common deletion mutation 657del5. Other frameshift as well as nonsense mutations have been reported.
<i>NIN</i> [OMIM#608064]	AR	Compound heterozygous missense mutations have been identified in the <i>NIN</i> gene in two sisters with Seckel syndrome 7 (19).
<i>NHEJ1</i> [OMIM#611290]	AR	Buck <i>et al.</i> (2006) identified <i>NHEJ1</i> mutations in patients with congenital microcephaly, growth restriction, dysmorphism (bird-like face), and immunodeficiency as well as variable bone and kidney abnormalities (20). Mutations observed included missense, nonsense, frameshift/splice site (in <i>cis</i>), and in-frame deletions.
<i>PCNT</i> [OMIM#605925]	AR	Mutations in <i>PCNT</i> have been identified in patients with microcephalic osteodysplastic primordial dwarfism type II (MOPD II) [OMIM#210720]. MOPD II is characterized by intrauterine growth retardation, severe proportionate short stature, and microcephaly (21). Rauch <i>et al.</i> (2008) identified 29 different homozygous or compound heterozygous mutations in the <i>PCNT</i> gene in 25 patients with MOPD2 (21).
<i>PNKP</i> [OMIM #605610]	AR	Mutations in the <i>PNKP</i> gene have been described in seven families with autosomal recessive microcephaly, infantile-onset seizures, and developmental delay (MCSZ) [OMIM#613402]. Both homozygous and compound heterozygous mutations have been reported. In patients with MCSZ, intellectual disability is usually severe to profound with variable behavioral problems and severe and intractable seizures (22).
<i>RAD50</i> [OMIM#604040]	AR	A patient of non-consanguineous German descent with a Nijmegen breakage syndrome-like disorder was found to have compound heterozygosity for a nonsense mutation and a mutation interrupting the stop codon of <i>RAD50</i> (23). The patient's features included significant microcephaly (43cm at 15yo) with other growth parameters well below the 3 rd percentile in addition to "bird-like" facies, areas of hypo- and hyperpigmentation, hyperopia, mild to moderate intellectual disability, and mildly impaired motor coordination.

<i>RBBP8</i> [OMIM#604124]	AR	A homozygous splicing mutation in <i>RBBP8</i> was identified in four siblings affected by Seckel syndrome [OMIM#606744] in a consanguineous Iraqi family (24). Seckel syndrome is characterized by severe proportionally short stature with severe microcephaly, a 'bird like' profile including a beak-like protrusion of the nose, narrow face, receding lower jaw and micrognathia, and intellectual disability (5).
<i>SLC25A19</i> [OMIM#606521]	AR	Amish lethal microcephaly [OMIM#607196] is characterized by the presence of microcephaly and a tenfold increase in the levels of urinary organic acid 2-ketoglutarate. To date, all affected individuals within the Old Order Amish population (in which the prevalence of this condition in this population is approximately 1 in 500 births) are homozygous for a founder mutation in <i>SLC25A19</i> (25).
<i>STAMBP</i> [OMIM#606247]	AR	McDonnell et al. identified mutations in <i>STAMBP</i> in a cohort of patients with Microcephaly-Capillary malformation (MIC-CAP) syndrome [OMIM#606247]. MIC-CAP is characterized by small scattered capillary malformations, congenital microcephaly, early-onset intractable epilepsy, profound global developmental delay, spastic quadriparesis, hypoplastic distal phalanges and poor growth (26).
<i>TRMT10A</i> [OMIM#616013]	AR	Homozygous nonsense and missense mutations in <i>TRMT10A</i> have been identified in two consanguineous families with multiple children with microcephaly, intellectual disability, short stature, delayed puberty, seizures, and disturbed glucose metabolism (27, 28).
<i>TUBGCP6</i> [OMIM#610053]	AR	In a Mennonite infant with primary microcephaly and chorioretinopathy, a homozygous missense mutation was identified in <i>TUBGCP6</i> (29). The carrier frequency among Old Order Amish and Mennonite was estimated at 2% (identified in 2/202 individuals).
<i>ZEB2</i> [OMIM#605802]	AD	Mutations in <i>ZEB2</i> are associated with Mowat-Wilson syndrome (MWS) [OMIM # 235730], which is characterized by distinctive facial features, moderate-to-severe mental retardation, microcephaly and seizures (30). Microcephaly may be either congenital or acquired postnatally. Congenital anomalies are also common, including Hirschsprung disease, genitourinary anomalies, congenital heart defects, agenesis of the corpus callosum and eye anomalies (30).

Autosomal Recessive Primary Microcephaly Genes*

Autosomal recessive primary microcephaly is a rare genetic disorder characterized by congenital microcephaly, mild to moderate intellectual disability (ID), but no other neurological findings (febrile or other mild seizures do not exclude the diagnosis), normal or mildly short stature and normal facial appearance except for features of apparent microcephaly (31).

***Please note, if a diagnosis of autosomal recessive primary microcephaly is strongly suspected, our Autosomal Recessive Primary Microcephaly Series is also available.**

Gene	Inheritance	Clinical Features
<i>ASPM</i> [OMIM#605481]	AR	Mutations in the <i>ASPM</i> gene are the most common cause of autosomal recessive primary microcephaly (32). Approximately 40% of patients with a strict diagnosis of MCPH have mutations in <i>ASPM</i> . However, fewer patients (<10%) with a less restrictive phenotype have mutations in <i>ASPM</i> (33).
<i>CASC5</i> [OMIM#609173]	AR	Genin et al. (2012) identified the same <i>CASC5</i> frameshift mutation in the homozygous state in three separate consanguineous families with autosomal recessive primary microcephaly (34).
<i>CDK5RAP2</i> [OMIM #608201]	AR	Homozygous mutations in <i>CDK5RAP2</i> have been identified in three Pakistani families with autosomal recessive primary microcephaly (35, 36).
<i>CDK6</i> [OMIM#603368]	AR	Homozygous missense mutations in <i>CDK6</i> were identified in a large Pakistani family with 10 individuals presenting with microcephaly (-4 SD to -6SD), sloping foreheads, and mild intellectual disability (37).
<i>CENPJ</i> [OMIM #609279]	AR	Four Pakistani families with autosomal recessive primary microcephaly have been reported with homozygous mutations in <i>CENPJ</i> (36, 38).
<i>CEP135</i> [OMIM#614673]	AR	Hussain et al. identified a homozygous frameshift mutation in <i>CEP135</i> in a consanguineous family with two siblings affected by autosomal recessive primary microcephaly (39).
<i>CEP152</i> [OMIM #613529]	AR	Homozygous or compound heterozygous mutations in the <i>CEP152</i> gene were identified in 3 unrelated Canadian families with MCPH (40).
<i>MCPH1</i> [OMIM #607117]	AR	Homozygous mutations in <i>MCPH1</i> have been reported in multiple populations, including at least one Pakistani family and at least one Caucasian family (41-43).
<i>PHC1</i> [OMIM#602978]	AR	A homozygous missense <i>PHC1</i> mutation was identified in a consanguineous Saudi family in which 2 of 6 children were affected with microcephaly (-4.3 SD and -5.8 SD) and short stature (-2.3 SD and -3.6 SD) with an IQ of 80 recorded in the older child (44).
<i>STIL</i> [OMIM #181590]	AR	Kumar et al (2009) reported three Indian families with autosomal recessive primary microcephaly and homozygous mutations in <i>STIL</i> (45).

<i>WDR62</i> [OMIM#613583]	AR	Mutations in <i>WDR62</i> have been reported in a subset of patients with microcephaly, cortical malformations, and moderate to severe ID. In addition to microcephaly, these patients also have various brain malformations including callosal abnormalities, polymicrogyria, schizencephaly and subcortical nodular heterotopia. A subset have seizures (46). Homozygous missense and frameshift mutations were first reported in seven consanguineous families (47).
<i>ZNF335</i> [OMIM#610827]	AR	Yang <i>et al.</i> (2012) identified a homozygous mutation in <i>ZNF335</i> in a large consanguineous Arab-Israeli family with severe autosomal recessive primary microcephaly (48).

Postnatal Microcephaly Genes

Gene	Inheritance	Clinical Features
<i>CDKL5</i> [OMIM#300203]	XL	<i>CDKL5</i> mutations have been described in females X-linked infantile spasms [OMIM#300672], which is associated with early-onset refractory epilepsy, severe developmental delay, absent or limited speech, in addition to postnatal microcephaly and hand stereotypies in some patients (49). Mutations in males are associated with a more severe phenotype of early-onset tonic and myoclonic seizures, intractable infantile spasms, severe global developmental delay, cortical visual impairment and sleep disturbances (49).
<i>DYRK1A</i> [OMIM#60085]	AD	The <i>DYRK1A</i> gene encodes a member of the dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family and participates in various cellular processes. It is a highly conserved gene located in the so-called Down Syndrome critical region (DSCR), a part of chromosome 21 that is responsible for the majority of phenotypic features in Down syndrome (50). Both <i>DYRK1A</i> mutations (51) and deletions (50) have been identified in patients with microcephaly and intellectual disability. Mutations in <i>DYRK1A</i> are typically <i>de novo</i> .
<i>FOXG1</i> [OMIM#164874]	AD	Abnormalities of the <i>FOXG1</i> gene have been identified in patients with the congenital variant of Rett syndrome [OMIM#613454] (52). Patients with <i>FOXG1</i> mutations typically have early onset epilepsy, severe cognitive impairment, progressive postnatal microcephaly, postnatal growth deficiency and dyskinetic movement disorders (52). Unlike classic Rett syndrome there is typically no observed period of normal development prior to onset of symptoms (52).
<i>MECP2</i> [OMIM#300005]	XL	<i>MECP2</i> mutations are present in 70-90% of females with classic Rett syndrome [OMIM#312750] and approximately 20% of females with atypical Rett syndrome (53). Classic Rett syndrome is a progressive disorder characterized by acquired microcephaly, epilepsy, poor growth, loss of purposeful hand movements, and autistic behaviors, following a period of normal growth and development (53). <i>MECP2</i> mutations appear to be more common in females than in males, and the majority of cases are <i>de novo</i> (53). There have been reports of unaffected or mildly affected <i>MECP2</i> carrier females due to skewed X inactivation.
<i>MED17</i> [OMIM#603810]	AR	A homozygous missense mutation in <i>MED17</i> was identified in 5 infants from 4 Jewish families with postnatal progressive microcephaly with seizures and brain atrophy [OMIM#613668] (16).
<i>RAB18</i> [OMIM#602207] <i>RAB3GAP1</i> [OMIM#602536] <i>RAB3GAP2</i> [OMIM#609275] <i>TBC1D20</i> [OMIM #611663]	AR	Mutations in <i>RAB18</i> , <i>RAB3GAP1</i> , <i>RAB3GAP2</i> , and <i>TBC1D20</i> are associated with Warburg Micro syndrome [OMIM#600118], which is characterized by ocular and neurodevelopmental abnormalities and hypothalamic hypogonadism (54-56). Key clinical features include microcephaly, microphthalmia, microcornea, congenital cataracts, optic atrophy, cortical dysplasia and atrophy, congenital hypotonia, severe intellectual disability, and spastic diplegia (54). Brain magnetic resonance imaging (MRI) of affected individuals consistently shows polymicrogyria in the frontal and parietal lobes, wide sylvian fissures, thin corpus callosum and increased subdural spaces (54).
<i>SLC2A1</i> [OMIM#138140]	AD	Glucose transporter-1 (GLUT-1) deficiency syndrome [OMIM#612126] is caused by mutations in the <i>SLC2A1</i> gene, which lead to impaired glucose transport in the brain. The classic GLUT-1 deficiency syndrome presentation is drug-resistant infantile-onset seizures, acquired microcephaly, developmental delay, hypotonia, spasticity, ataxia and dystonia (57). A ketogenic diet is effective in mitigating clinical findings in affected individuals.
<i>SLC9A6</i> [OMIM#300231]	XL	Mutations in the <i>SLC9A6</i> gene have been identified in patients with X-linked Angelman-like syndrome [OMIM#300243] (58). Features of males with <i>SLC9A6</i> mutations include progressive microcephaly, grand mal epilepsy, lack of speech, truncl ataxia, excessive drooling, and a happy demeanor with spontaneous smiling and laughter (58). Mutations in <i>SLC9A6</i> result in clinical features in affected males and occasionally some mild features in carrier females (58).

<i>TCF4</i> [OMIM#602272]	AD	Mutations in <i>TCF4</i> are associated with Pitt-Hopkins syndrome (PHS) [OMIM#610954]. PHS is characterized by severe mental retardation and dysmorphic facial features, which tend to coarsen with age (59). Other common features include acquired microcephaly, epilepsy, hyperventilation episodes, short stature, stereotypic hand movements, and absent speech (59).
<i>TRAPPC9</i> [OMIM#611966]	AR	Marangi <i>et al.</i> (2013) concluded that the phenotype associated with loss-of-function mutations in the <i>TRAPPC9</i> gene is recognizable and can be characterized by dysmorphic facial appearance, obesity, hypotonia, moderate to severe intellectual disability, and consistent brain abnormalities (60). <i>Trappc9</i> is highly expressed in the mouse brain (61). All mutations reported to date have been homozygous and protein truncating.
<i>TSEN2</i> [OMIM#608753] <i>TSEN34</i> [OMIM#608755] <i>TSEN54</i> [OMIM#608755]	AR	Mutations in <i>TSEN2</i> , <i>TSEN34</i> and <i>TSEN54</i> are associated with pontocerebellar hypoplasia, a rare neurodegenerative disorder with prenatal onset, characterized by cerebellar hypoplasia in addition to varying degrees of atrophy of the cerebellum and pons (62). Significant microcephaly develops after birth (62). MRI findings include a small cerebellum and brainstem, variable neocortical atrophy, severe and progressive microcephaly and variable ventriculomegaly (63). Clinically, most patients have severe intellectual disability, swallowing problems, and seizures (63).
<i>UBE3A</i> [OMIM#601623]	AD	Mutations in <i>UBE3A</i> are one of the causes of Angelman syndrome [OMIM#105830], which is characterized by severe intellectual disability, frequent laughing/smiling, easy excitability, and severe speech impairment (64). Other characteristics noted in over 80% of patients include microcephaly, seizures, and a specific, abnormal EEG pattern (64). Most mutations in <i>UBE3A</i> are <i>de novo</i> , with a <1% recurrence rate, however some cases may be familial (64).

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 novel and/or potentially 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.

Microcephaly Sequencing Panel (56 genes)*

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$4000
CPT codes:	81407
Turn-around time:	8 weeks

***Note: We cannot bill insurance for the Microcephaly Sequencing Panel.**

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